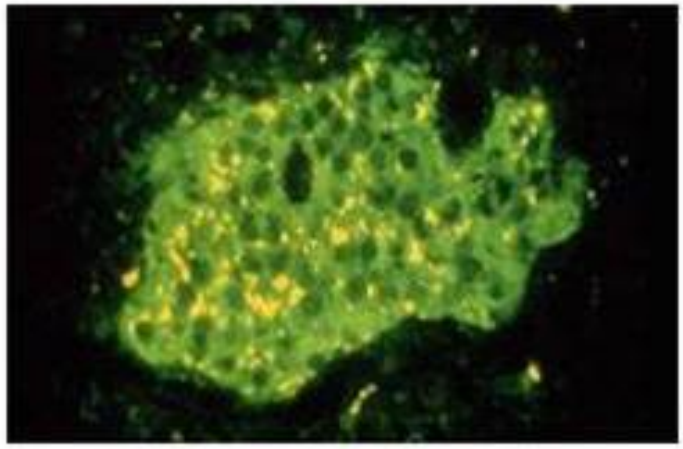
Diabetes mellitus type 1 predictie en preventie



Dr Dick Mul, kinderarts Diabeter Rotterdam

SKML/HIM symposium, 16 februari 2023
De Reehorst, Ede

roadmap

Pathofysiologie & epidemiologie childhood T1DM

Predictie: screening auto-antibodies & genetica

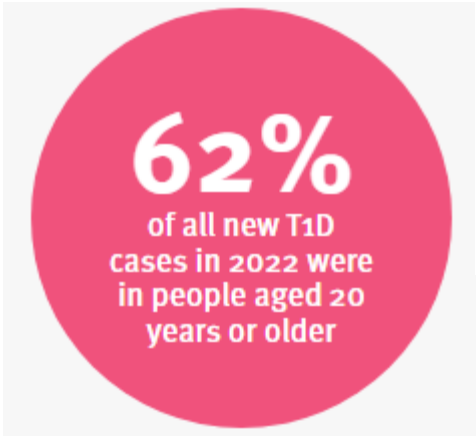
Preventie: waarom & hoe

Incidentie

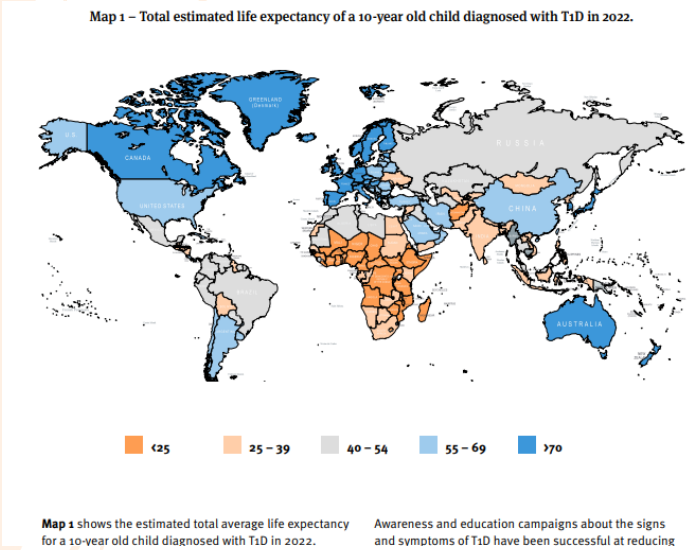
5-10% van alle patienten met diabetes = Type 1

Wereldwijde incidentie neemt toe met ca ~3 % per jaar

Grote geografische variatie: hoogste incidentie Finland



In 2022, there were 530,000 new cases of T1D diagnosed at all ages, with 201,000 of these less than 20 years of age.



Bron: IDF atlas, T1D index

Nederland

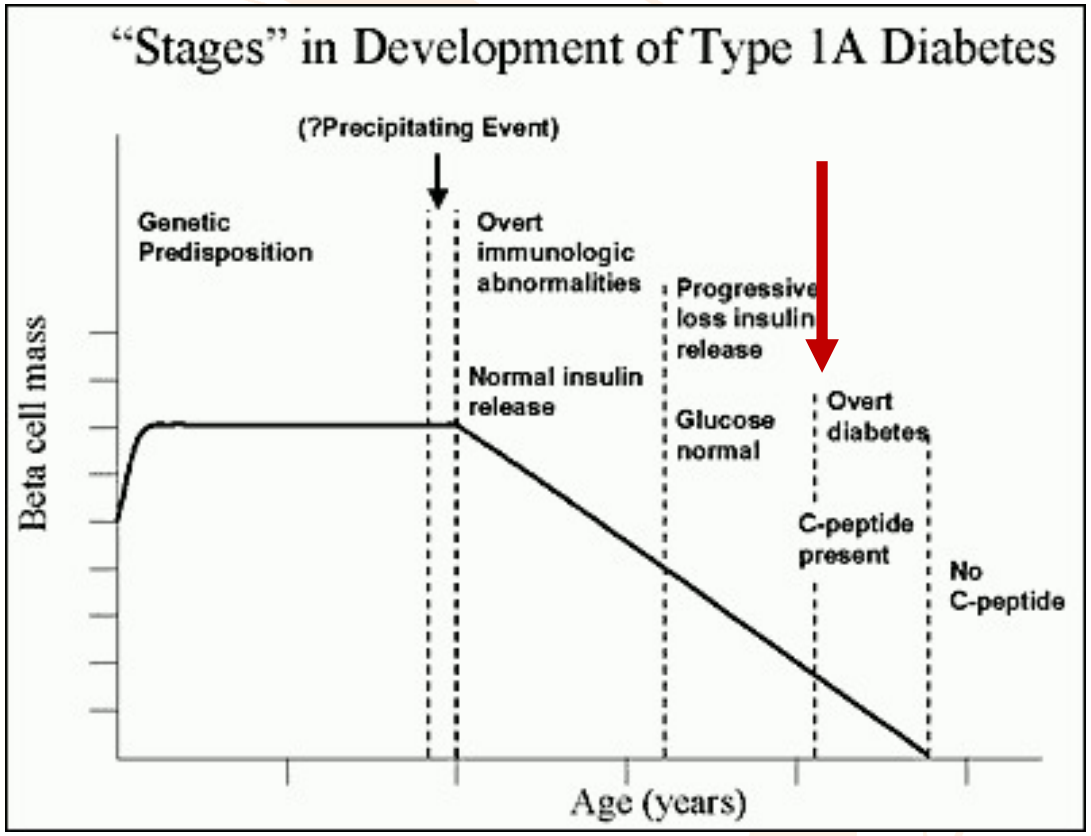
1. Incidentie kinderleeftijd, ca:20/100.000
2. DPARD registratie

Polygene aandoening

- Type 1 > 50% erfelijk
- ..85% heeft geen aangedaan familielid
- HLA sterkste bijdrage aan risico (DR3/DR4) OR16
  - > 70 regio´s bijdragend
- "*genetics loads the gun, environment pulls the trigger*" (Bray 1998)

