Screenig del diabete tipo 1 nella popolazione generale

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La dr.ssa Elisa Borgonovo dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

WHO 10 principles of screening
Wilson and Juger criteria 1968

- The condition sought should be an important health problem.
- The natural history of the condition, including development from latent to declared disease, should be adequately understood.
- There should be a recognizable latent or early symptomatic stage.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- There should be an agreed policy on whom to treat as patients.
- There should be an accepted treatment for patients with recognized disease.
- Facilities for diagnosis and treatment should be available.
- The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case-finding should be a continuing process and not a “once and for all” project.

Italian Republic Law 130/2023
15 sept 2023

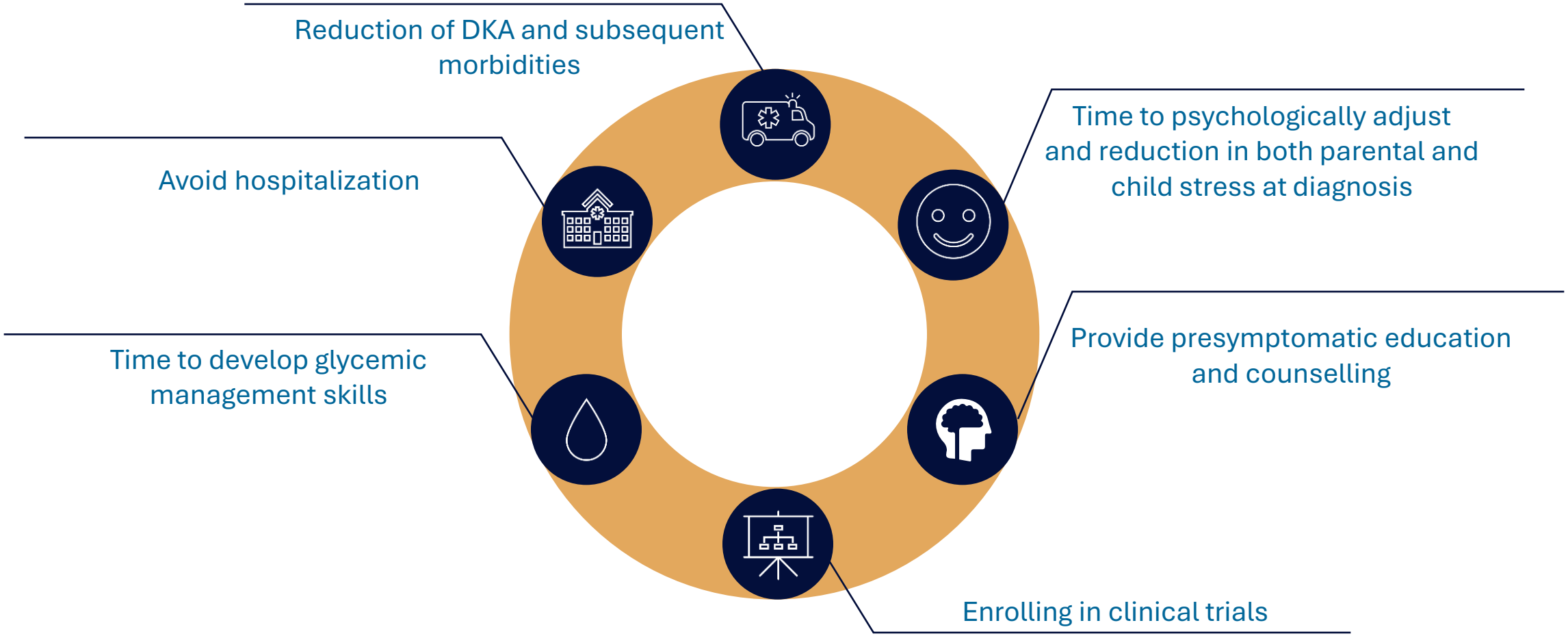
Nationwide screening for T1D and coeliac disease in general population aged 1-17 years

Aims:

- Prevent diabetic ketoacidosis associated (DKA) and receive disease-modifying therapies
- Early diagnosis of atypical or silent CD, allowing treatment and prevent long-term complications

Bosi E, Catassi C. Lancet Diabetes Endocrinol. 2024 Jan;12(1):12-14

Potential benefits of identifying presymptomatic T1D



Besser REJ, et al. Arch Dis Child. 2022;107:790-5. ; Scheiner G, et al. ADCES in Practice. 2022;10(5):20-5.

Epidemiology

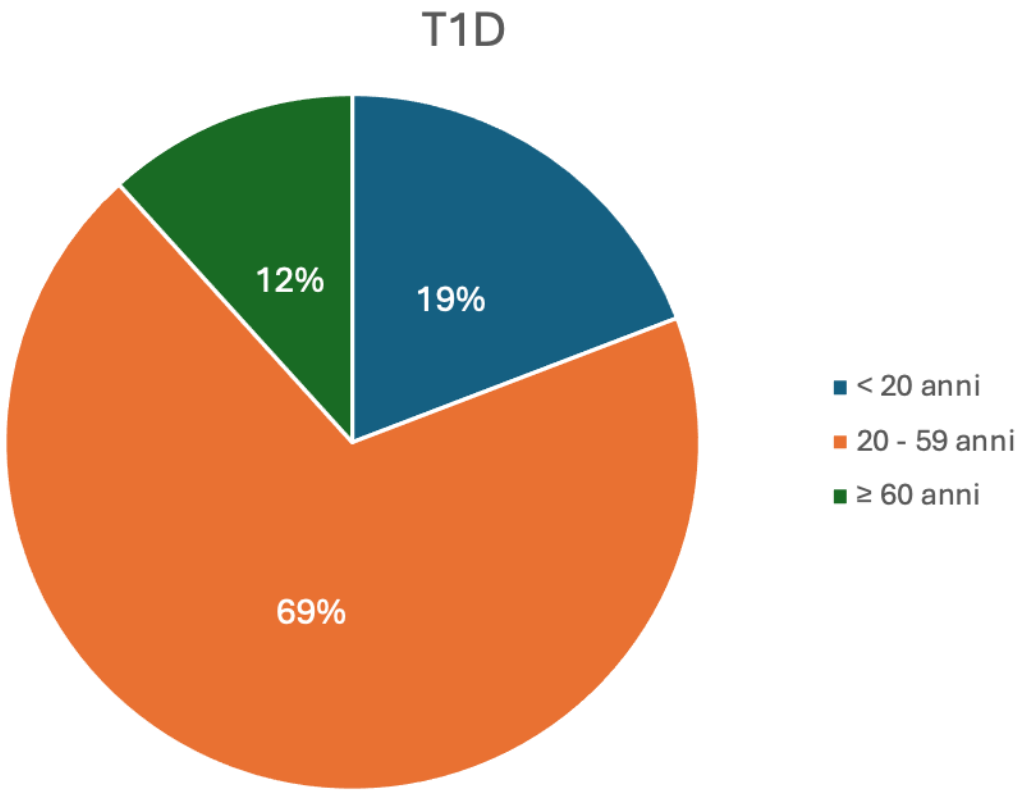
T1D global prevalence in 2025:

9.5 million people

Median age 36 years (IQR 26)

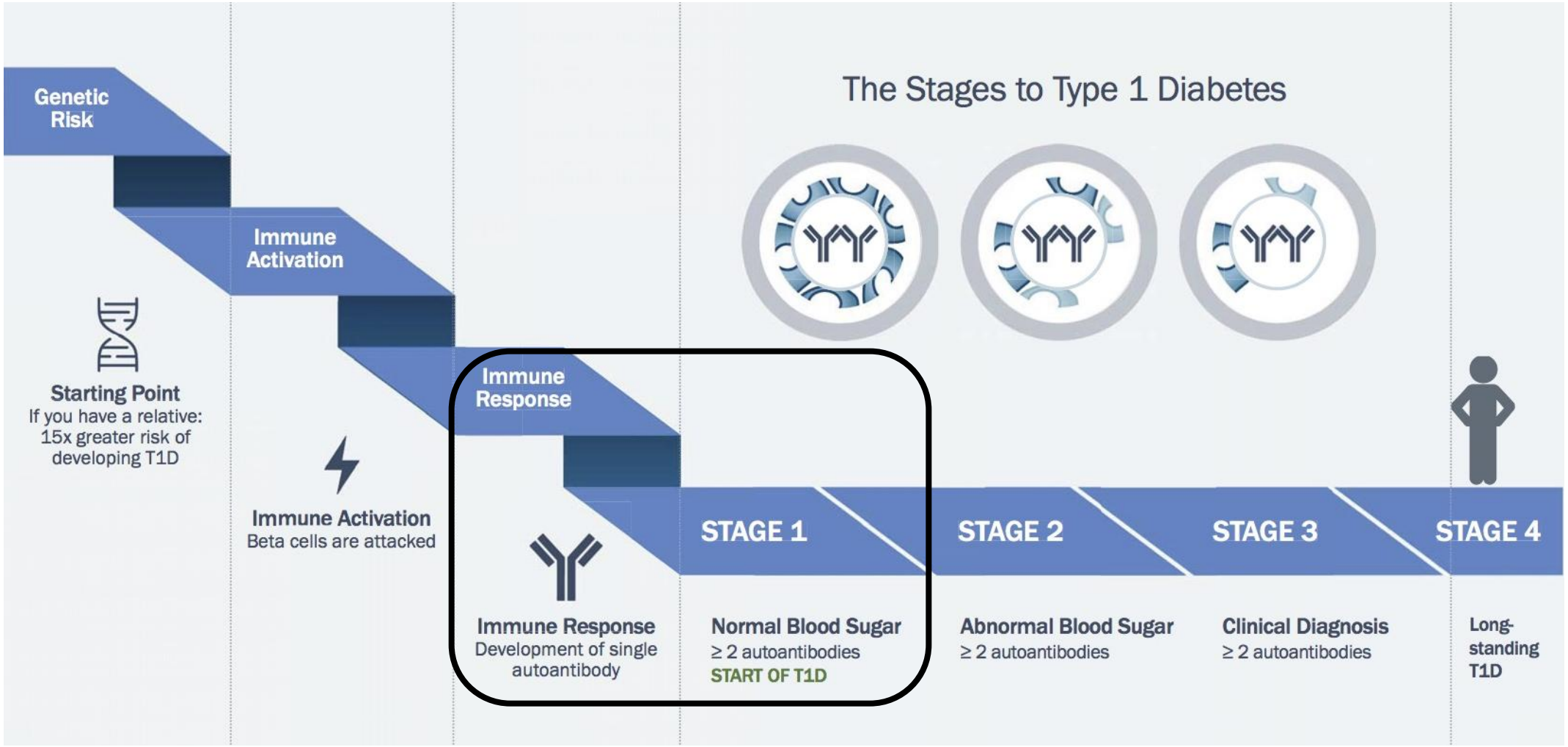
1.9 million < 20 years
6.5 million 20 – 59 years
1.1 million ≥ 60 years

513,000 newly diagnosed cases in 2025
222,000 (43.3%) in people aged < 20 years



Global type1 diabetes prevalence, incidence and mortality estimates 2025: results from the IDF Atlas, *Diabetes Research and Clinical Practice* May 2025

T1D Natural History



ADA Standards of Care in Diabetes 2025, *Diabetes Care* January 2025, Vol 48, Suppl. 1

Number of IAbs predicts progression to Stage 3

Children genetically at risk for T1D

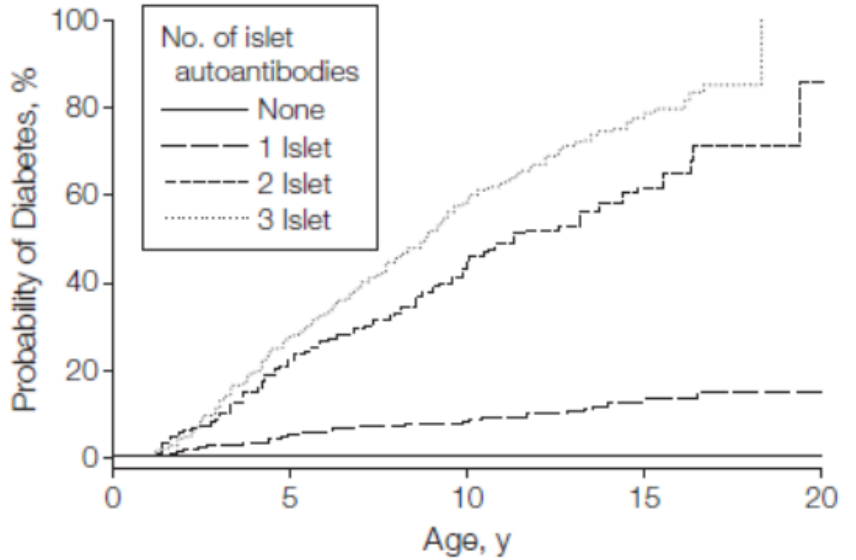
Progression to T1D
Within 10 years after seroconversion:

None	0.4%
1 IAb	14.5%
≥ 2 IAbs	69.7%

Median time after seroconversion

≥ 2 IAbs	3.5 years

Figure 1. Development of Diabetes in Children Stratified for Islet Autoantibody Outcome



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12 318	8875	5253	1161	44

The numbers at risk represent the children receiving follow-up at age 0, 5, 10, 15, and 20 years.

Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children , JAMA. 2013 June 19; 309(23): 2473–2479

EARLY STAGE T1D IS NOT JUST A RISK

- People in the **early stages of T1D (Stage 1 and Stage 2)** are not merely at risk of developing diabetes: they **already HAVE T1D**.

- This is an important concept that has been recognized also in the ICD-10 (International Classification of Diseases, 10th Revision), a coding system developed by the World Health Organization (WHO).

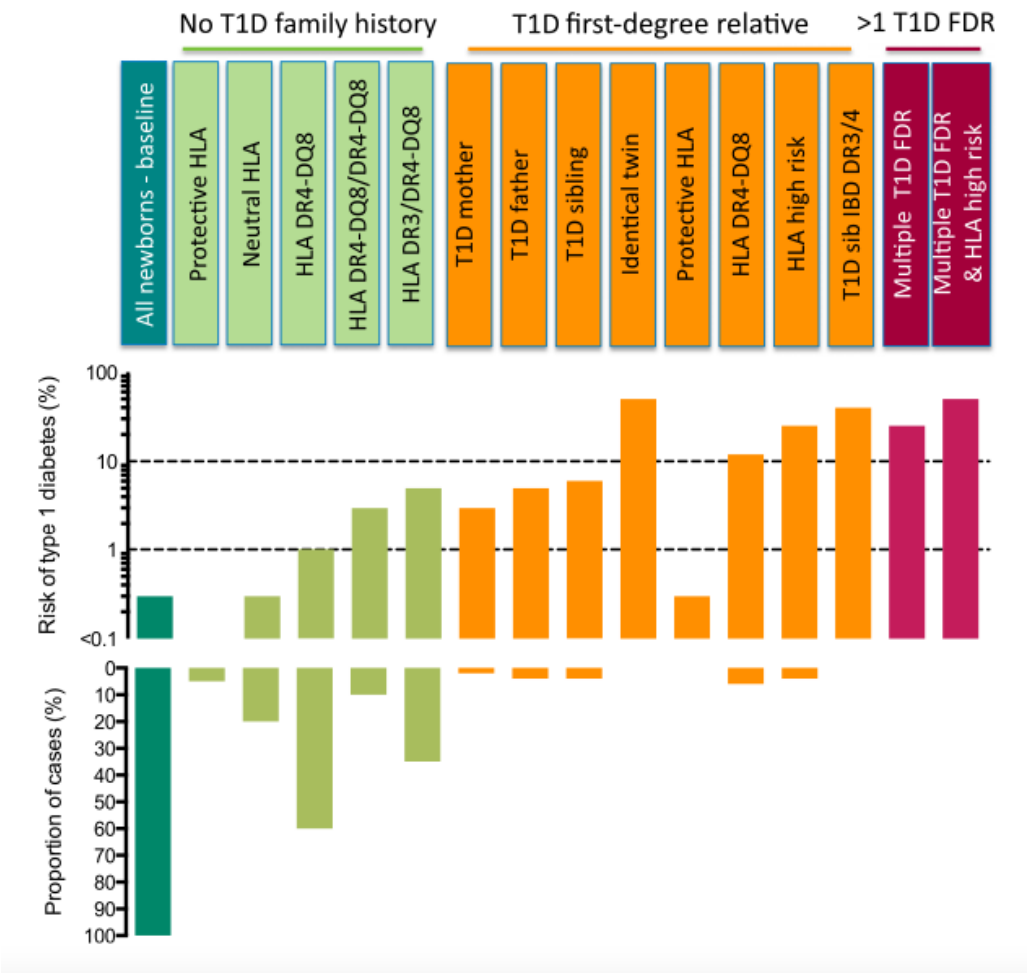
- The ICD-10 is a global standard for classifying diseases and medical conditions, and in **October 2024, early-stage diabetes was assigned its own specific code:**

  E10.A0 Type 1 diabetes, pre-symptomatic, unspecified

  E10.A1 Type 1 diabetes, pre-symptomatic, Stage 1

  E10.A2 Type 1 diabetes, pre-symptomatic, Stage 2

Risk for T1D according to HLA and first-degree family history status



European infants' approximate risk for T1D by age 20 years

Family history of T1D:
15–20 times higher in relatives than in general population

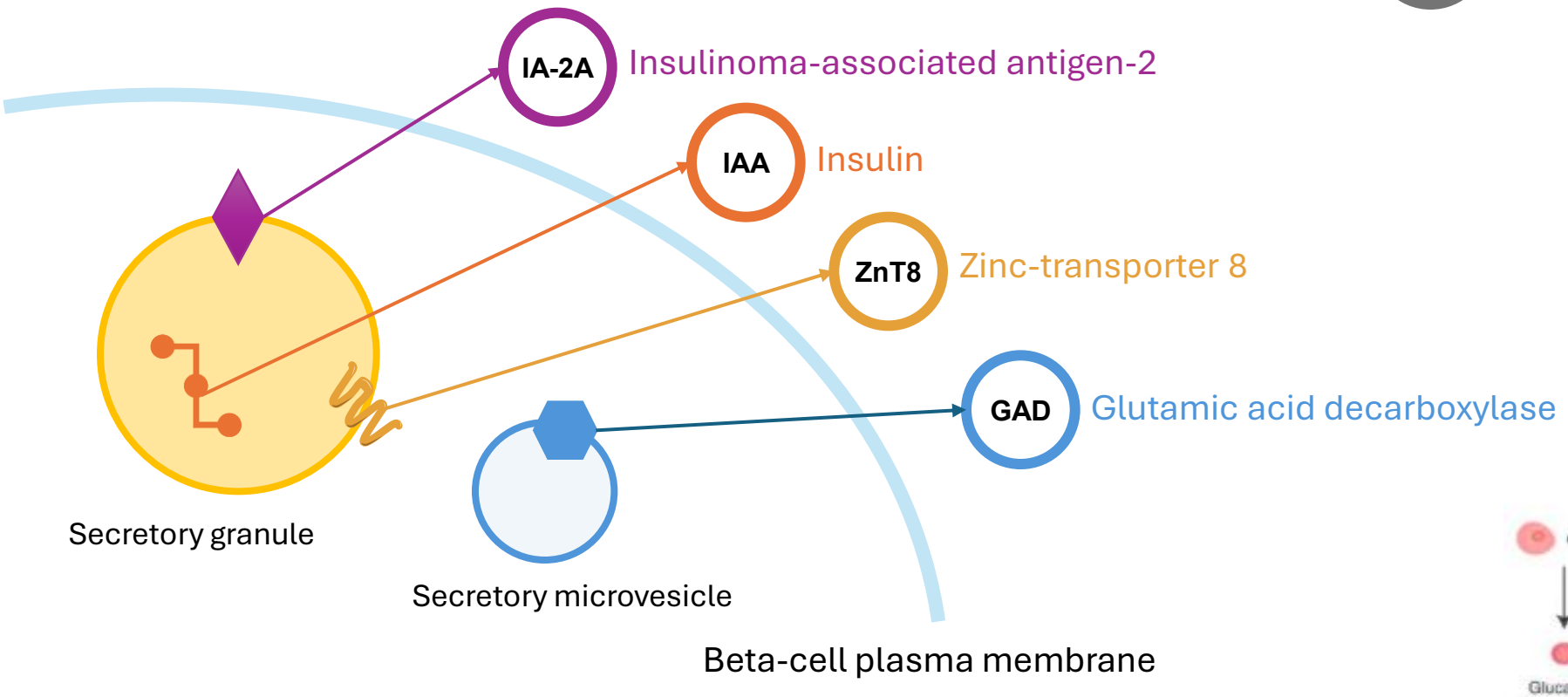
Risk of T1D onset by 20 years age:
5–8% if father affected
2–5% if mother affected
20-30% if both affected
5-10% if sibling affected

HLA genotype:
- Heterozygosis DR3/DR4-DQ8 highest risk
- Homozygosis for DR3 or DR4-DQ8 increased risk

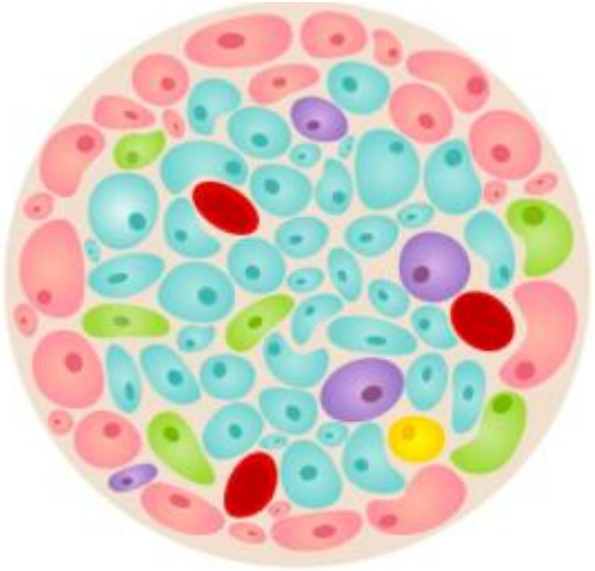
Predicting Type 1 Diabetes Using Biomarkers, Diabetes Care 2015;38:989–996

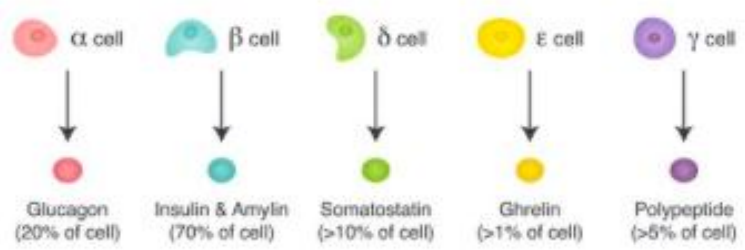
What to screen for T1D

Islet autoantibodies (IAbs) are markers of T1D autoimmunity



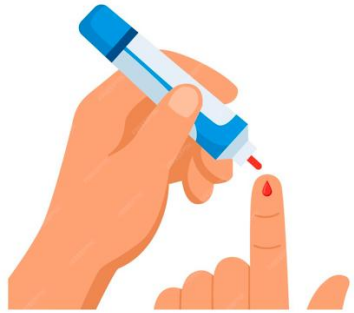
ICA Islet Cell Cytoplasmatic Autoantibodies





Practical Clinical Applications of Islet Autoantibody Testing in Type 1 Diabetes, Winter WE et al., JALM 2022;7:197-205

Samples



Capillary Samples (CB)

microtube with serum-gel separator

200 mcL

Dried Blood Spots (DBS)

Guthrie/DBS cards

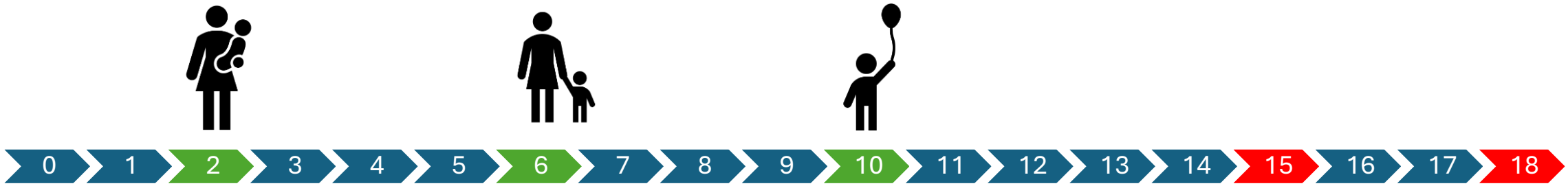
5 drops

Enzyme-linked immunosorbent assay (ELISA) 3-screen assay
Electrochemiluminescence (ECL)
Antibody detection by agglutination-PCR (ADAP)
Luciferase immunoprecipitation system (LIPS)

Dissociation-enhanced lanthanide fluorescent immunoassay (DELFI)

Separate radio binding assays (RBA)

When?



