Team-Science Approaches in Type 1 Diabetes and the Value of Early Screening

T1D Exchange, QI Learning Session, Miami, November 7, 2022

Alberto Pugliese, MD
Professor and Chair, Department of Diabetes Immunology
Samuel Rahbar Endowed Chair in Diabetes & Drug Discovery
Director, The Wanek Family Project for Type 1 Diabetes
Arthur Riggs Diabetes and Metabolism Research Institute, City of Hope
Duarte, California apugliese@coh.org

Executive Co-Director, JDRF Network for the Pancreatic Organ Donor with Diabetes (nPOD)

Until October 2022
The J. Enloe and Eugenia J. Dodson Chair in Diabetes Research
Professor of Medicine, Division of Diabetes Endocrinology and Metabolism
Professor of Microbiology and Immunology
Leonard Miller School of Medicine
University of Miami
Deputy Director for Immune Tolerance Research
Head, Immunogenetics Program
Diabetes Research Institute

Disclosure

Consultant for Provention Bio

Amazing advances during the last 35 years

- Improved understanding of T1D pathogenesis and natural history
- Identification of target autoantigens
- Identification genetic factors modulating risk and progression
- Improved prediction and biomarkers – moving into secondary and primary prevention (also in the general population)
- Therapeutic effects observed in clinical trials, at least with some treatments, pre and post diagnosis
- Improvements in transplantation and beta cell replacement
- Availability of sophisticated disease models (in vivo, in vitro)
- Technologies for improved insulin therapy, delivery and glucose monitoring
- And much more….

Critically, team science approaches and collaborative networks have played a key role in discovery

Selected Team Science efforts in T1D research

- The Type 1 Diabetes Genetics Consortium (T1DGC) (NIDDK)
- The Type 1 Diabetes TrialNet (NIDDK)
- Immune Tolerance Network (ITN) (NIH)
- The Environmental Determinants of Diabetes in the Young (TEDDY) (NIDDK)
- Diabetes Prediction and Prevention (DIPP), Finland
- INNODIA (Europe)
- Human Islet Research Network (HIRN) (NIDDK)
- Network for the Pancreatic Organ Donor with Diabetes (nPOD) (JDRF, Helmsley Charitable Trust)
- *And more…..*

Welcome to Type 1 Diabetes Genetics Consortium

The T1DGC originally focused on recruiting families with at least two siblings (brothers and/or sisters) who have type 1 diabetes (affected sibling pair or ASP families). The T1DGC completed enrollment for these families in August 2009.

We completed enrollment of trios (father, mother, and a child with type 1 diabetes), as well as cases (people with type 1 diabetes) and controls (people with no history of type 1 diabetes) from populations with a low prevalence of this disease in January 2010.

The final enrollment numbers overall and by Network are provided below:

T1DGC enrollment, by network and overall, February 11, 2011

Network	ASP Families (Individuals)	Trio Families (Individuals)	Cases	Controls
Asia-Pacific	326 (1341)	290 (870)	23	77
European	1209 (4786)	10 (30)	5	2
North American	1140 (4828)	193 (579)	802	889
United Kingdom	161 (671)	N/A	N/A	N/A
Overall	2836 (11,626)	493 (1479)	830	968

Genetics of Type 1 Diabetes: What's Next?

Flemming Pociot,[1,2] Beena Akolkar,[3] Patrick Concannon,[4,5] Henry A. Erlich,[6] Cécile Julier,[7] Grant Morahan,[8] Concepcion R. Nierras,[9] John A. Todd,[10] Stephen S. Rich,[4,11] and Jørn Nerup[1]