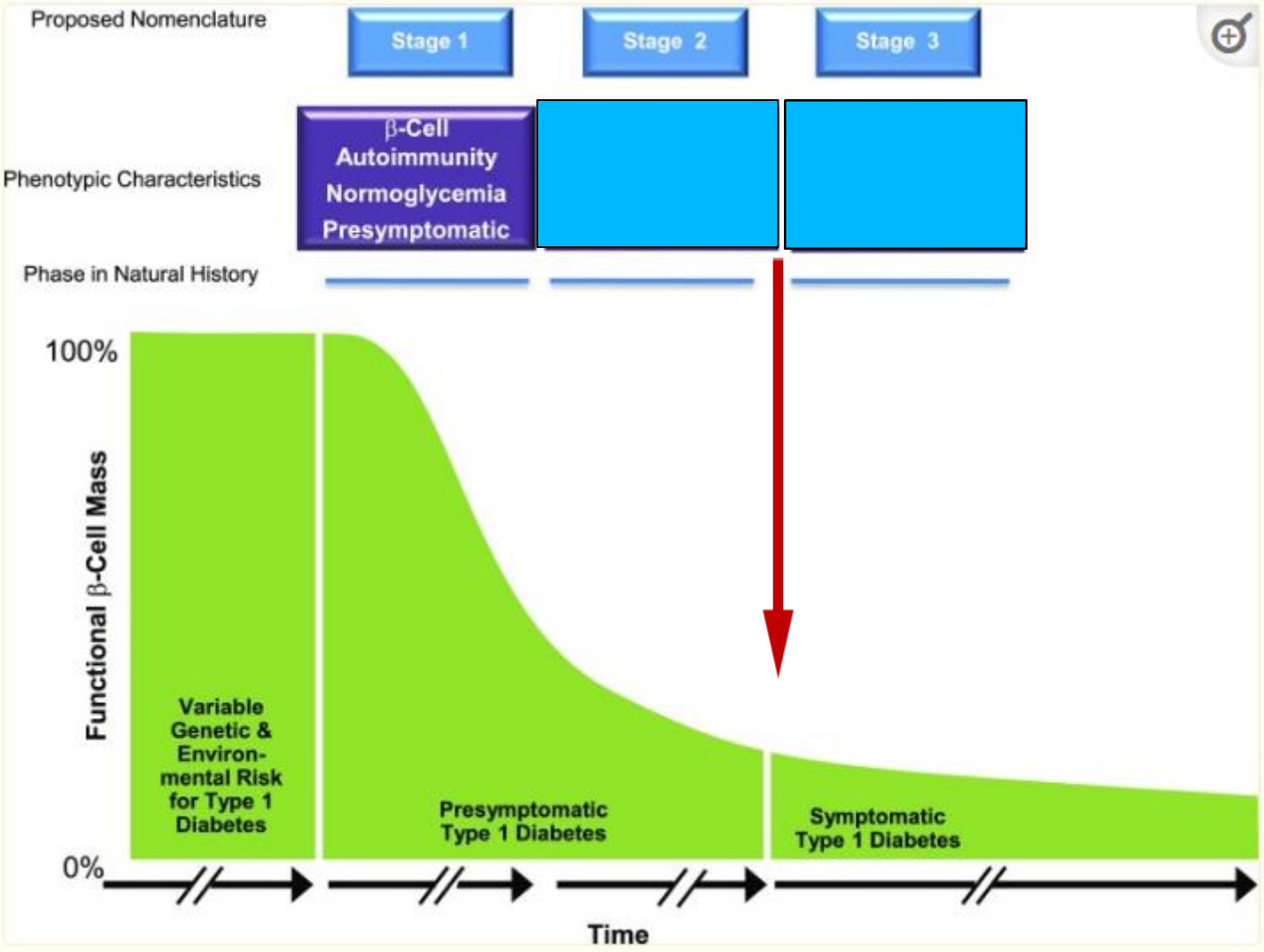
- Trigger

Model pathofysiologie: Eisenbarth



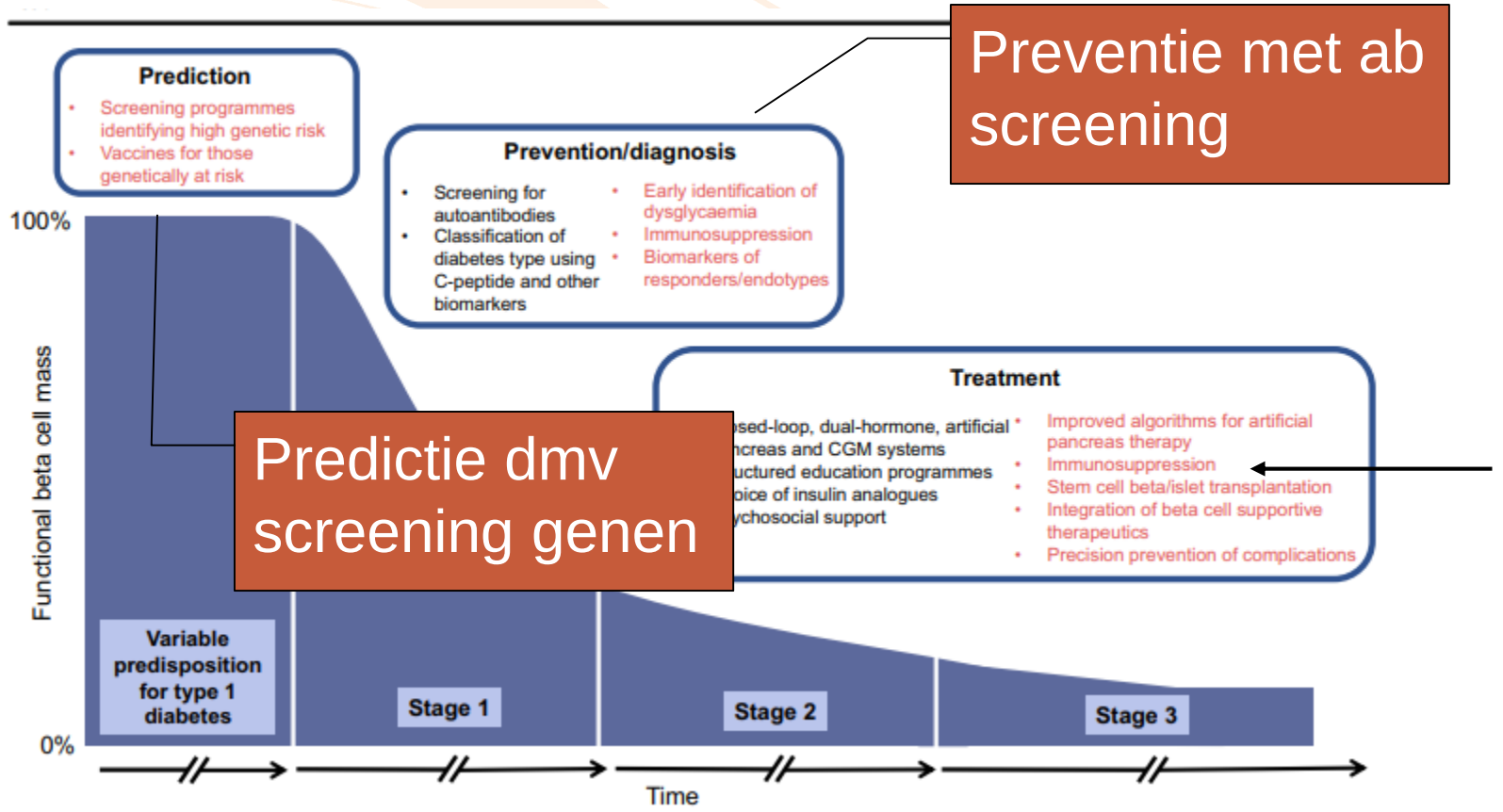
Hypothetical stages and loss of beta cells in an individual progressing to type 1A diabetes. From Eisenbarth, NEJM,1986