Data harmonised from prospective cohort studies, Europe (DIPP, DiPiS and BABY-DIAB) and US (DEW-IT and DAISY)

6722 enrolled before 2 years and followed until age **15 years** or T1D onset, 672 developed T1D

Screening at **2 and 6 years**, sensitivity 82% and PPV 79%[1]

1890 followed until age **18 years** or T1D onset, 262 developed T1D

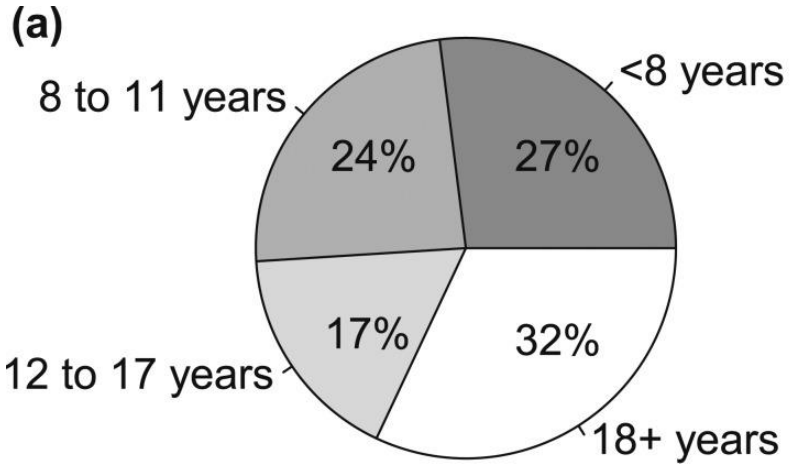
Screening at **10 years**, sensitivity 90% and PPV 66%[2]

1 Ghalwash M et al., The Lancet, vol 10, issue 8, P589-596, Aug 2022 2 Ghalwash M et al., The Lancet, vol 7, issue 4, P261-268, Apr 2023

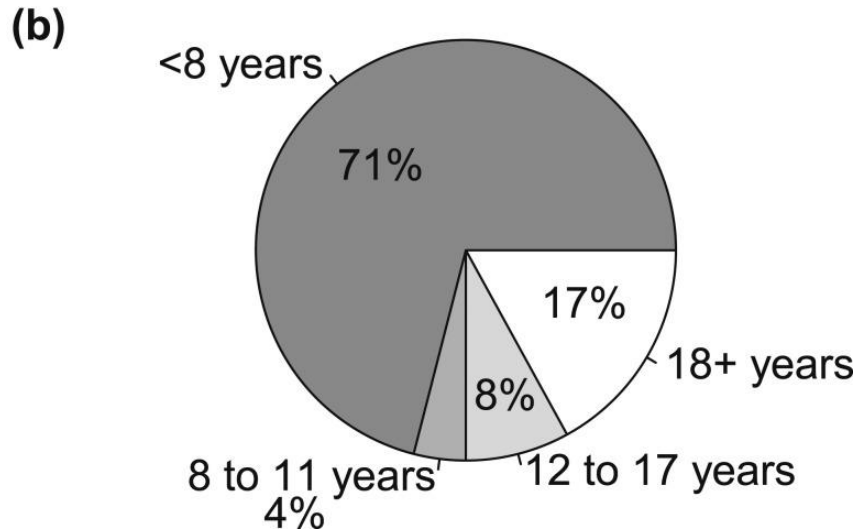
Progression to a multiple IA+ after single IA+

Additional IAb within 5 years

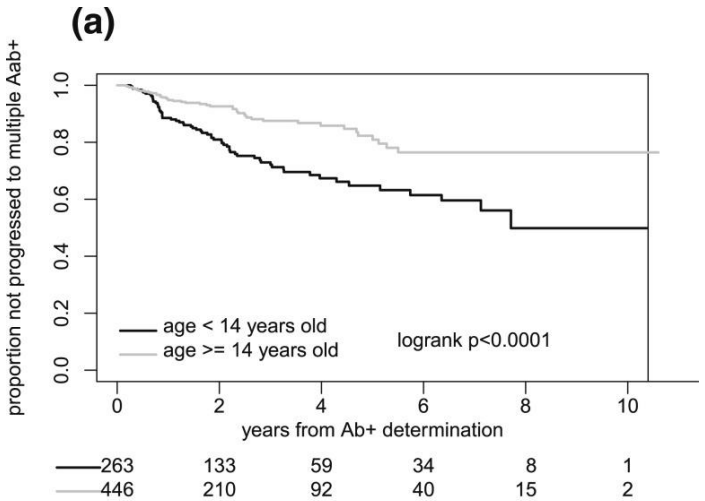
GADA first

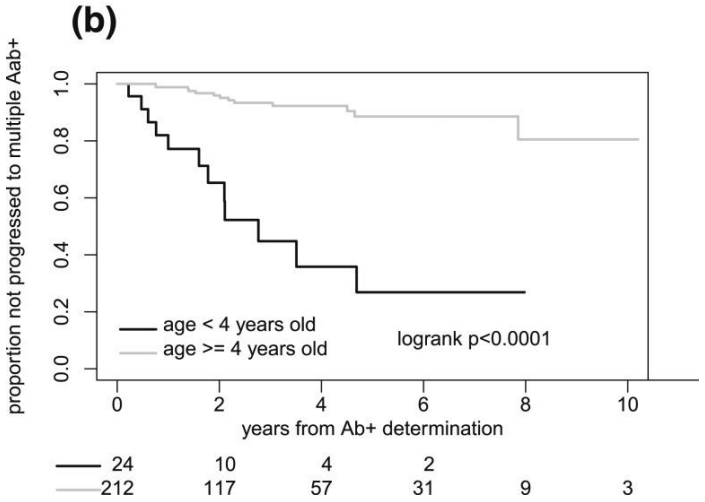


IAA first



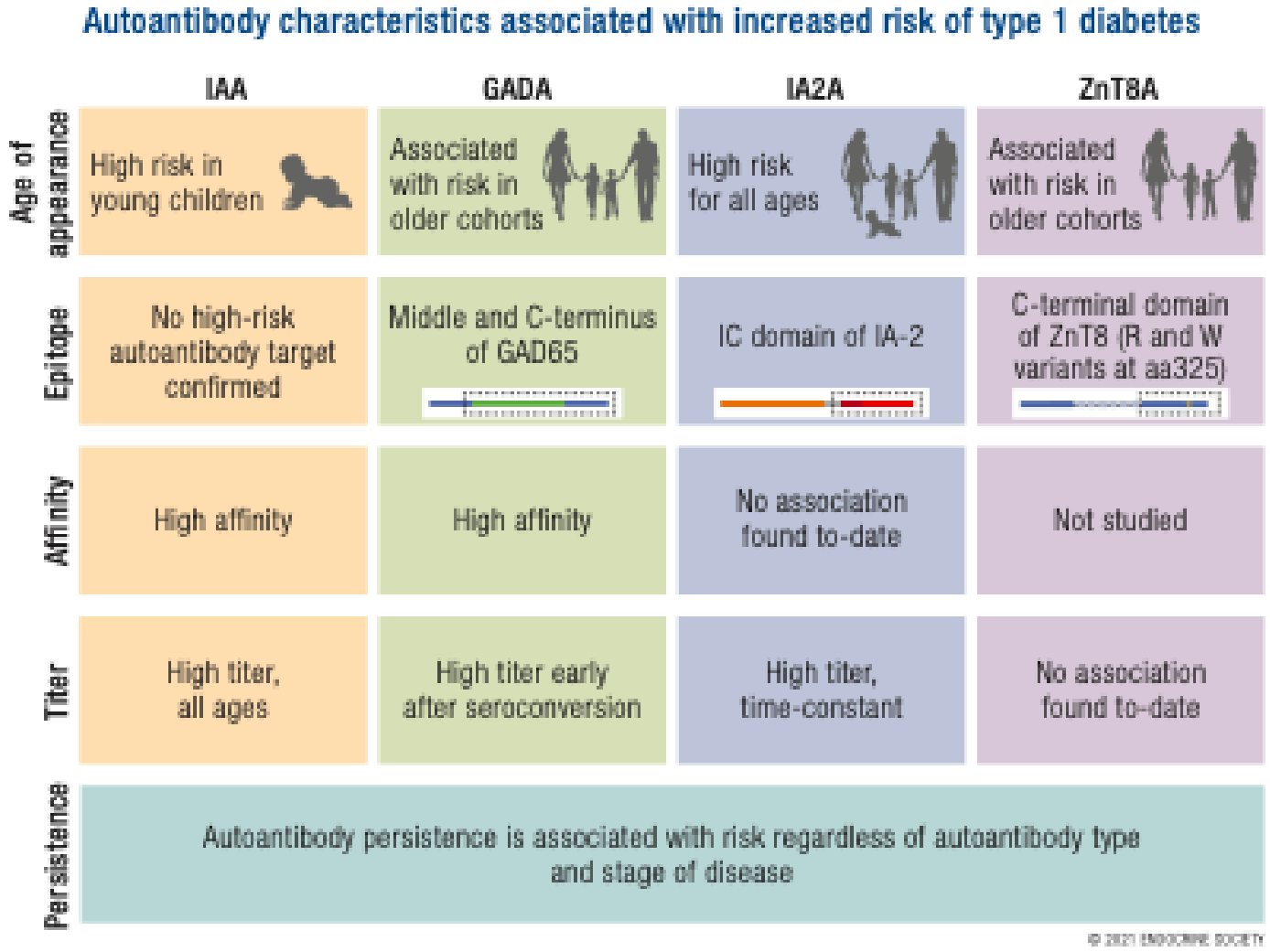
Time from initial detection to multiple detection





Bosi E et al. J Clin Endocrinol Metab 102: 2881–2886, 2017

IA characteristics



Endocrine Reviews, 2021, Vol. 42, No. 5, 584–604 doi:10.1210/endrev/bnab013

Risk for T1D in individuals with celiac and autoimmune thyroid disease

Retrospective, observational, equal number matched-control study, median 2 years follow-up