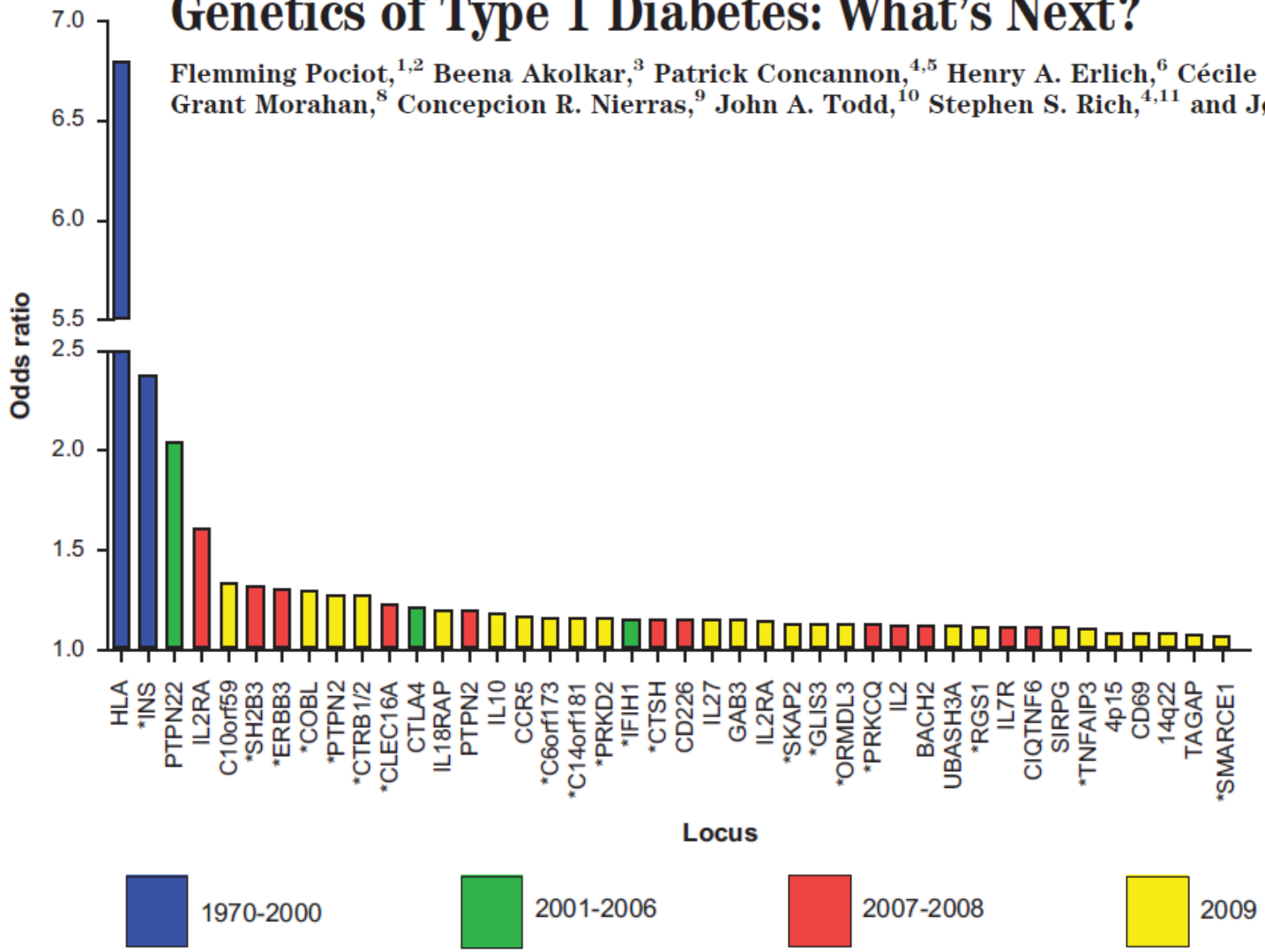
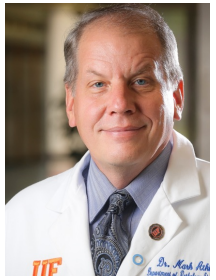


FIG. 2. GWA studies have significantly accelerated the pace of gene discovery in type 1 diabetes. However, most genetic associations discovered currently are weak. Color-coding designates year of discovery of these candidate genes. The *y*-axis indicates the best estimate of the OR for risk alleles at each of the indicated loci on the basis of currently published data (47). For each genomic region where convincing association with type 1 diabetes has been reported, the gene of interest or containing the most associated SNP is indicated on the x-axis. The majority of these genes are implicated in the immune response, but several of the non-HLA genes are expressed in human pancreatic islets (marked with *) (www.t1dbase.org) (82). (A high-quality digital representation of this figure is available in the online issue.)