Eisenbarth update 2015



Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964–1974. doi: 10.2337/dc15-1419

Eisenbarth update 2: naar precision medicine



Carr ALJ, Evans-Molina C, Oram RA. Precision medicine in type 1 diabetes. Diabetologia. 2022 Nov;65(11):1854-1866. doi: 10.1007/s00125-022-05778-3. Epub 2022 Aug 22

C peptide als marker van betacell massa

Keenan et al: Residual insulin production and pancreatic ß-cell turnover after 50 years of diabetes: Joslin Medalist Study. Diabetes 2010;59(11):2846-53

Davis et al:Prevalence of detectable C-Peptide according to age at diagnosis and duration of type 1 diabetes. Diabetes Care 2015 Mar;38(3):476-81

Vollenbrock CE, Fasting and meal-stimulated serum C-peptide in long-standing type 1 diabetes mellitus. Diabet Med. 2023 Feb;40(2)

How low is really low? Comparison of two C-peptide assays to establish residual C-peptide production in type 1 diabetes

Kitty de Leur, Charlotte Vollenbrock, Pim Dekker, Martine de Vries, Erwin Birnie, Dick Mul, Bruce H. R. Wolffenbuttel, Joost Groen, Henk-Jan Aanstoot, Lianne Boesten

DIABETIC Medicine 2022

assays. We compared the Mercodia ultrasensitive ELISA with the Beckman IRMA and found the Beckman IRMA to have superior analytical performance at low C-peptide concentrations, in contrast to the manufacturers' details. Our results demonstrate the importance of in-house verification of manufacturer-specified performance of laboratory assays, especially when used for a new indication for which clinically meaningful results are outside of the previously used range.

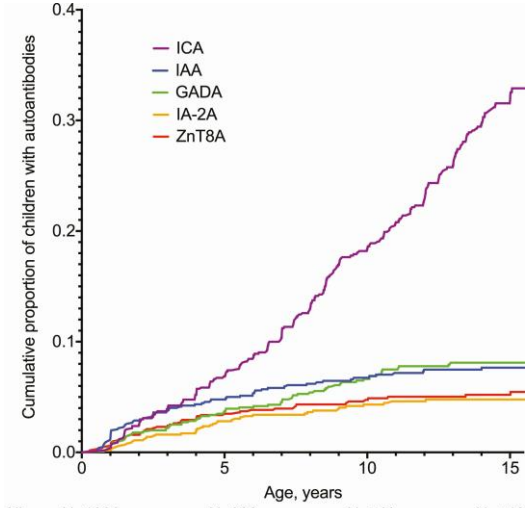
The dynamics of islet autoantibodies: seroconversion

Dynamics of Islet Autoantibodies During Prospective Follow-Up From Birth to Age 15 Years

Petra M Pöllänen, Samppa J Ryhänen, Jorma Toppari, Jorma Ilonen, Paula Vähäsalo, Riitta Veijola, Heli Siljander, Mikael Knip ✉ Author Notes

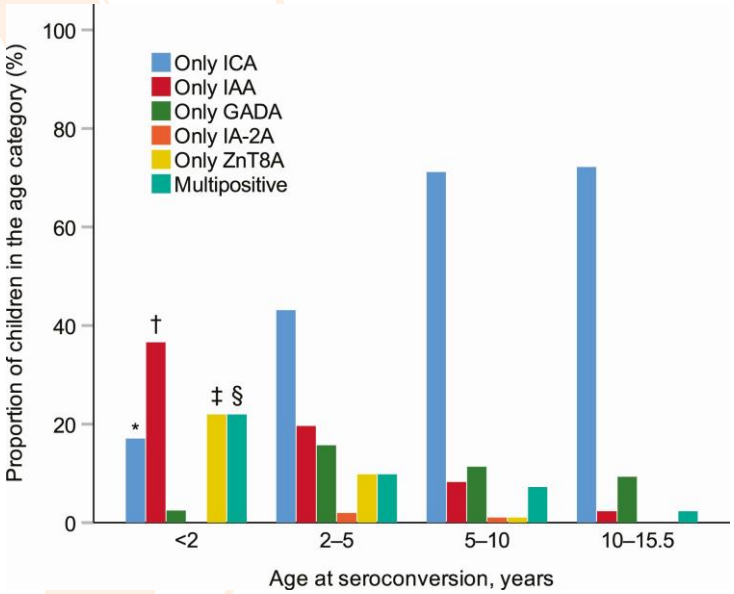
The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 12, December 2020, Pages e4638–e4651, https://doi.org/10.1210/clinem/dgaa624

Finland - DIPP study
n=1005. Participants carried either the high-risk HLA genotype DQB1*02/*0302 or the moderate-risk genotypes DQB1*0302/x (x≠*02, *0301, or *0602) (16, 17)



All	N=1006	N=898	N=711	N=542
ICA	N=1006	N=842	N=589	N=378
IAA	N=1006	N=861	N=674	N=512
GADA	N=1006	N=871	N=675	N=512
IA-2A	N=1006	N=877	N=691	N=528
ZnT8A	N=1006	N=872	N=691	N=528

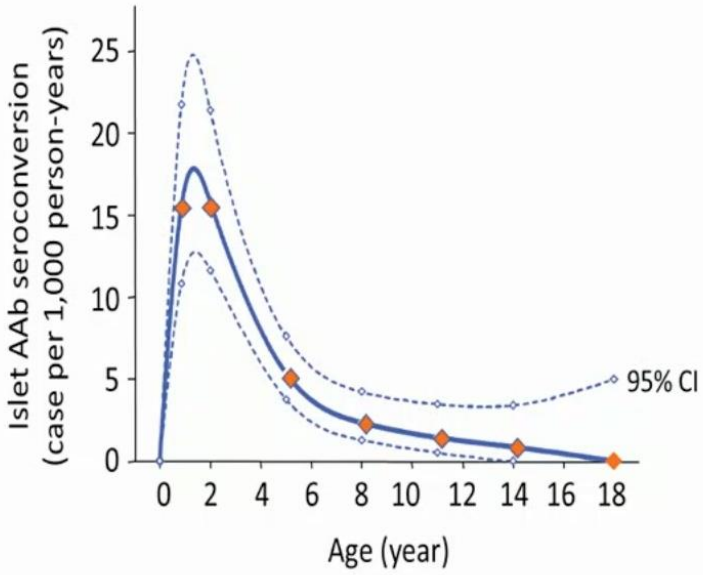
Development of islet cell (ICA), insulin (IAA), glutamate decarboxylase (GADA), islet antigen-2 (IA-2A), and zinc transporter 8 (ZnT8A) antibodies by age 15.5 years.