Celiac disease

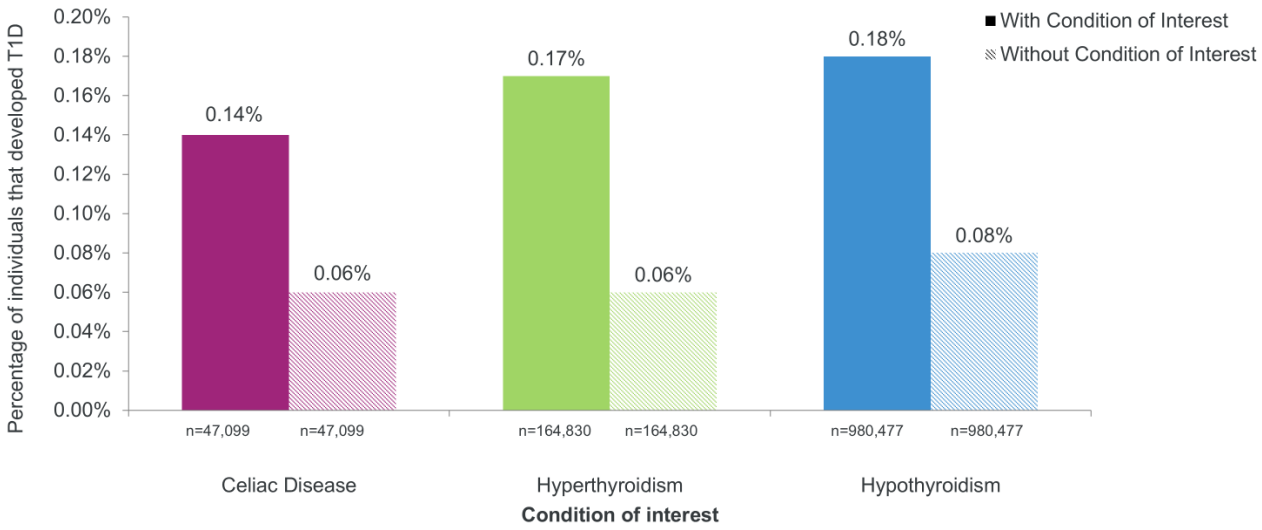
n = 47099
Mean age 48.4 y

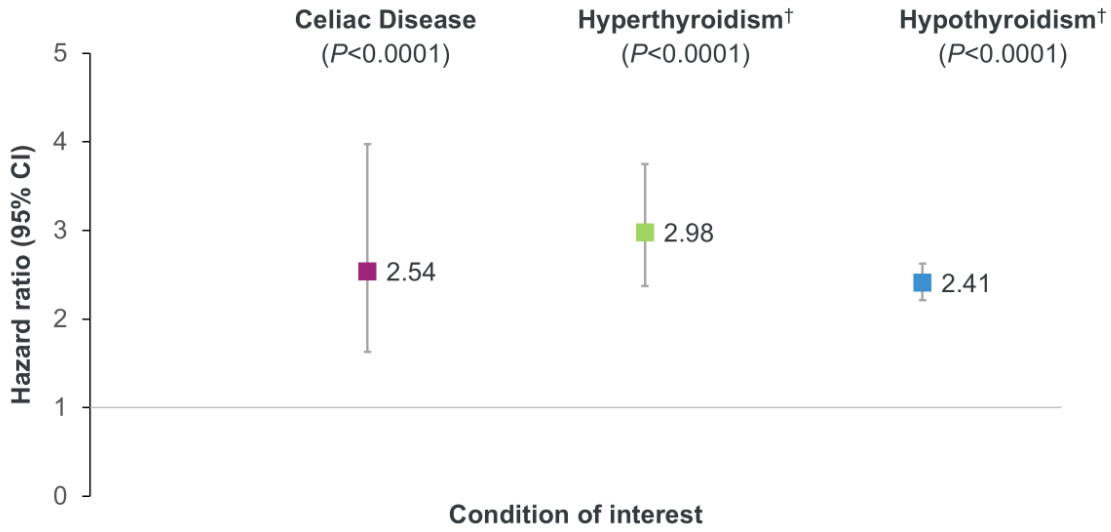
Hyperthyroidism

n = 164830
Mean age 61.0 y

Hypothyroidism

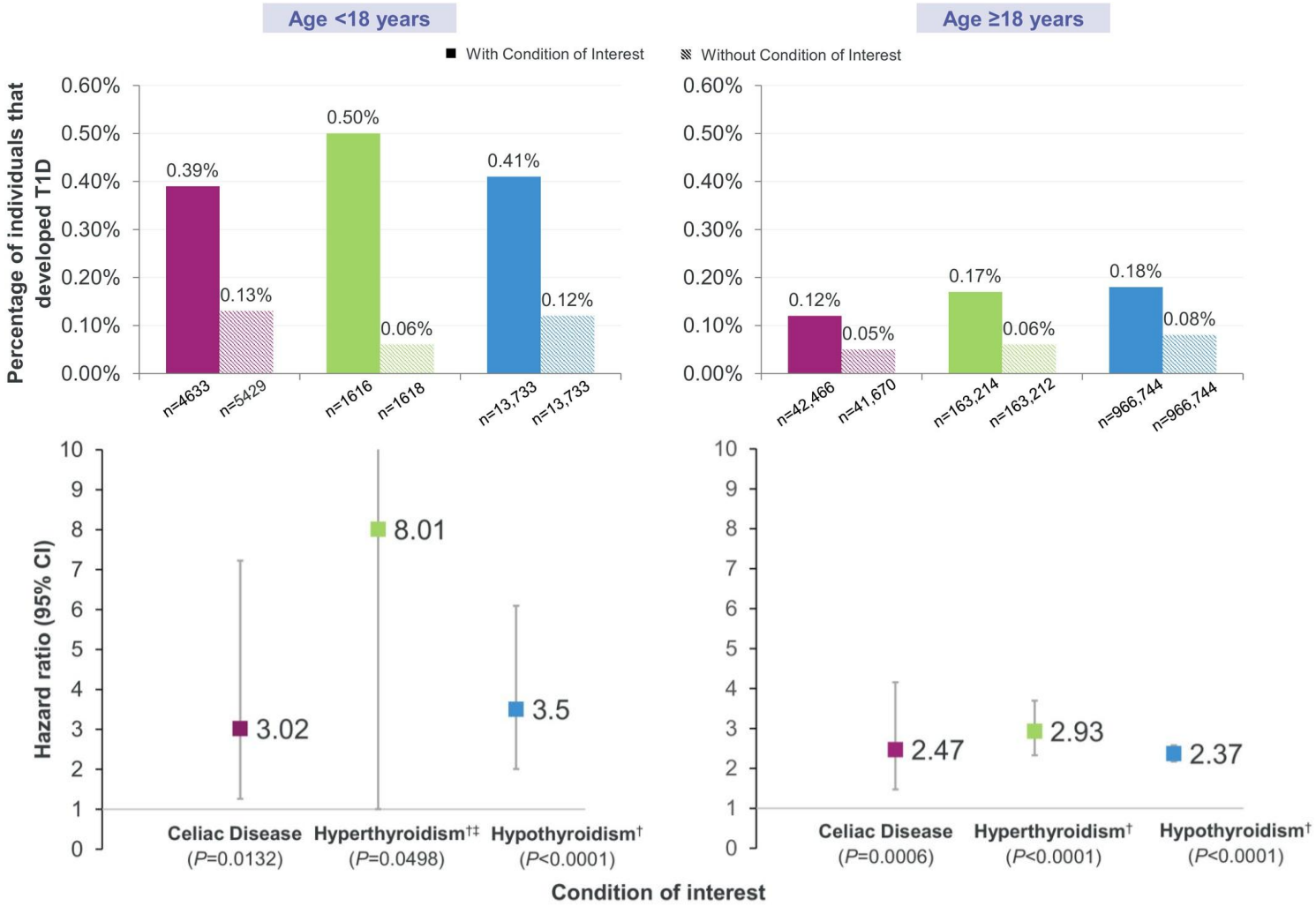
n = 980477
Mean age 61.9 y





Edelman SV et al., Diabetes Obes Metab. 2025;27:4229–4238

Risk for T1D in individuals with celiac and autoimmune thyroid disease



Edelman SV et al., Diabetes Obes Metab. 2025;27:4229–4238

Follow-up and monitoring in children

Age (years)	Previous Screening	Previous Screening Results	Current Screening Results	Ab confirmatory test	Blood glucose pattern	Follow-Up Program
2-2.9	no		neg			Repeat screening at age 6-6.9 years
2-2.9	no		pos	Neg	normoglycaemia	Repeat screening at age 6-6.9 years
2-2.9	no		pos	S-iAb pos	normoglycaemia	Program for Intermediate Risk
2-2.9	no		pos	M-iAb pos	normoglycaemia	Monitoring as Stage 1
2-2.9	no		pos	S- or M-iAb pos	dysglycaemia	Monitoring as Stage 2
6-6.9	No		neg			Repeat screening at age 10-10.9 years
6-6.9	No		pos	Neg		Repeat screening at age 10-10.9 years
6-6.9	Yes	neg	neg			Stop Screening
6-6.9	yes	S-iAb pos	neg	Neg	normoglycaemia	Repeat screening at age 10-10.9 years
6-6.9	yes	S-iAb pos	pos	S-iAb pos	normoglycaemia	Monitoring as Intermediate Risk
6-6.9	yes	S-iAb pos	pos	M-iAb pos	normoglycaemia	Monitoring as Stage 1
6-6.9	yes	S-iAb pos	pos	S- or M-iAb pos	dysglycaemia	Monitoring as Stage 2
10-10.9	no		neg			Stop Screening
10-10.9	no		pos			Stop Screening
10-10.9	yes	neg	neg			Stop Screening
10-10.9	yes	S-iAb pos	neg	Neg	normoglycaemia	Stop Screening
10-10.9	yes	S-iAb pos	pos	S-iAb pos	normoglycaemia	Monitoring as Intermediate Risk
10-10.9	yes	S-iAb pos	pos	M-iAb pos	normoglycaemia	Monitoring as Stage 1
10-10.9	yes	S-iAb pos	pos	S- or M-iAb pos	dysglycaemia	Monitoring as Stage 2

Cherubini et al., Diabetes Obes Metab; Vol 26, Issue10,Oct 2024, P4197-4202

Screening in general population Worldwide

Frlda
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Feb 2015 – Jun 2025
Bavaria, Germany

211464 children
1.75-10 years

Paediatrically checkups

GADA, IA-2A, ZnT8, IAA

CB 200 mcL
and venous confirmation

Educational programme
PHQ-9
Psychological consult
Progression stage 3

Autoimmunity Screening for Kids
ask
A SIMPLE TEST TO DETECT
Type 1 Diabetes (T1D) + Celiac

Jan 2017 – 2020
Colorado, US

>50000 children
2-17 years

10029 screened by Jul 2018

Paediatrics, family practitioners,
hospitals and community events

GADA, IA-2A, ZnT8, IAA
TGAs

Capillary blood/DBS

Costs

TRIAD

Aug 2021 – Feb 2022
Skåne, Sweden

2271 children
6–9 and 13–16 years

Home capillary sampling

GADA, IA-2A, IAA, ZnT8
IgA-tTG, IgG-tTG
TPOA THGA

CB 250 mcL
CB or venous confirmation

Success rate, quality, AE

Screening in general population in Italy

D1Ce Screen

May 2024 – Mar 2025
Lombardy, Marche,
Campania and Sardinia, Italy

5363 children
2–2.9, 6–6.9, 10–10.9 years

Primary care paediatricians

GADA, IA-2A, ZnT8, IAA
IgA-tTG, IgG-tTG
HLA-DQ2, DQ8

Capillary blood/DBS

HADS, SAI-6, EQ-5D-5L

UNISCREEN
SCREENING UNIVERSALE CANTALUPO

Apr 2023 – Oct 2025
Cantalupo, Cerro Maggiore Milan

1535 of 3061 inhabitants
1-100 years

Voulontary

GADA, IA-2A, ZnT8
IgA-tTG, IgG-tTG
Glucose, HbA1c, lipid pannel
Blood pressure

Capillary blood

Feasibility and acceptability
(11-15 questions)