The JDRF nPOD (Network for the Pancreatic Organ Donor with Diabetes)



Mark Atkinson, PhD
University of Florida
Executive Director
Since 2007

Alberto Pugliese, MD
University of Miami
Executive Co-Director
Since 2010

Carmella Evans-Molina, MD, PhD
Indiana University
Executive Co-Director
Since 2018

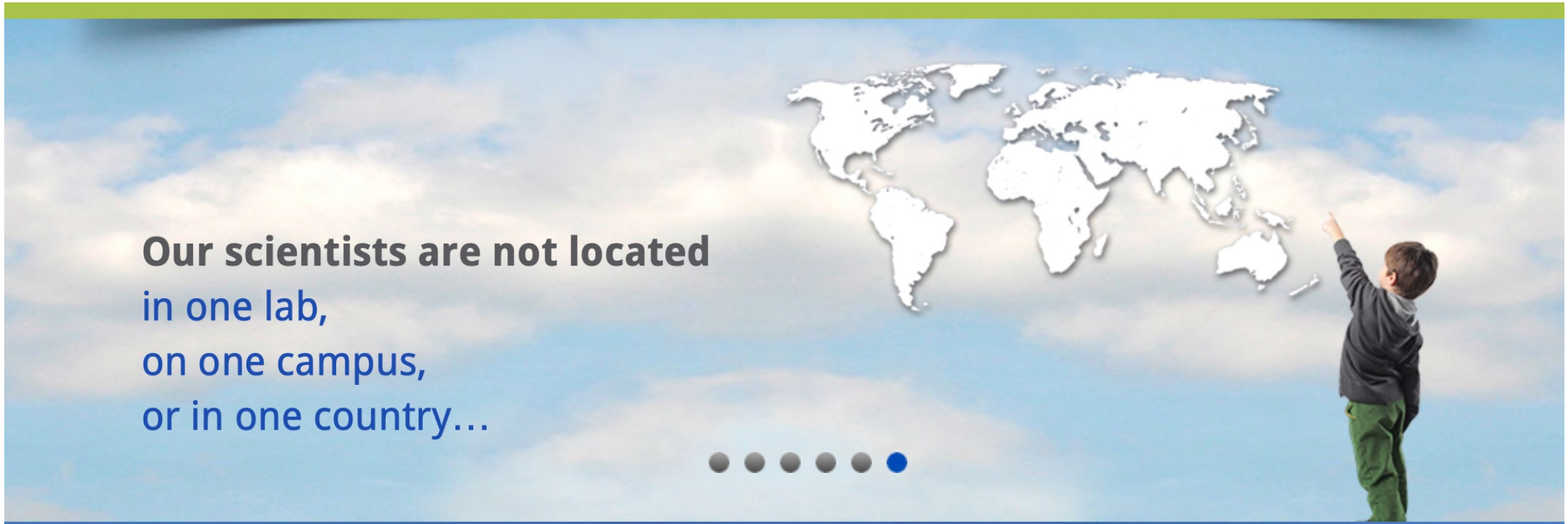
- Established in 2007, supported by JDRF & the Helmsley Charitable Trust
- Aims at promoting a comprehensive understanding of human T1D and at identifying new therapeutic targets
- nPOD obtains tissues from organ donors with T1D and from donors without diabetes who test positive for autoantibodies in our screening program (>12,000 screened since inception)
- As of May 25, 2022:
  - 246 non-diabetic “control” donors
  - 185 donors with T1D - Average age 25.4 years (Range 3.75-71.2) - Average T1D 12.3 years (Range 0-57)
  - 45 Aab+ (33 single Aab+; 12 multiple Aab+) – “prediabetes”
- Distribute tissues to approved projects (~275 since 2007), internationally
- Promote tissue and data sharing, collaboration, manage project interactions and collaborative working groups

nPOD
Network for Pancreatic Organ Donors with Diabetes

Sharing for a Cure!