Autoantibody profiles at initial seroconversion in the age groups 0 to 2 (N = 41), 2 to 5 (N = 51), 5 to 10 (N = 97), and 10 to 15.5 (N = 86) years

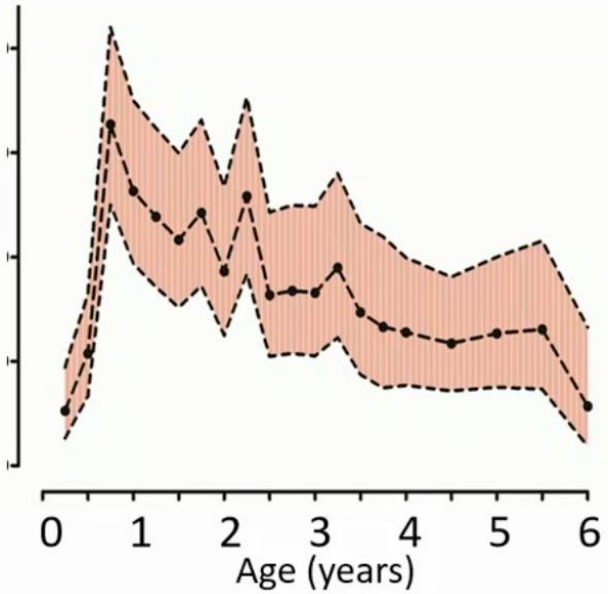
The early peak incidence of islet autoimmunity

Germany



Ziegler et al, 2012

TEDDY (Finland, Sweden, Germany, USA)



TEDDY study, 2015

Antistoffen in stage 1 diabetes: predictie

Bottomline:

"the number of detectable islet autoantibodies correlates with risk" (Ziegler JAMA 2013)

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	12318	8875	5253	1161	44

Figure 1.
Development of Diabetes in Children Stratified for Islet Autoantibody Outcome
The numbers at risk represent the children receiving follow-up at age 0, 5, 10, 15, and 20 years.

Progressietijd is variabel

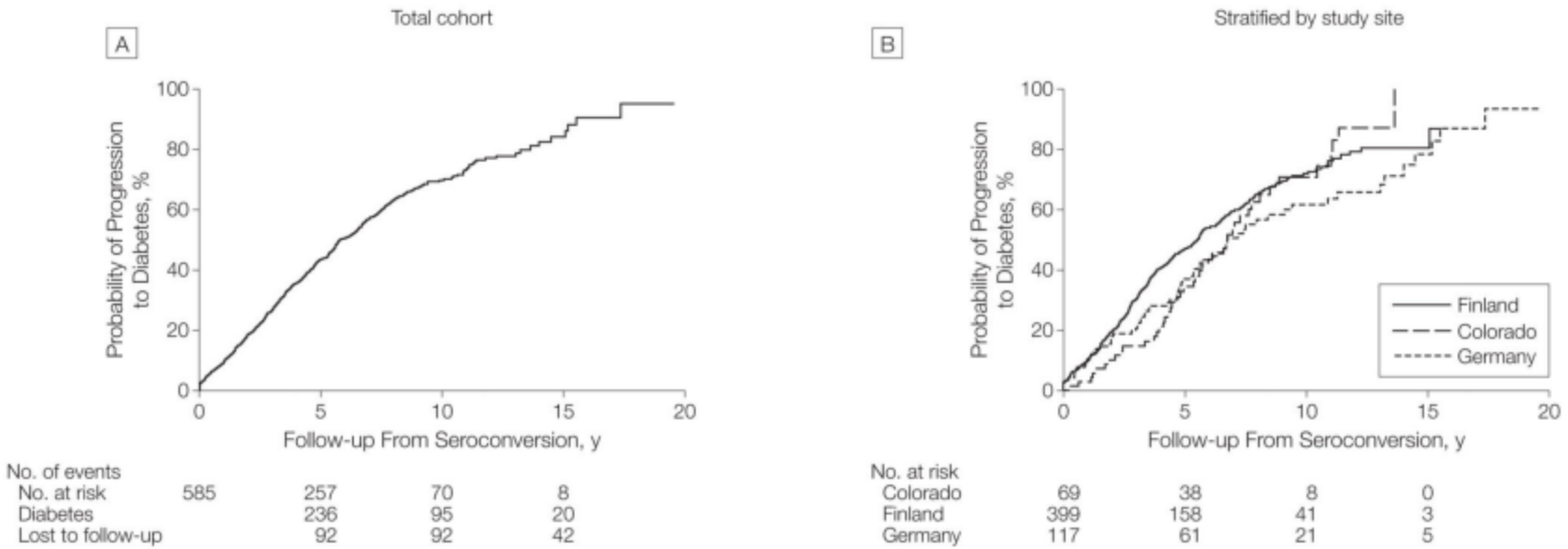


Figure 2.
Progression to Diabetes From the Time of Seroconversion in Children With Multiple Islet Autoantibodies

Factoren: leeftijd seroconversie, genetic markers, geslacht, type auto ab

sex, and the type of islet autoantibody. A faster rate of progression in children with early seroconversion was previously reported in a subset of the German cohort