EDENT1FI

Nov 2023 – Oct 2028
Czech Republic, Denmark,
Germany, Italy, Poland, Portugal,
Sweden and UK

2000000 expected
1-17 years

GADA, IA-2A, ZnT8, IAA
TGA and TPO

Capillary blood
and venous confirmation

Educational programme
Disease-modifying therapy
HADS, SDQ
Psychological consult
Feasibility and acceptability

Fr1da

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Sensitive screening tool: multiplex 3-screen ELISA 25 mcL (GADA, IA-2A, ZnT8) >97.5th

↓

Specific confirmation: single RBA 4 mcL (GADA, IA-2A), 8 mcL (ZnT8), 20 mcL (IAA) >99th

↓

Standardized assay: if 2 IAbs positive confirmation with venous blood sample >99th

Both 96.7%, RBA-only 2.8%, inadequate 0.54%, haemolysed 33.3%

GADA, IA-2A and ZnT8 show high correlation between capillary and venous sample, the 99th percentile cut-offs are comparable

Haemolysis determined IAA false positivity

Raab J, et al. BMJ Open 2016;6:e011144. doi:10.1136/bmjopen-2016-011144

Fr1da

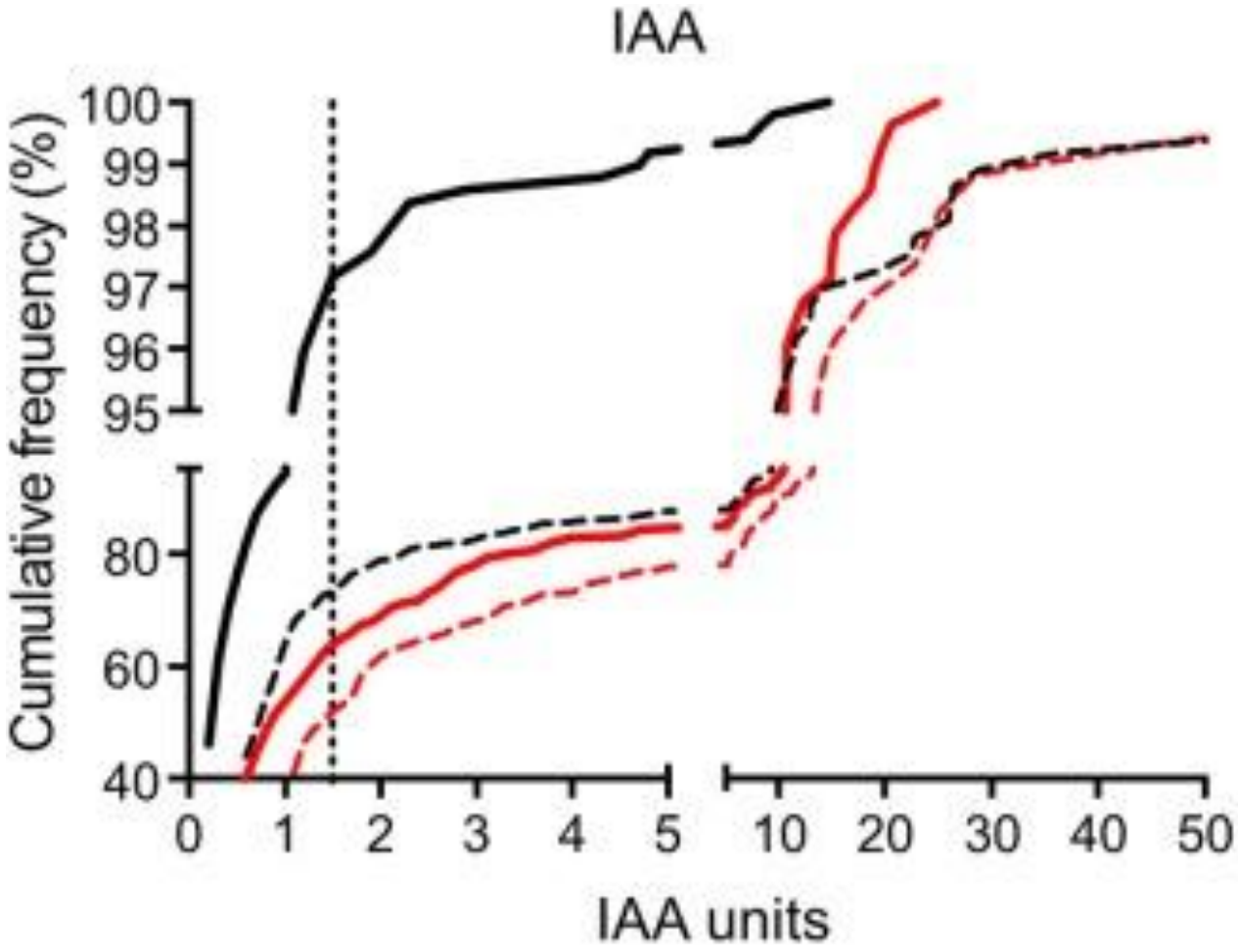
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Cumulative IAA distribution

RBA values (x axis)

Percentage of samples with equal or lower value (y axis)

.....	Dotted line: Venous serum threshold for positivity
-----	Broken line: samples <97.5th at 3-screen ELISA
____	Solid line: samples >97.5th at 3-screen ELISA
--- __	Black lines: non-haemolysed samples
--- __	Red lines: haemolysed samples



Raab J, et al. BMJ Open 2016;6:e011144. doi:10.1136/bmjopen-2016-011144

Fr1da

Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Invited to educational programme by local paediatric diabetes centre team:

- Urine and blood glucose monitoring
- Symptoms of hyperglycaemia
- Pathogenesis of T1D
- Insulin action
- Normal and pathological glucose levels

Provided with guide-book and assigned to contact person

At 2, 6 and 12 months acknowledgements were tested with questionnaire

PHQ-9 at diagnosis, 6 and 12 months later, if elevated anxiety and depression the family was referred to a local psychologist

Raab J, et al. BMJ Open 2016;6:e011144. doi:10.1136/bmjopen-2016-011144

Fr1da

Examine the performance of Progression Likelihood Score (PLS)

CPH: exp [(HbA1c (%) −5.233)×1.125+(OGTT90 (mg/dl) −107.6)×0.0195+(IA-2Acat−1.27)×0.662]

High risk

Stage 1b Score 4.0 90th centile

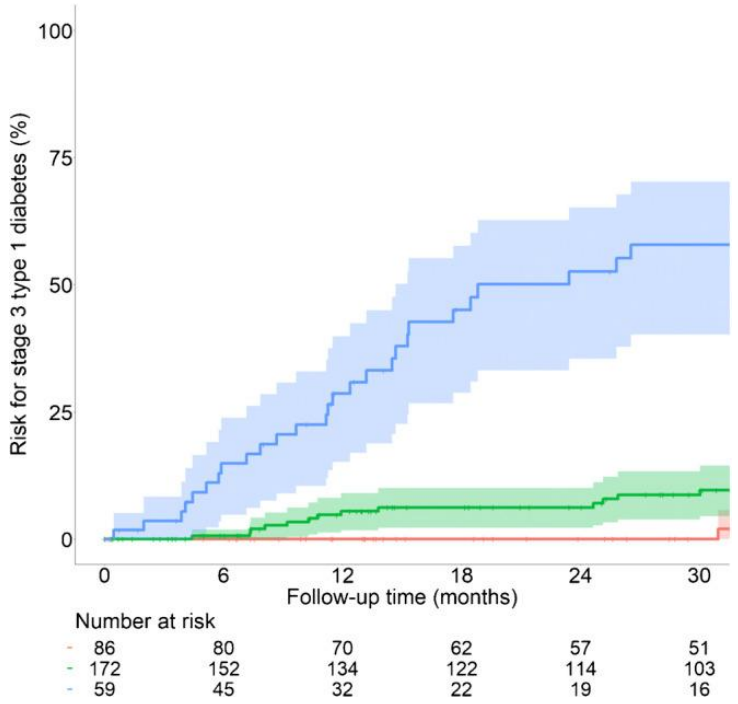
46% 2 years risk of progressing to stage 3 T1D

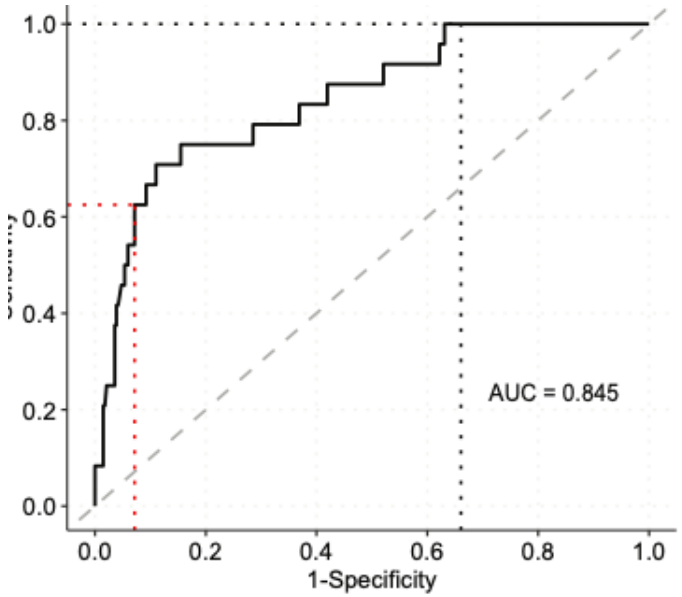
Intermediate risk

Stage 1a Score 4.0-0.5 90th - 30th centile

4.1% 2 years risk of progressing to stage 3 T1D

Adding obesity improved the model





Diabetes Care 2026;49(2):352–360 | https://doi.org/10.2337/dc25-2184

Fr1da

Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Examine the performance of Progression Likelihood Score (PLS)

CPH: exp [(HbA1c (%) −5.233)×1.125+(OGTT90 (mg/dl) −107.6)×0.0195+(IA-2Acat−1.27)×0.662]