HELMSLEY CHARITABLE TRUST JDRF

ABOUT | FOR INVESTIGATORS | FOR PARTNERS | PROJECTS & PUBLICATIONS | NEWS & EVENTS | CONTACT

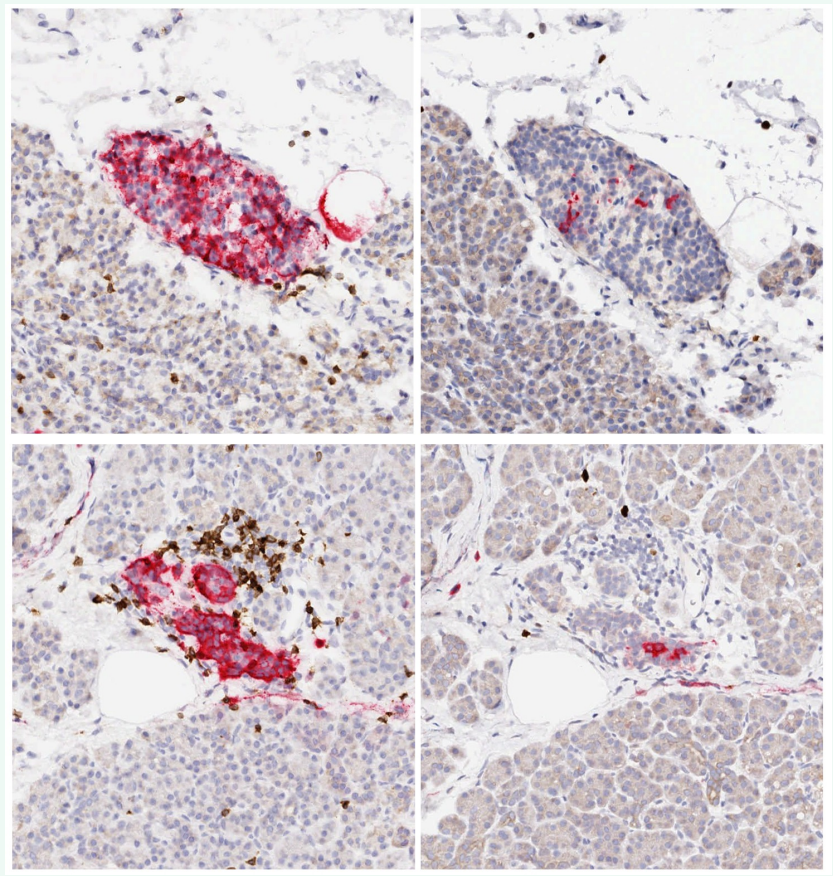


About **nPOD**

For **Investigators**

For **Partners**

Insulitis and beta cell loss in a non-diabetic, organ donor with 2 autoantibodies and high-risk HLA alleles for T1D



Raising Awareness: The Need to Promote Allocation of Pancreata From Rare Nondiabetic Donors With Pancreatic Islet Autoimmunity to Type 1 Diabetes Research

American Journal of Transplantation 2017; 17: 306–307
Wiley Periodicals Inc.

doi: 10.1111/ajt.13983

Letter to the Editor

G. W. Burke III[1,2], A. L. Posgai[3], C. H. Wasserfall[3], M. A. Atkinson[3] and A. Pugliese[1,4,5,]*

Organ donors with multiple autoantibodies are rare; some may have evidence of beta cell loss and insulitis

Yet less than 50% of such donors are recovered for research

No evidence of insulitis/beta cell loss in nPOD donors with a single autoantibody

However, donors with a single autoantibody (most often GAD-Ab) have several alterations, including dysfunction of alpha cells and beta cells