Progressietijd is variabel

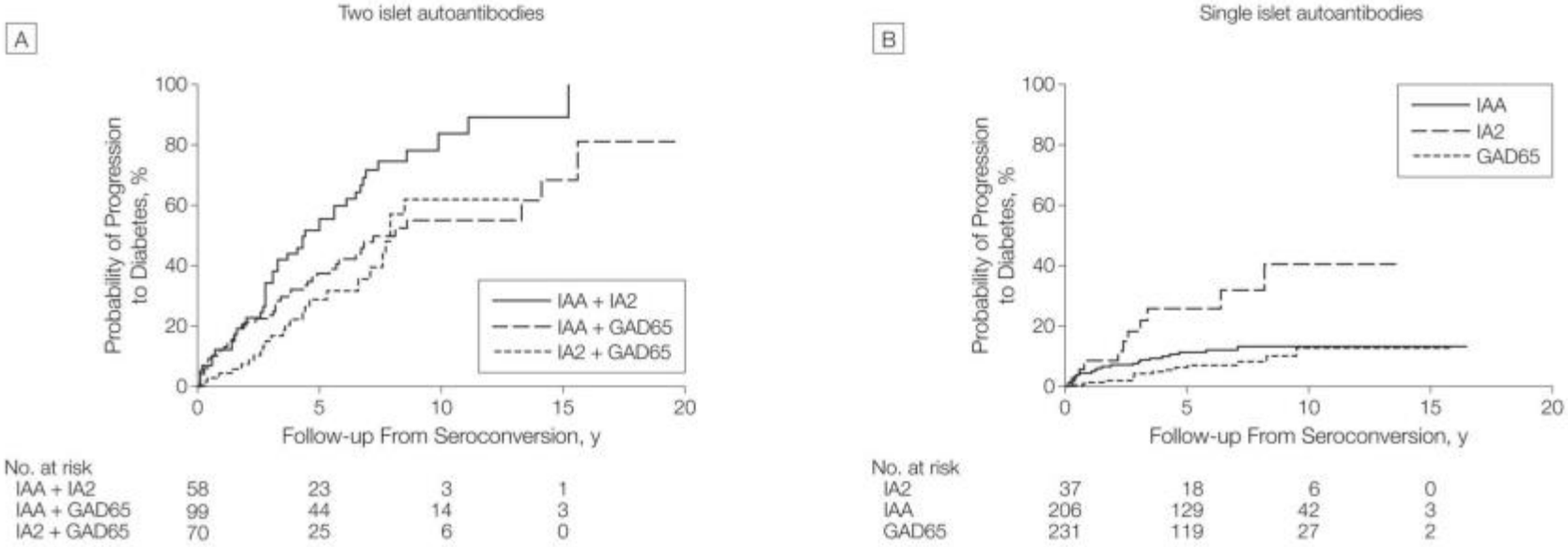
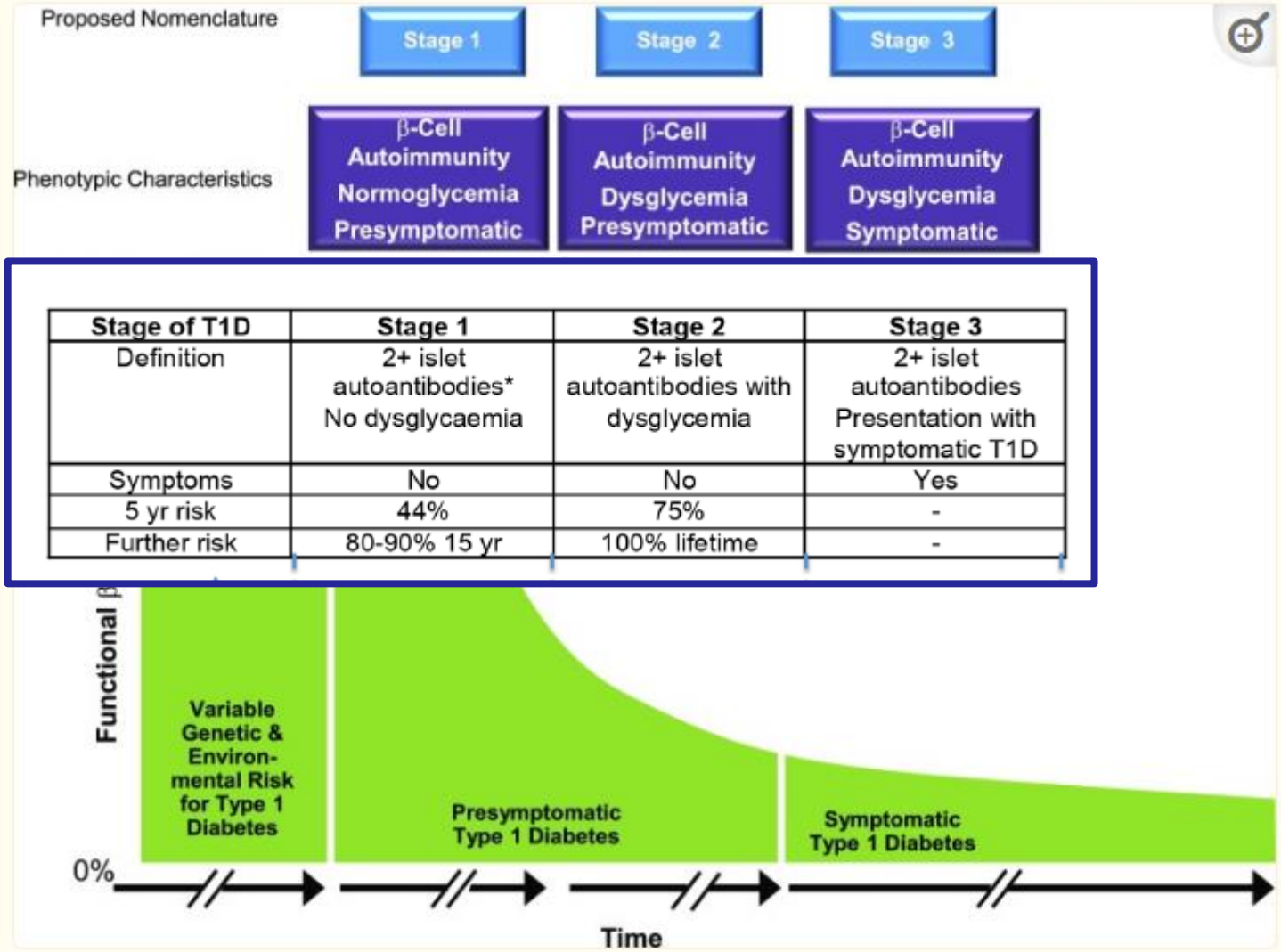


Figure 3.
Progression to Diabetes in Children From the Time of Seroconversion According to Islet Autoantibody Type
IAA indicates insulin autoantibodies; IA2, insulinoma antigen 2 autoantibodies; and GAD65, glutamic acid decarboxylase 65 autoantibodies. The numbers at risk represent the children receiving follow-up at year 0, 5, 10, and 15.

Factoren: leeftijd seroconversie, genetic markers, geslacht, type auto ab

Eisenbarth update 2015



Stage of T1D	Stage 1	Stage 2	Stage 3
Definition	2+ islet autoantibodies* No dysglycaemia	2+ islet autoantibodies with dysglycemia	2+ islet autoantibodies Presentation with symptomatic T1D
Symptoms	No	No	Yes
5 yr risk	44%	75%	-
Further risk	80-90% 15 yr	100% lifetime	-

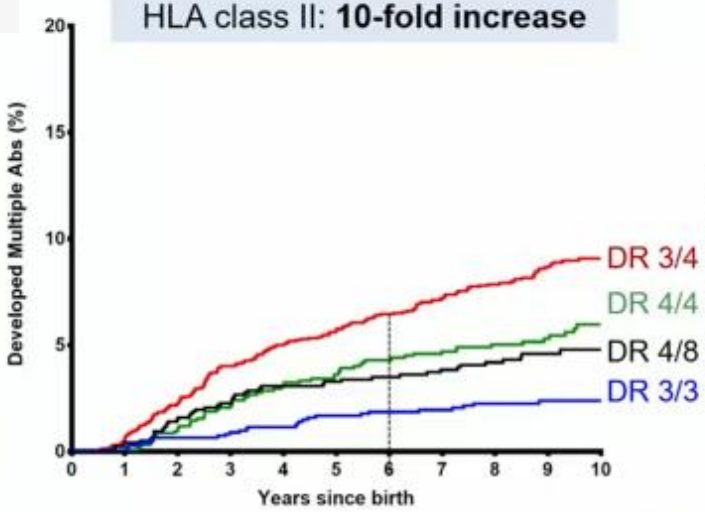
Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care. 2015;38(10):1964–1974. doi: 10.2337/dc15-1419

Genes

Genetic susceptibility is important

Most T1D susceptibility genes affect the immune response

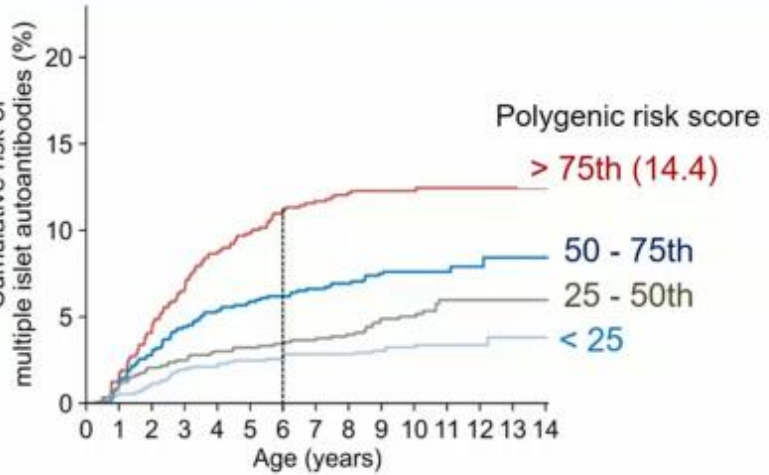
HLA class II: **10-fold increase**



Bonifacio E, Plos Medicine 2018

TEDDY

HLA class II and non-HLA genes: **25-fold increase**



-> combined risk score

Ferrat LA, et al & TEDDY Study Group.