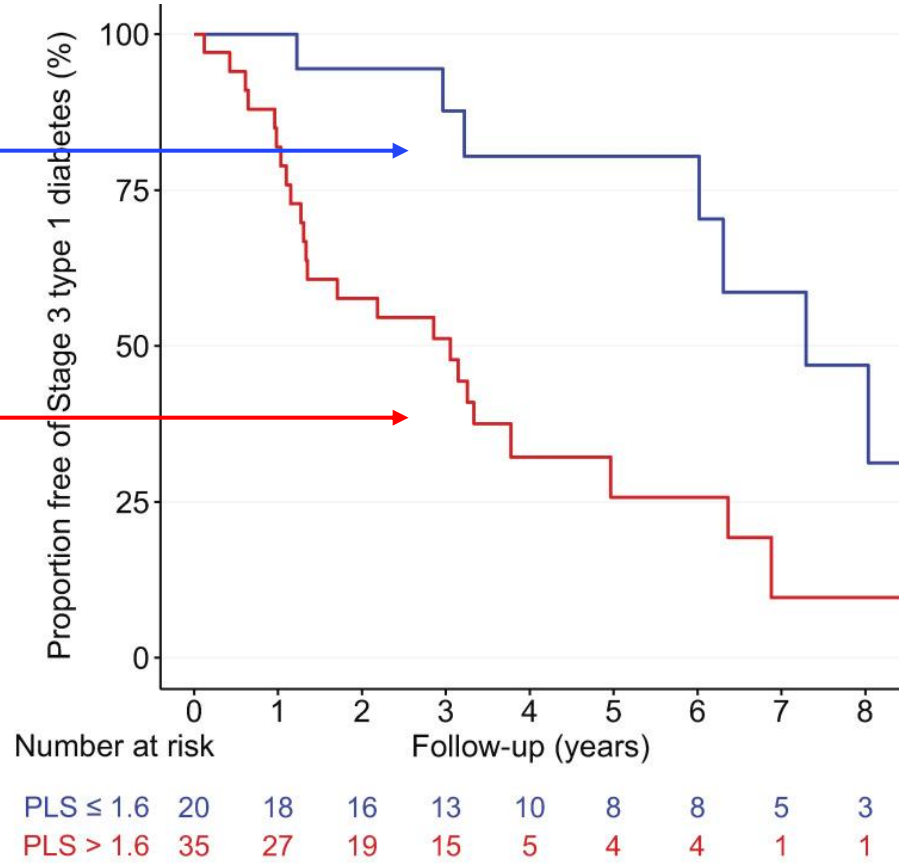
Score ≤ 1.6

5.6 % 2 years risk of progressing to stage 2 T1D

Score > 1.6

42.4% 2 years risk of progressing to stage 2 T1D

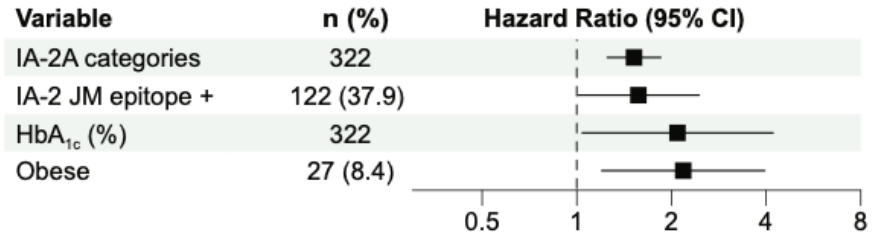
ROC AUC 0.680



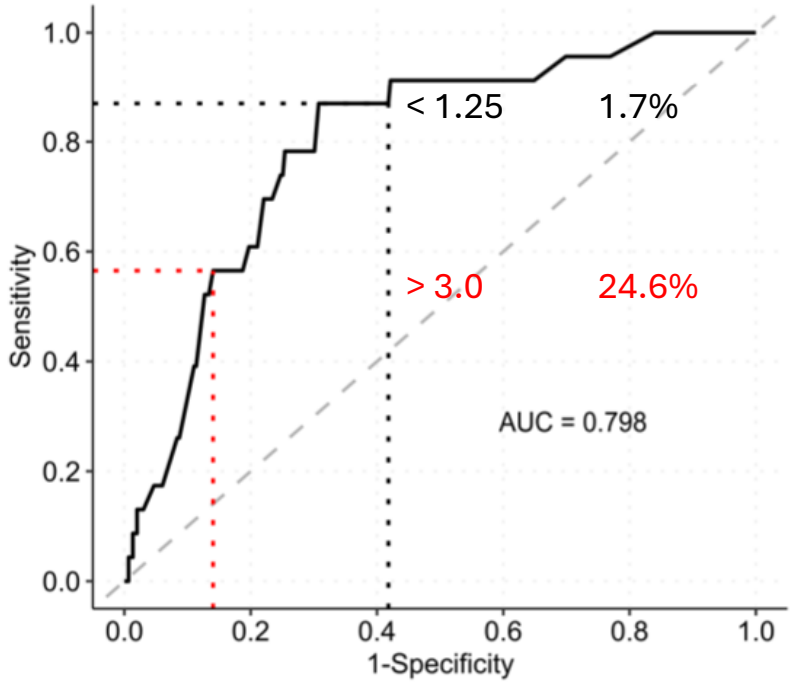
Fr1da

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

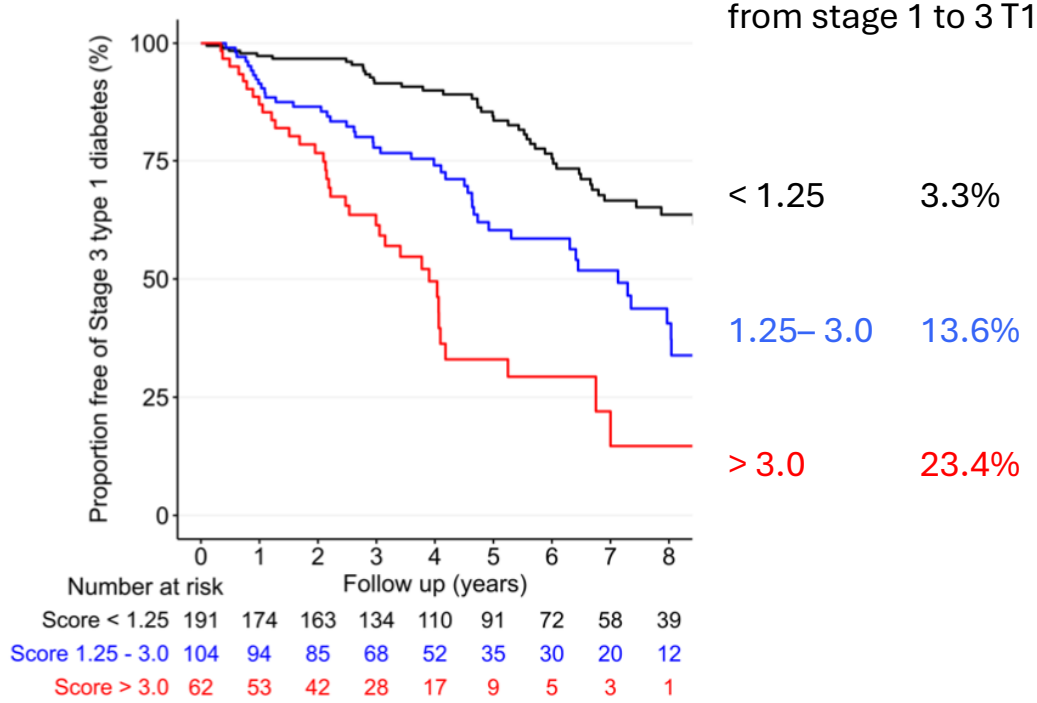
Determine additional markers to allow risk stratification without OGTT, multiple variable model that include:



Progression within 2 years:



Progression to stage 3 T1D:



Following 2-years risk of progression from stage 1 to 3 T1D

< 1.25	3.3%
1.25– 3.0	13.6%
> 3.0	23.4%

Fr1da

Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

in Fr1da

Cost per child screened

28.17 € (95%, CI 19.96; 39.63)

Cost per child diagnosed

9117 € (95%, CI 6460; 12827)

In Standard Care

Cost per child screened

21.73 € (95%, CI 16.76; 328.19)

Cost per child diagnosed

7035 € (95%, CI 5426; 9124)

Diabetes Care 2022;45:837–844 | https://doi.org/10.2337/dc21-1648

ASK

10.000 screened, 9.3 years mean age, 101 (1%) IA positive (0,53% multiple), 81 estimated to progress to T1D

Cost per person screened 47 $ (ASK) and 141 $ (routine screening)

Bridge Model: cost per positive case detected until 18 years 4.700 $ (ASK) and 14.000 $ (routine screening)
Lifetime Simulation Model: patients diagnosed of T1D followed over 30 years

Value thresholds of 50.000-100.000 $ per QALY gained

Avoid 20% in DKA events at diagnosis in addition to 0,1% (1 mmol/mol) improvement in HbA1c over a lifetime

Limits: no screening schedule, teplizumab intervention, long-run knowledge, generalized to all clinical setting

Diabetes Care 2020;43:1496–1503 | https://doi.org/10.2337/dc19-2003

ASK

ASK study team members also recruited and screened between February 2021 and February 2022

This adult cohort was not part of the original paediatric ASK screening population

Same screening framework an IA assay

1087 adults, 40.7 years mean age

42 positive for at least 1 IA (3.86%), of them 6 had multiple IA (0.55%), 2 progressed to stage

Prevalence in multiple IA was similar to that from a matched youth

GADA was the most prevalent (2.67% of adults screened)

Autoimmunity may be present even in adults without family history of T1D

Journal of Endocrine Society, Vol. 9, No. 8 | https://doi.org/10.1210/jendso/bvaf095