Journal of Endocrinology | S J Richardson and A Pugliese | Pancreas pathology in type 1 diabetes | 252:2

INVITED REVIEW

100 YEARS OF INSULIN

Pancreas pathology in type 1 diabetes: an evolving story

Sarah J Richardson[1] and Alberto Pugliese[2]

nPOD Network for Pancreatic Organ Donors with Diabetes

Pathology of the T1D Pancreas according to stage and disease duration current nPOD evidence

	Single AAb	Multiple AAb (Stage 1 T1D)*	T1D onset	0-10 years T1D duration	>10 years T1D duration
Beta cell loss	-	+	++	+++	++++
Insulitis	-	+	+++	++	-
Increased HLA-I	-	+	+++	++	-
Viral Infection	+/-	+	++	++	-

*nPOD has not recovered pancreas from donors at Stage 2 T1D

Hypotheses

- Beta cell loss may be limited before onset, perhaps occurs late, closer to diagnosis, is not always complete at onset and becomes more severe over time
- Insulitis/islet autoimmunity/inflammation is chronic; could it be more prevalent after diagnosis (at least for a few years)?

TEDDY

The Environmental Determinants of Diabetes in the Young

Thank you for your interest in the TEDDY Study! We have reached our screening goal and are no longer accepting any new TEDDY subjects

- Information for Participants and Families
- What is Type-1 Diabetes?
- What is the TEDDY Study?
- Clinical Centers
- News and Publications
- Information for Researchers
- TEDDY Participant Portal

TEDDY Staff Members Website

Finding diabetes early can prevent serious illness and complications

Most of the new cases of type 1 diabetes occur in children who have **no family history** of the disease.

What is Type-1 Diabetes?

Type 1 diabetes is one of the most common and serious long-term diseases in children. It is a disease where the body's immune system attacks the cells that make insulin. Insulin helps sugar (glucose) get into your cells so it can be used as energy.

Children with type 1 diabetes must take insulin several times a day to stay alive and healthy. Right now, there is no cure for type 1 diabetes.

- T1D is a serious disease affecting 1 out of every 300 (1/300) children in the United States.
- T1D occurs when special cells in the pancreas, called beta cells, are destroyed by the body's own immune system. When the beta cells are destroyed, the body can no longer make insulin.
- Insulin is needed to keep blood sugar levels normal. If there is no insulin, your body can't use the sugars from the food you eat, causing serious illness or even death.
- A child with T1D must take insulin shots or use an insulin pump every day to stay well. Insulin has to be taken every day for the rest of the life of a child with diabetes.

What is the TEDDY Study?

Every child in TEDDY helps us come closer to preventing this disease.

The TEDDY study - **T**he **E**nvironmental **D**eterminants of **D**iabetes in the **Y**oung - is looking for the causes of type 1 diabetes mellitus (T1DM). T1DM used to be called childhood diabetes or insulin-dependent diabetes.

Research tells us that children who get diabetes have certain kind of genes. Other children who have these genes are at higher risk for getting diabetes. However, not all children who are higher risk get diabetes. We think that something happens that "triggers" or causes a child with higher risk genes to actually get diabetes. It is the purpose of this study to try and find out what are the triggers that cause children to get diabetes.