A combined risk score enhances prediction of type 1 diabetes among susceptible children. Nat Med. 2020 Aug;26(8):1247-1255.

we sought accurate, cost-effective estimation of future T1D risk by developing a **Combined Risk Score** (CRS) incorporating both fixed and variable factors (genetic, clinical and immunological) in 7,798 high-risk children followed closely from birth for 9.3 years.

Compared to autoantibodies alone, the combined model dramatically improves T1D prediction at ages ≥2 over horizons up to 8 years (ROC-AUC ≥0.9), doubles the estimated efficiency of population-based newborn screening to prevent ketoacidosis, and enables individualized risk estimates for better prevention trial selection

Verdere differentiatie

- Progression trajectories (Kwon 2022)
- Role of 1st appearing ab (Krischer 2022)
- Predictie klin beloop o.b.v. ab patroon (Terada 2022)
- En: wannéer screenen?

Wannéer screenen?

Ghalwash M, Dunne JL, Lundgren M, et al. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol 2022; 10: 589–96.

Screening of children at 2 years and 6 years of age effectively identifies most individuals who develop type 1 diabetes before 15 years of age.

Ghalwash M, Anand V, Lou O, Martin F, Rewers M, Ziegler AG, Toppari J, Hagopian WA, Veijola R; Type 1 Diabetes Intelligence Study Group. Islet autoantibody screening in at-risk adolescents to predict type 1 diabetes until young adulthood: a prospective cohort study. Lancet Child Adolesc Health. 2023 Jan 18

Double screening at the ages of 10 years and 14 years, or even single screening at 10 years, was highly sensitive in detecting adolescents who will develop type 1 diabetes.

Interventie: Teplizumab (anti-CD3)

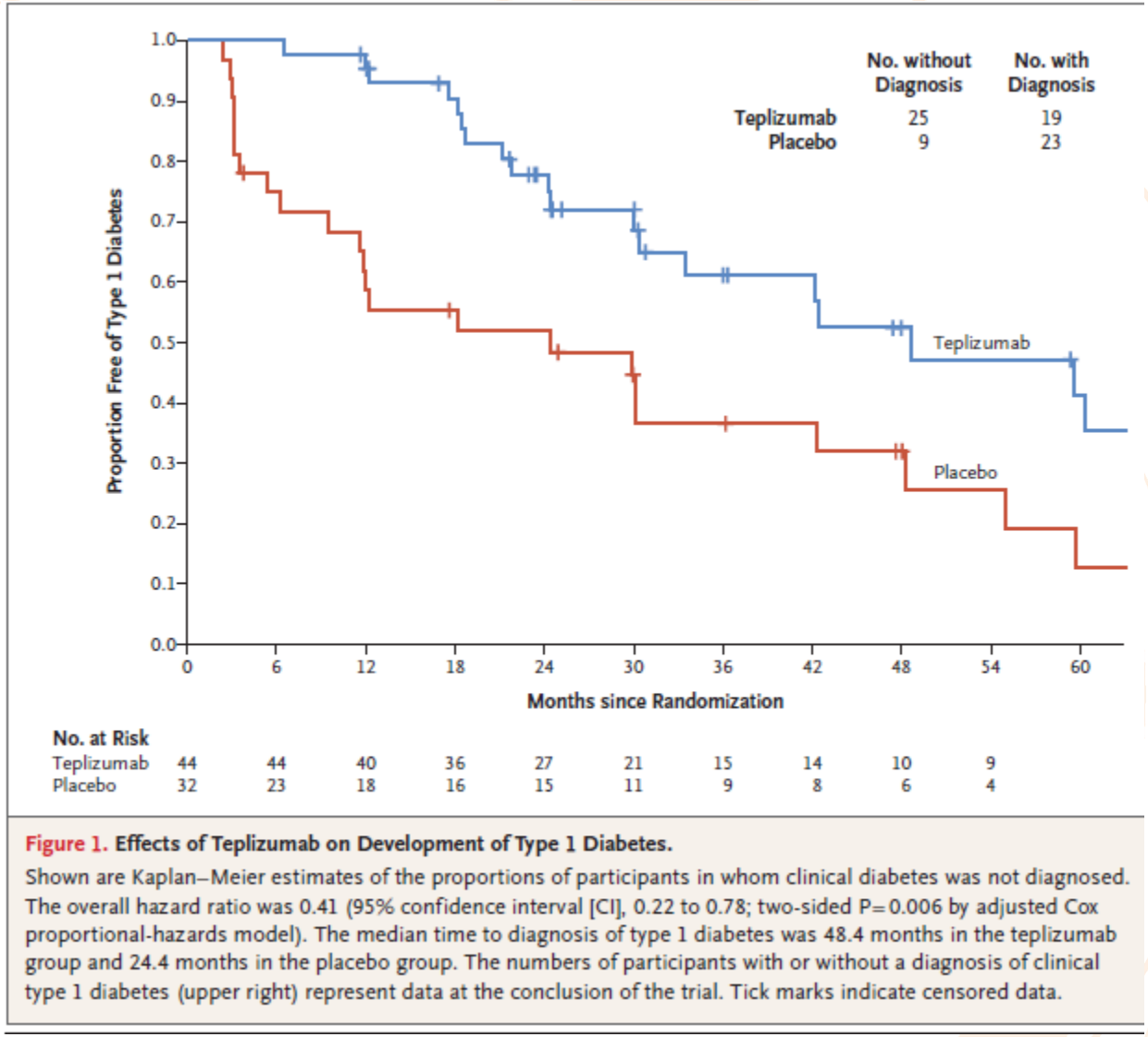


Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes.
Shown are Kaplan–Meier estimates of the proportions of participants in whom clinical diabetes was not diagnosed. The overall hazard ratio was 0.41 (95% confidence interval [CI], 0.22 to 0.78; two-sided P=0.006 by adjusted Cox proportional-hazards model). The median time to diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group. The numbers of participants with or without a diagnosis of clinical type 1 diabetes (upper right) represent data at the conclusion of the trial. Tick marks indicate censored data.