TRIAD

Overlap of autoantibody-positive and detected disease children

2271 screened

211 Aab +

35 diagnosed

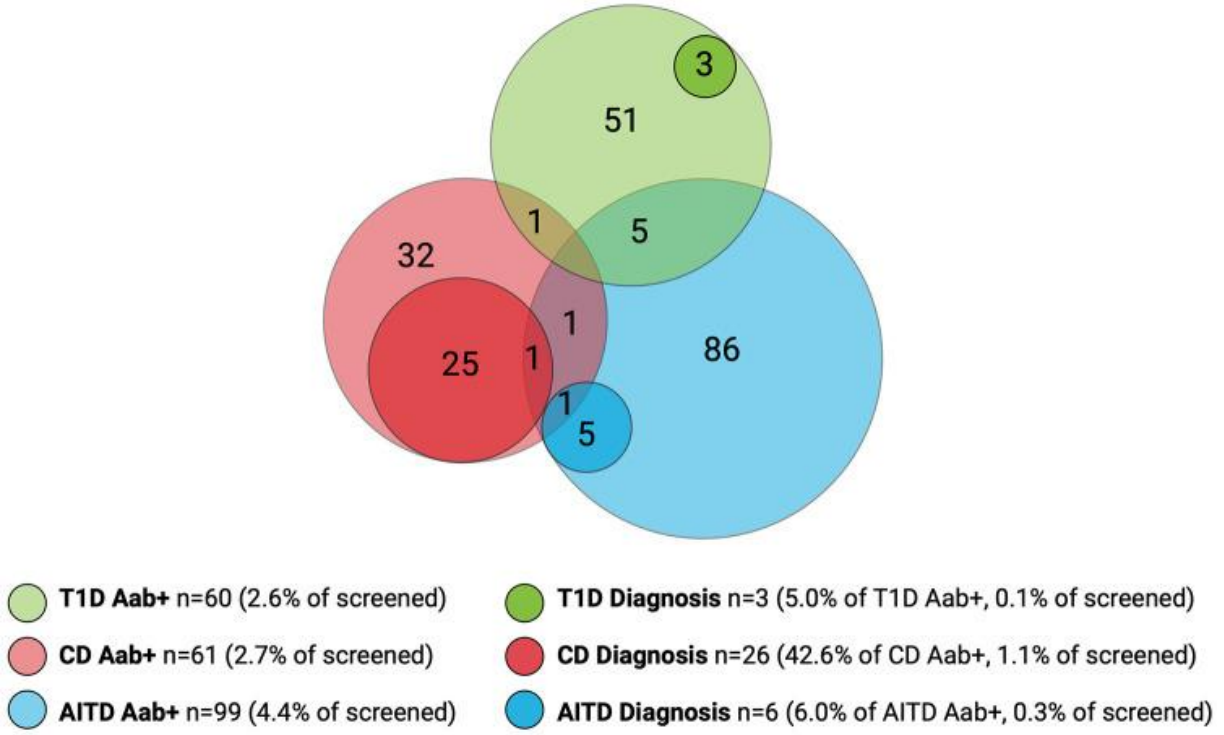
46/2271 (2.0%) 1 IAb

14/2271 (0.6%) ≥ 2 IAbs

3/60 diagnosed

Higer prevalence in 6-9 yo than 13-16 yo group

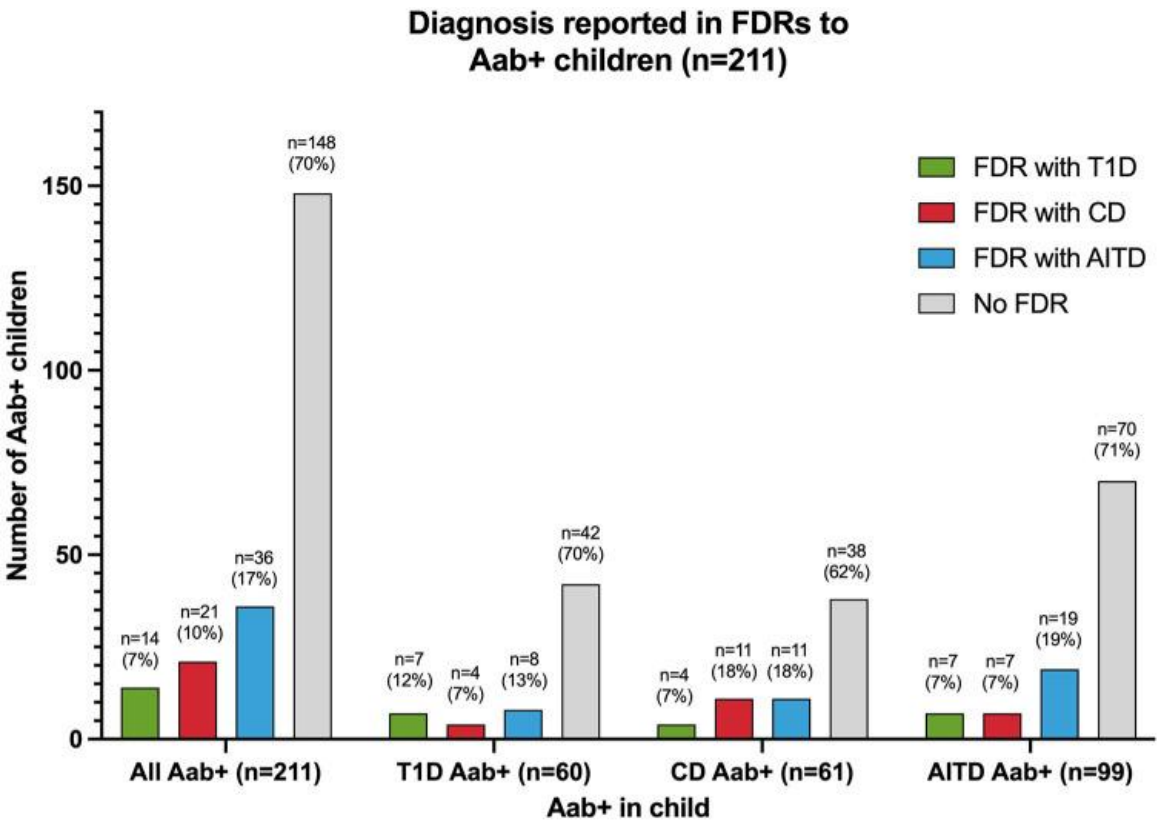
3.5% vs 1.9%, p = 0.0015 or 1.91 95% CI 1.12-3.26

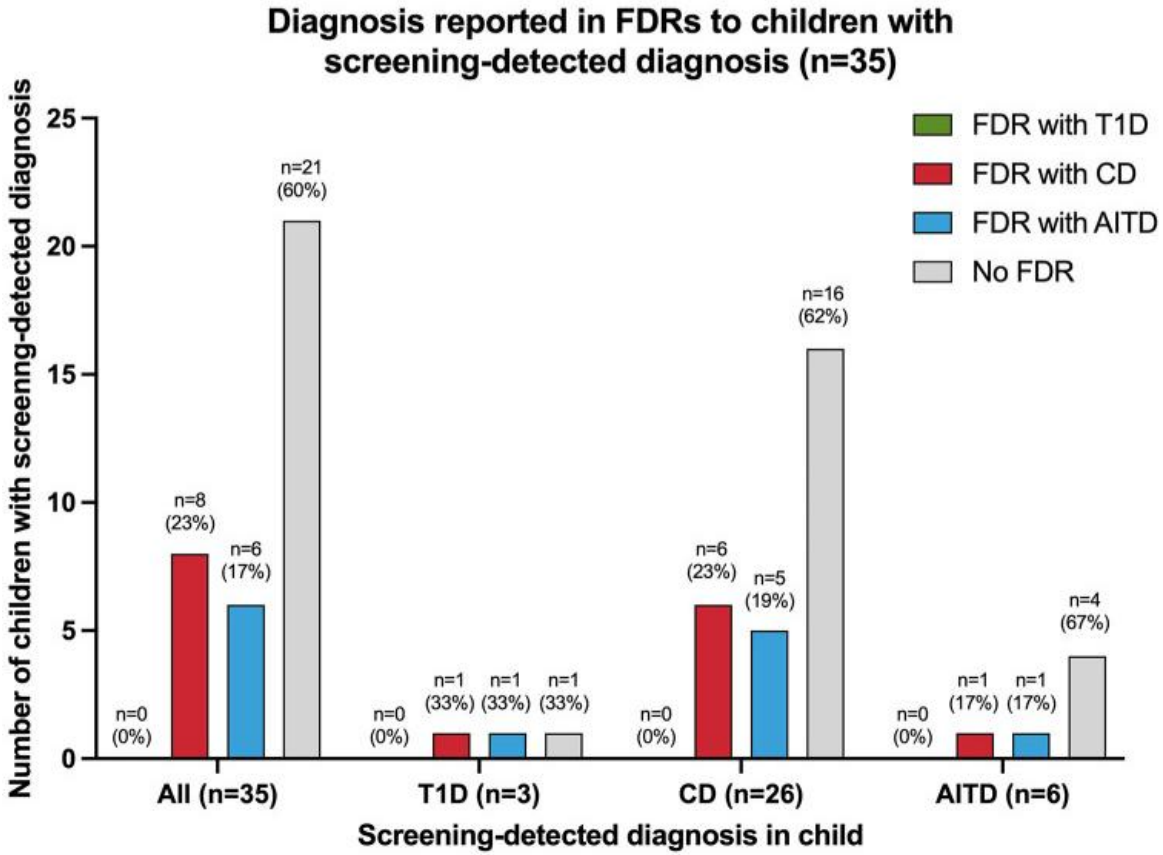


Front. Pediatr. April 2024. 12:1386513. doi: 10.3389/fped.2024.1386513

TRIAD

First-degree relative (FDR) diagnosed with T1D





TRIAD

Lower cost for home capillary sampling

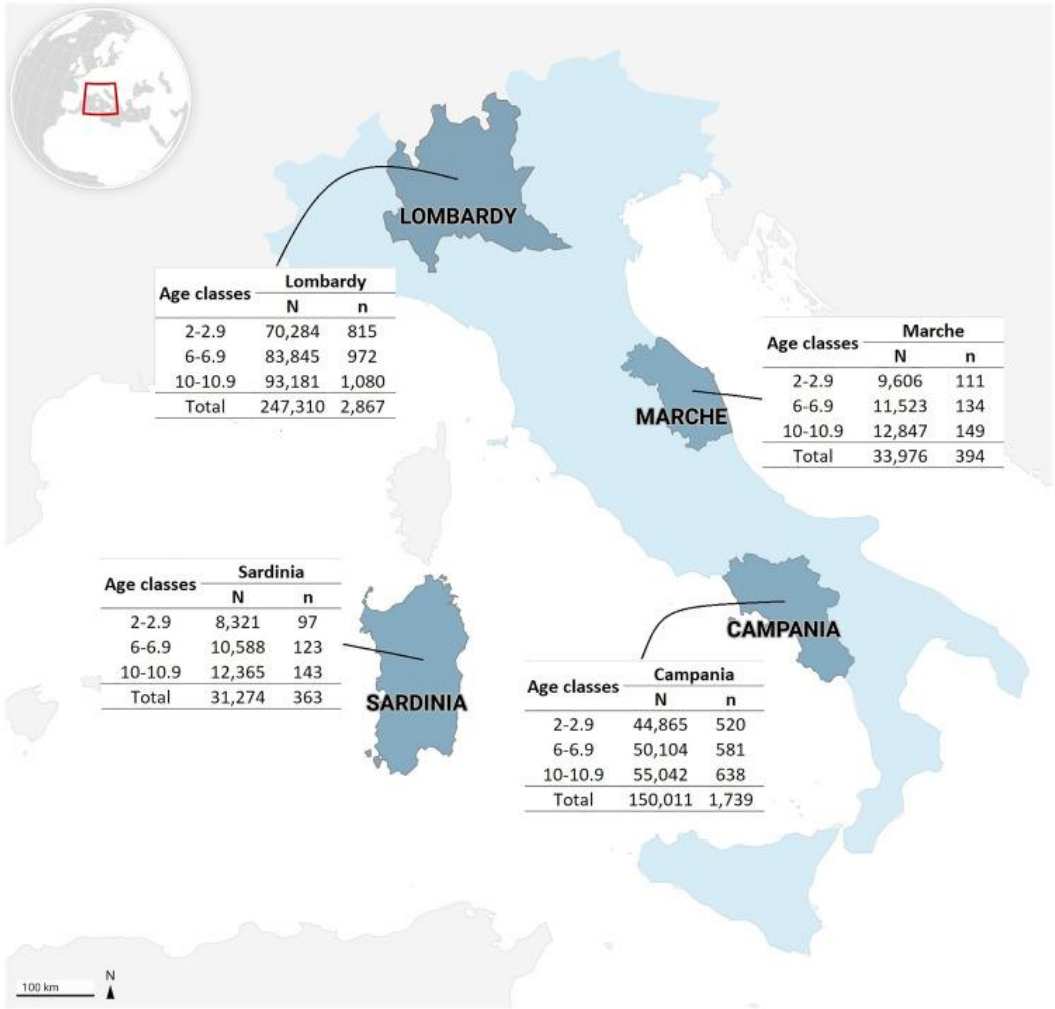
but

Large volume needed for single-plex RBA

Difficulty of reaching sufficient volume (65.6%)
Large number of haemolysed samples (9.1%)
with high risk of IAA false positive result

D1Ce

Evaluate the feasibility of a national screening programme

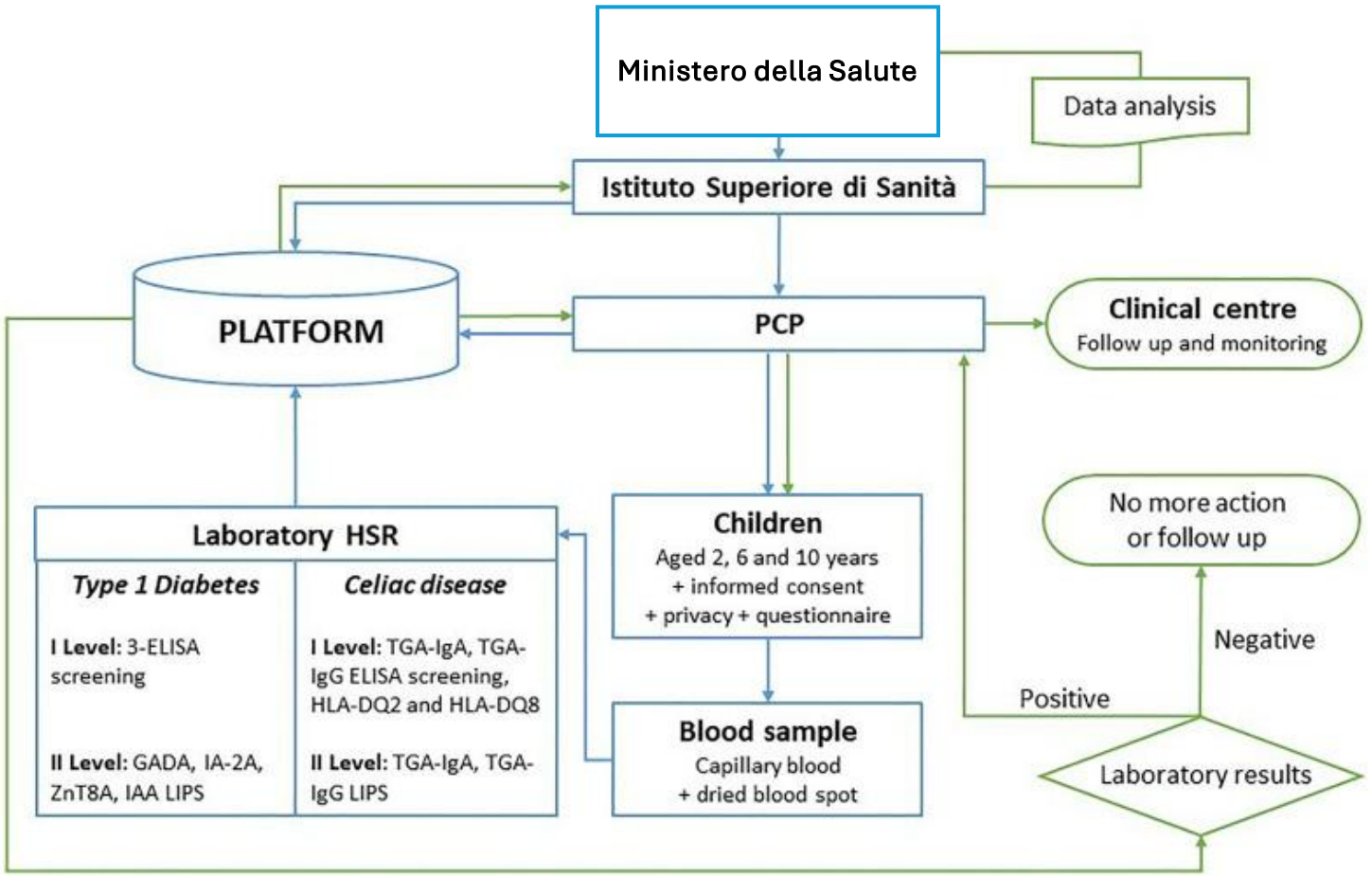


Age classes	Lombardy N	Lombardy n
2-2.9	70,284	815
6-6.9	83,845	972
10-10.9	93,181	1,080
Total	247,310	2,867