Learn about the TEDDY Study >>>

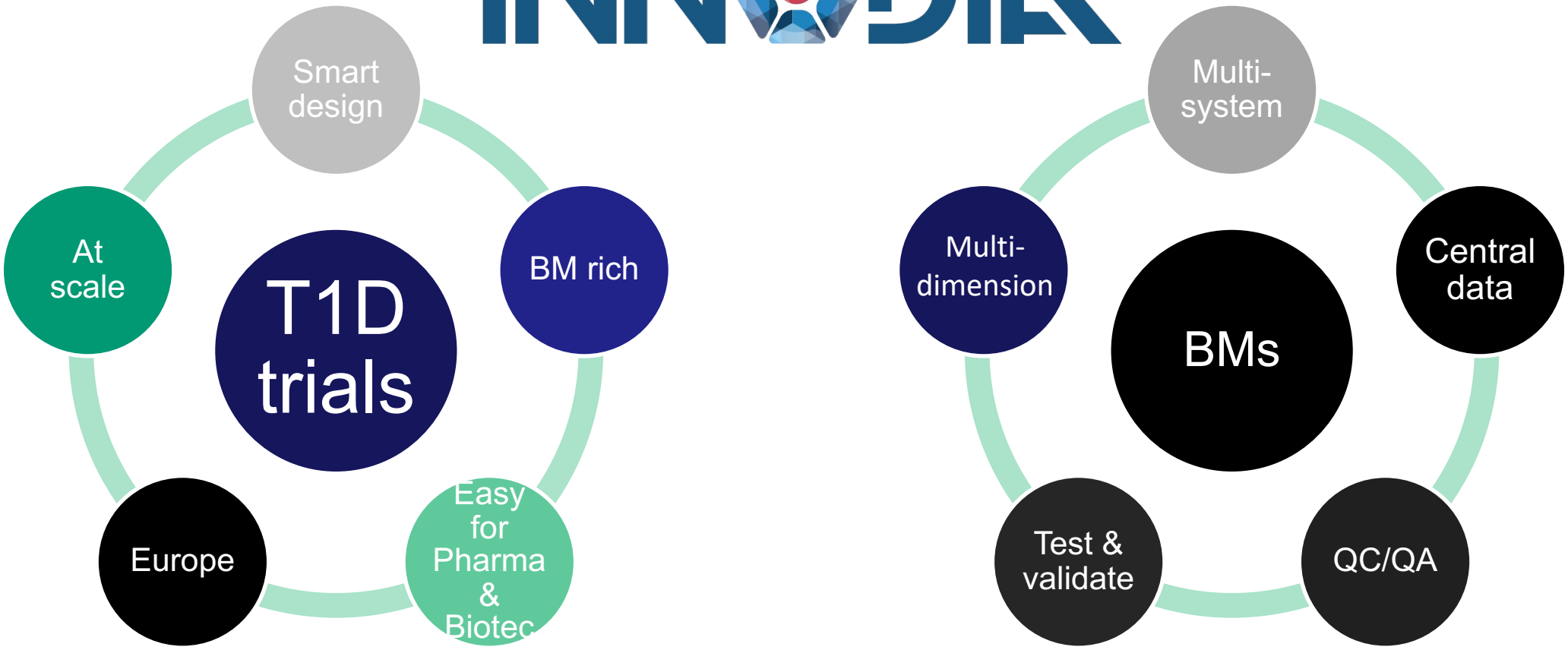
The TEDDY Study is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), Juvenile Diabetes Research Foundation (JDRF), and Centers for Disease Control and Prevention (CDC).

TEDDY European Clinical Centers Web Sites:

Germany Sweden Finland

An IMI (Innovative Medicines Intitiative) supported public private partnership

www.innodia.eu



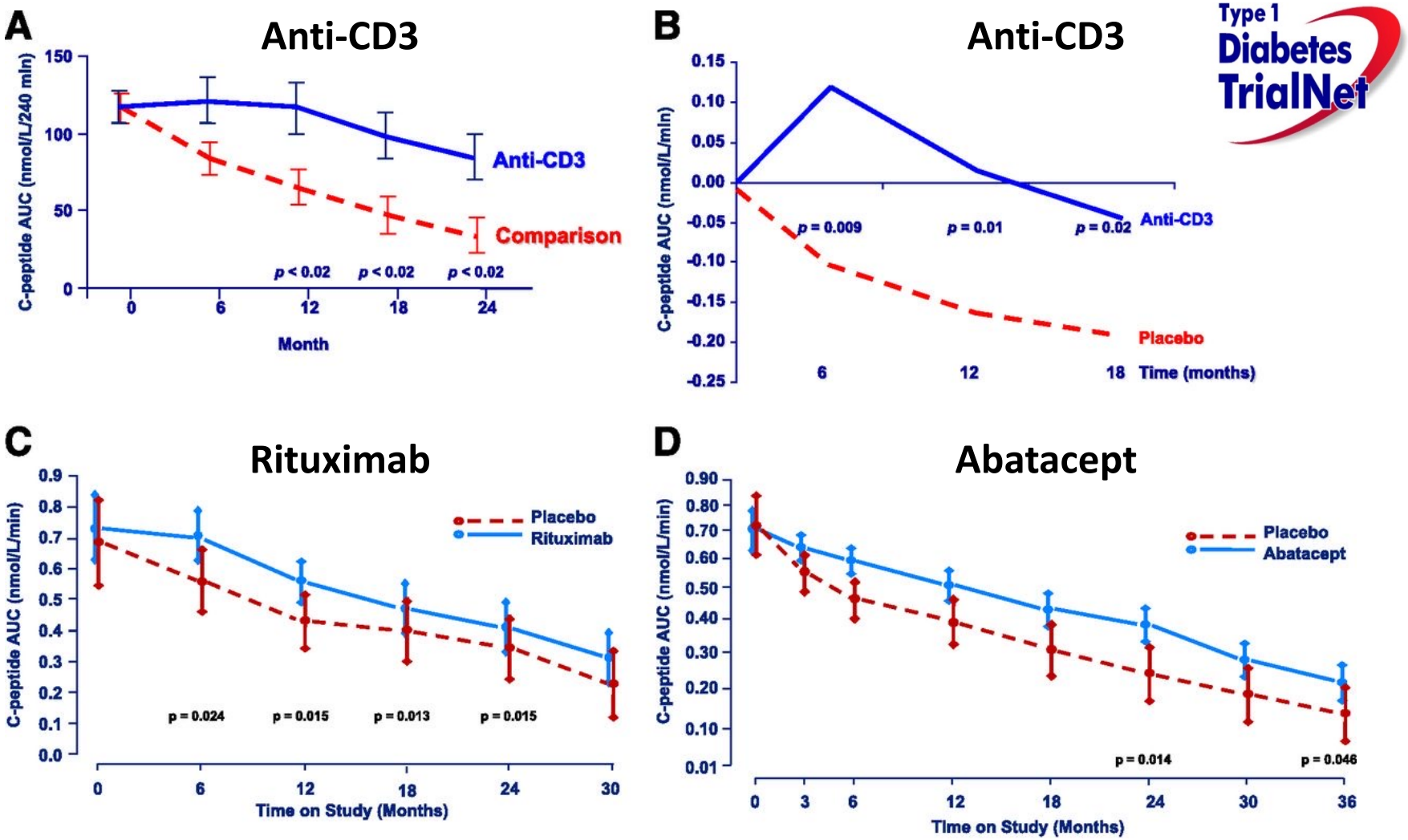
Side-by-side summay of Trials in INNODIA and INNODIA HARVEST

	MELD-ATG A CLINICAL TRIAL BY INNODIA	Impact	Ver-A-TID A CLINICAL TRIAL BY INNODIA	CFZ533 ISCALIMAB IN COLLABORATION WITH INNODIA
Age groups (years)	**5 – 25**	**18 – 45*** (*pediatric study Q4 2022)	**18 – 45**	**6 – 21**
Number of participants	**N=114**	**N=108**	**N=120**	**N=102**
Design	Randomised to different parallel arm of amount of trial medication (total 32 placebo) (ATG)	Randomised to different cohorts based on treatment arm and age (Immotope)	Randomised 2:1 (Verapamil SR: placebo)	Randomised 2:1 (CFZ533: placebo) (fully-human anti-CD40 monoclonal antibody non-depleting for B lymphocytes)
Treatment	**Infusion** 2 consecutive days	**SC Injections** 6 times fortnightly (booster dose at 24 weeks)	**Tablets** Once daily for 1 year (titrated 120mg to 360mg)	**IV infusion / SC injections** 1st dose IV, then home SC injections for 1 year
Visits	1, 2, 4 weeks 3, 6, 12 months	4, 24 and 48 weeks	4 and 6 weeks 3, 6, 9, 12 months	Monthly for 1st year, then twice per year
Duration	~12 months	~12 months	~12 months	12 mo treatment ~16 - 36 mo total