TrialNet deelnemers
- 1e en 2e graads verwanten
- >8jr
- 2x 2+ AA afgelopen 6m
- Dysglycemie op OGTT

1dd x14d infusie anti-CD3 monoclonal Ab

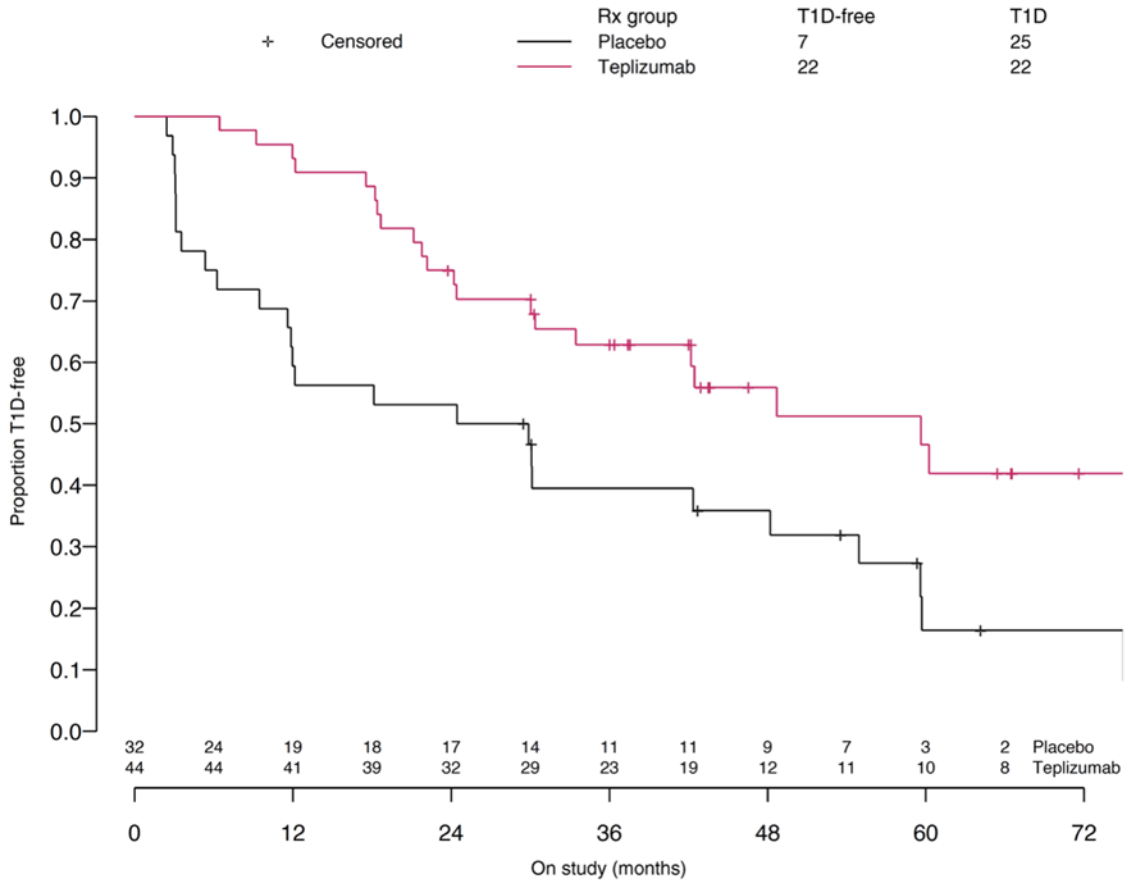
Tijd tot stadium 3 vertraagd met 24 mnd (HR 0.41)

Bijwerking: verlaagde t-cellen
Zonder infectieuze consequenties.

Betere respons ZnT8-, DR3-, DR4+

Kleine studie (76…44/32)
Middel erg duur

Herold et al NEJM June 2019



Sims2021

" In an extended follow-up (923-day median) of a previous report of teplizumab treatment, we found that the median times to diagnosis were 59.6 and 27.1 months for teplizumab- and placebo-treated participants, respectively (HR = 0.457, P = 0.01). Fifty percent of teplizumab-treated but only 22% of the placebo-treated remained diabetes-free"

Teplizumab (3)

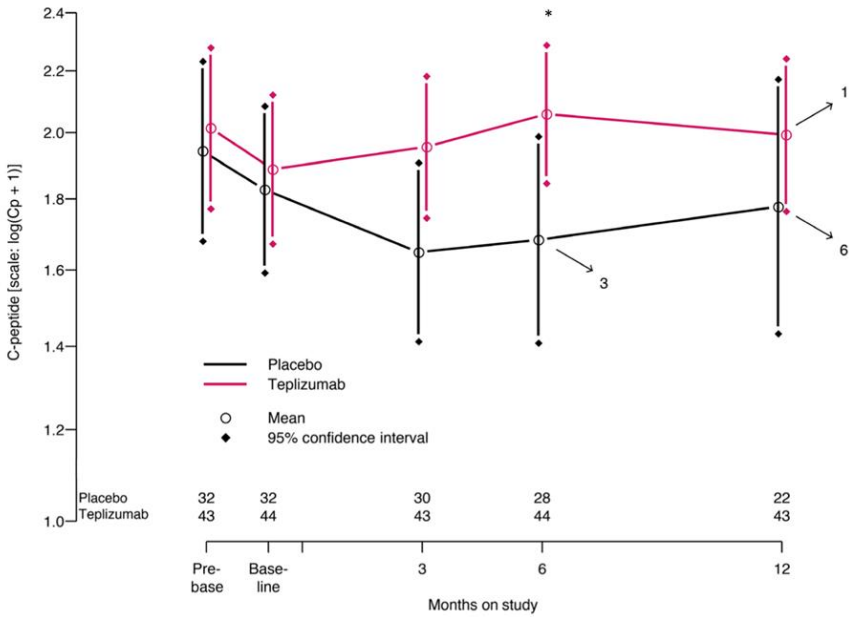


Fig. 4. C-peptide over time in the two treatment arms over the first year. The log-transformed mean C-peptide (Cp) AUC is shown. Arrows indicate the number of individuals who dropped out from OGTT monitoring because of diabetes development at each time point. Median C-peptide AUC value for "pre-baseline" time point was 24; median value for "baseline" time point was 0.85 months before randomization. *$P < 0.05$ for comparisons of 6-month on-treatment C-peptide AUC values to baseline in the teplizumab group and 6-month C-peptide AUC values in the teplizumab group to 6-month C-peptide AUC values in the placebo group.

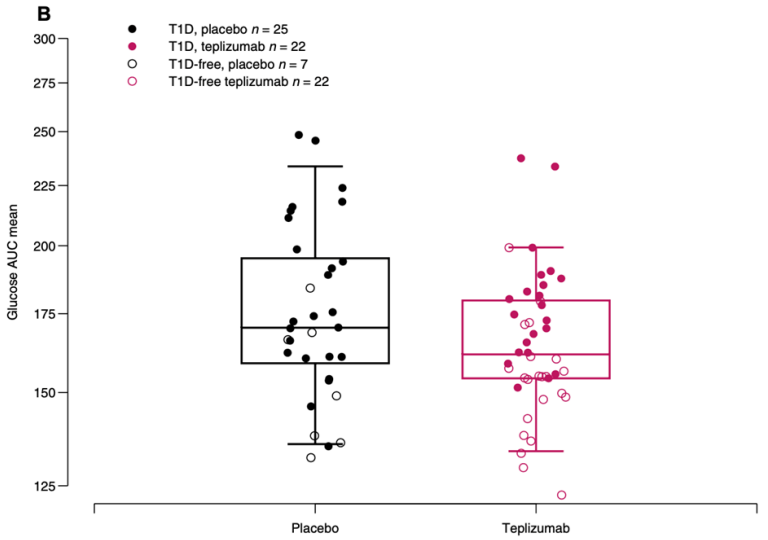


Fig. 2. Improved glycemia in teplizumab-treated participants is associated with maintenance of dysglycemic status. (**A**) OGTT classifications for participants in each group over 36 months of follow-up. The data are shown to 36 months because of loss of placebo-treated participants due to a clinical diagnosis of T1D (for individual participants see fig. S2). (**B**) Box plot displaying median and interquartile ranges for on-study OGTT glucose AUC mean for participants from placebo- and teplizumab-treated groups. An ANCOVA model incorporating baseline value, age, and treatment group showed that treatment significantly decreased average on-study glucose AUC (ANCOVA teplizumab effect: $p = 0.02$).