Age classes	Marche N	Marche n
2-2.9	9,606	111
6-6.9	11,523	134
10-10.9	12,847	149
Total	33,976	394

Age classes	Sardinia N	Sardinia n
2-2.9	8,321	97
6-6.9	10,588	123
10-10.9	12,365	143
Total	31,274	363

Age classes	Campania N	Campania n
2-2.9	44,865	520
6-6.9	50,104	581
10-10.9	55,042	638
Total	150,011	1,739



PLOS One | https://doi.org/10.1371/journal.pone.0328624 August 13, 2025

D1Ce

Data of 15 December 2024:

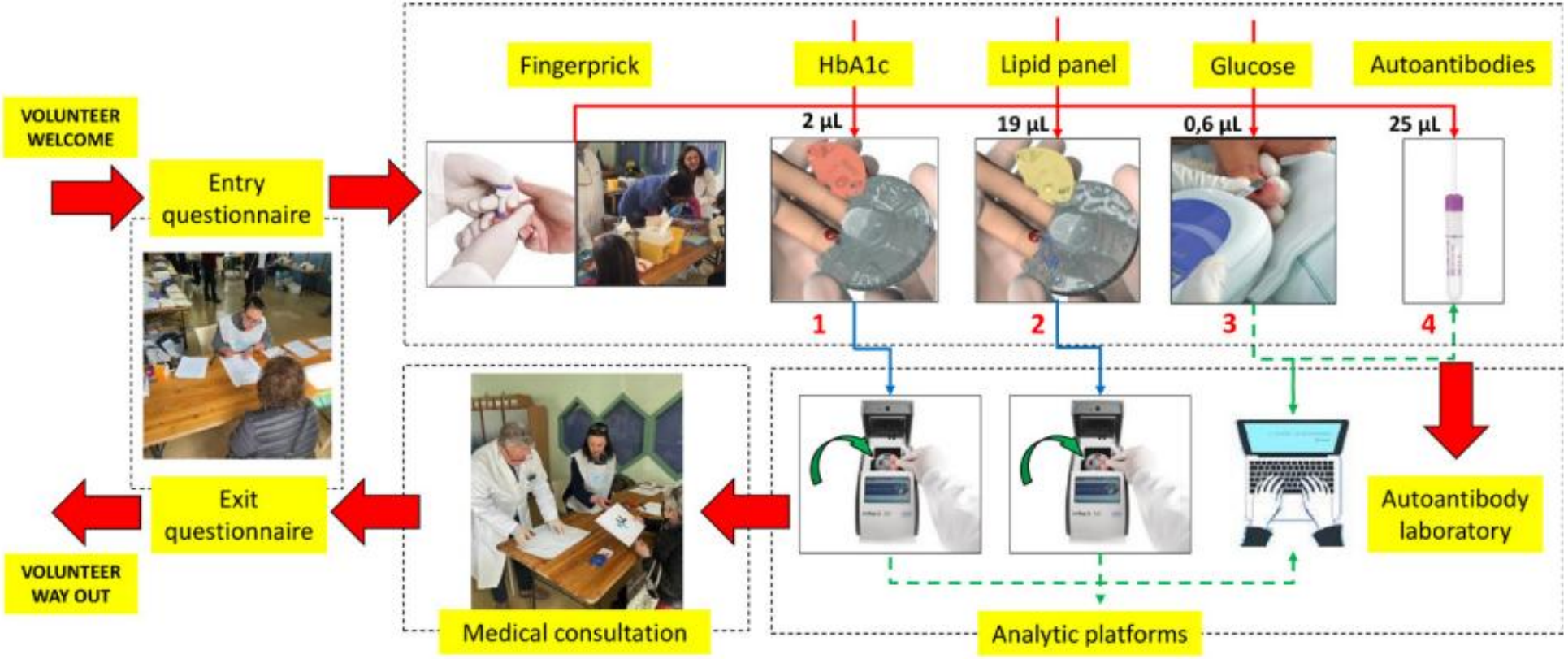
4567 children screened

88.1% samples suitable for IAbs analysis

Recruitment rates variated by region and age group

34 positive case, 24 confirmed, 8 (0.2%) ≥ 2 IAbs

UNISCREEN


VOLUNTEER WELCOME
Entry questionnaire
Exit questionnaire
VOLUNTEER WAY OUT
Fingerprick
HbA1c
Lipid panel
Glucose
Autoantibodies
2 µL
19 µL
0,6 µL
25 µL
1
2
3
4
Medical consultation
Analytic platforms
Autoantibody laboratory

UNISCREEN

1454 individuals screened (50,1% of eligible population)

31 (2,1%) positive for IAbs using 3-screen scLIPS and 2 (0,1%) positive for IAA only

36 retested using individual LIPS assay:

2 (5,6%) negative

24 (70,6%) have single IAb

10 (29,4%) have multiple IAbs

Of 34 autoantibody-positive individuals (2,3%), 20 provided a venous sample, all remained positive

Most common GADA only 21 (61,8%)

Higher median IAbs levels among individuals > 15 years (53,5 AU [15,3-1375,1] vs 19,3 AU [16,1-21,6], p =0.006)

Diabetologia (2026) 69:1282–1294 https://doi.org/10.1007/s00125-026-06680-y

UNISCREEN

Fingerpick needed: 1 (47.1%), 2 (39.8%), 3 (10.2%), 4 (2.0%), ≥ 5 (0.9%)

More than one in the 75-100 age range (61.1%)

Sufficient serum for IAbs test was obtained in 99.7% of participants

Acceptability and feasibility evaluated with questionnaires collected before and after the screening

Single answer measured with 5-point ordinal scale

More than 90% of participants felt capillary sampling is easy and painless and believe the screening useful

Before screening 24.0% of adults and 31.7% of children's parents were worried about results, after procedures worries decreased to 21.3% and 23.4%

Front. Public Health. February 2025. 13:1506240. doi: 10.3389/fpubh.2025.1506240

An opportunity for stage 2 patients

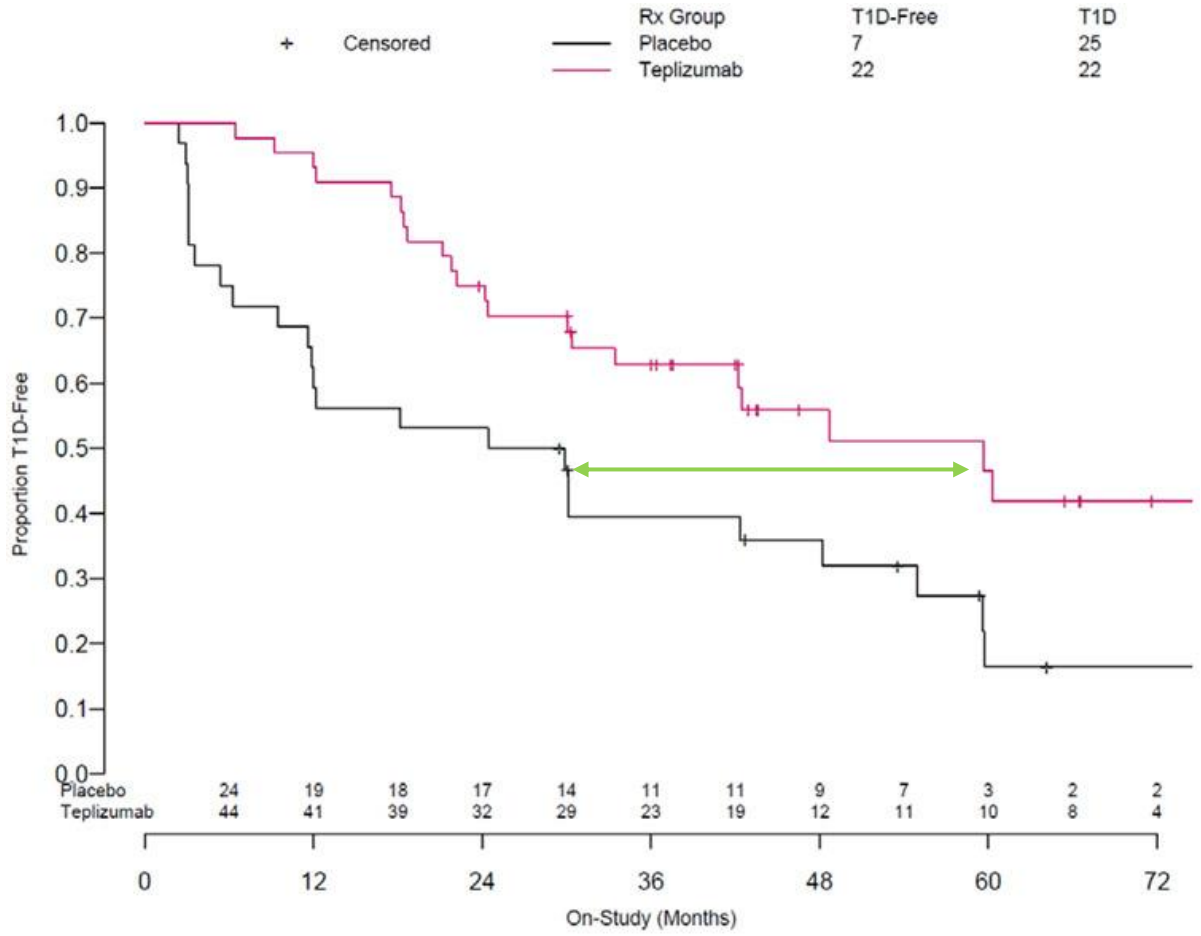
A total of 76 relatives at high-risk
923 days of follow up

The median time to diabetes was:
27.1 months in placebo group
59.6 months in Teplizumab group

32.5 month of delay

Participants not diagnosed of T1D:
7 (22%) in placebo group
22 (50%) in Teplizumab group

Hazard ratio = 0.457 (p=0.01)



Sims EK cet al. Sci Trans Med 2021;13,eabc8980

TAKE HOME MESSAGE

- Incidence of T1D has increased steadily over years.
- Most people who develop T1D have no family history.
- Screening for islet autoantibodies enables identification of presymptomatic T1D.
- Early detection can prevent complications, reduce healthcare costs and psychological burden.
- Immunotherapy may delay progression to stage 3 T1D.
- Pilot studies are essential to guide effective national screening strategies.