THE LANCET
Diabetes & Endocrinology

IN FOCUS | VOLUME 11, ISSUE 1, P18, JANUARY 2023

FDA approves teplizumab: a milestone in type 1 diabetes

James S Hirsch

Published: November 24, 2022 • DOI: https://doi.org/10.1016/S2213-8587(22)00351-5 •

General population screening for childhood type 1 diabetes: is it time for a UK strategy?

Rachel Elizabeth Jane Besser ,[1,2] Sze May Ng ,[3,4] John W Gregory,[5] Colin M Dayan,[6] Tabitha Randell,[7] Timothy Barrett[8]

Arch Dis Childh 2021

Table 1 General population screening for type 1 diabetes (T1D) according to modified Wilson and Jungner criteria

Modified Wilson and Jungner classic screening criteria	Yes	No	Uncertain	Comments
1. The condition sought should be an important health problem.	✓			
2. The target population for screening should be clearly defined and able to be reached.			✓	Ages for testing need to be agreed
3. There should be an accepted treatment or course of action for patients who test positive that results in improved outcomes.			✓	Need to define follow-up for both multiple and single IAb positive Need of T1D preventive treatments
4. Facilities for diagnosis and treatment should be available.		✓		Implementation in routine laboratories needed
5. There should be a recognisable latent or early symptomatic stage.	✓			
6. There should be a suitable test or examination with appropriate performance characteristics.			✓	Test performance needs validation on population level
7. The test should be acceptable to the population.			✓	Will need testing in individual countries and communities
8. The screening test results should be clearly interpretable.			✓	Double IAb positive defined Single IAb positive result not fully established
9. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	✓			
10.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.		✓		UK-specific cost-effectiveness needs to be tested
11.The overall benefit of the programme should outweigh its harms.			✓	More data needed on benefits and harm
12.Case finding should be a continuing process and not a 'once and for all' project, with ongoing monitoring and development of the programme.		✓		National screening programmes embedded in clinical care are required

Table 2 Pros and cons of screening for type 1 diabetes (T1D)

Pros	Cons
► Potential to prevent DKA at diagnosis by education on symptoms of diabetes ► Opportunity for time to adjust to diagnosis ► Genetic testing for high-risk genes/genetic risk scores possible at birth for use in combination with autoantibodies ► IAb detectable with fingerprick test, so easy test to administer ► IAb sensitive and specific ► May be intervention studies to delay development or prevent T1D in future	1. Potential increased anxiety in parents/carers knowing child is at risk 2. High numbers of individuals genetically at risk but who don't develop T1D 3. If using IAb alone: – Likely need testing more than once – Will miss those diagnosed before screening and those who seroconvert after screening test 4. Treatment of early hyperglycaemia can be challenging 5. No licensed treatment to prevent T1D at present

DKA, diabetic ketoacidosis.

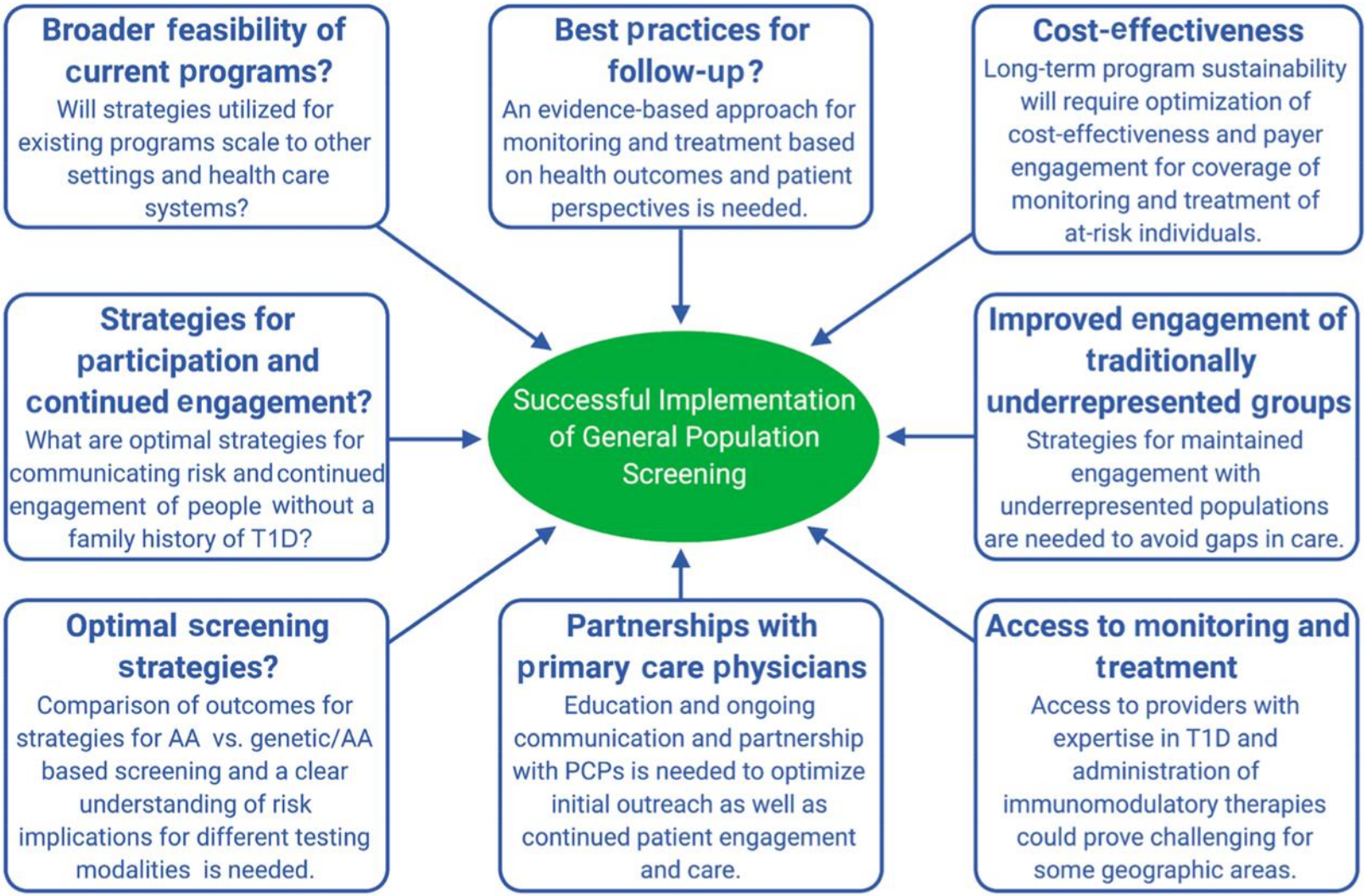


Figure 3—Logistical needs and uncertainties that remain to be answered for optimal implementation and sustainability of large-scale general population screening for type 1 diabetes (T1D).

Algemene screening?

Ethiek

Psychologie

Infrastructuur

Kosten

samenvattend

Stagering fase 1,2,3

Steeds meer tools in handen voor predictie T1DM

Interventie in fase 2: eerste resultaten

Algemene screening nog veel haken en ogen