TrialNet Goals

- Delay, prevent, or modify the course of T1D
  - Secondary prevention – antibody-positive relatives “at risk” of T1D
  - Primary prevention – high genetic risk infants without evidence of autoimmunity
  - New-onset T1D
  - Further define epidemiology, natural history, and risk factors of T1D
  - Advance translational science to lay groundwork for future generations of trials and clinical use
- Clinical trial organization with sites in the U.S., Europe, and Australia, since 2000

Immunotherapies at onset typically reduce but do not block the decline of insulin secretion, or effects wanes over time

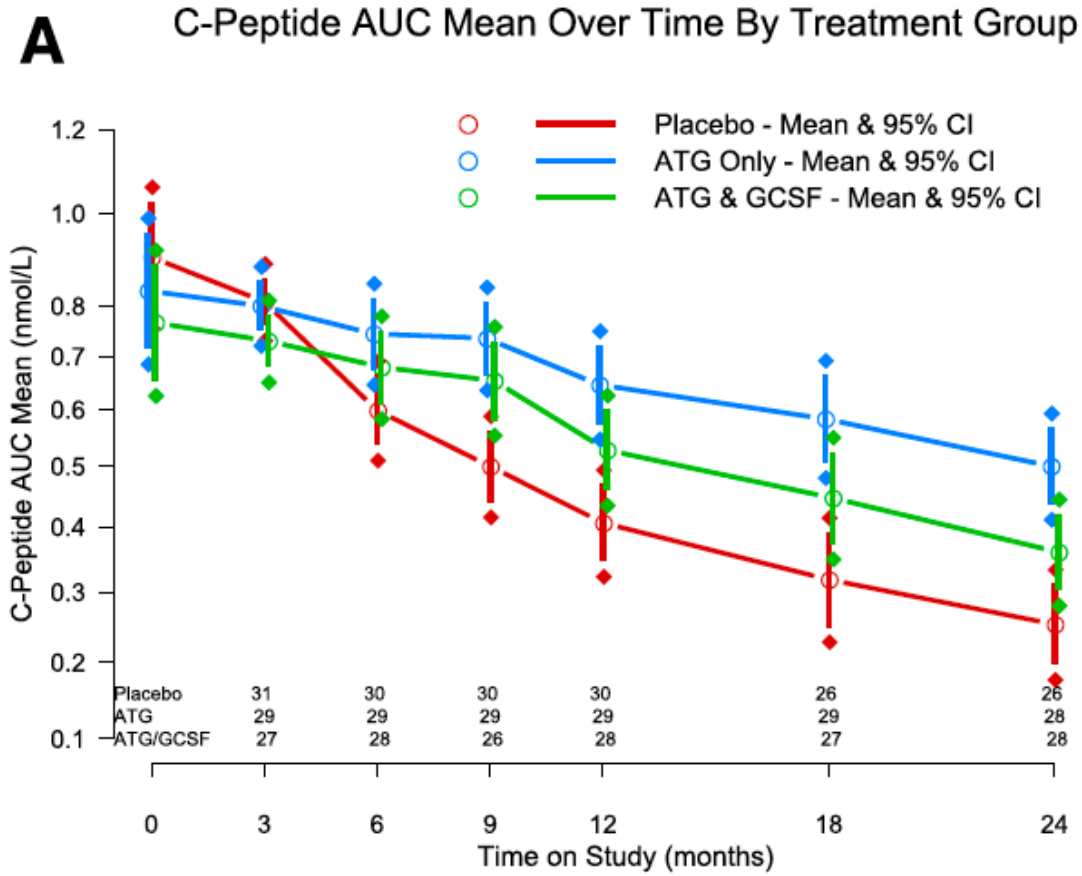


Jay S. Skyler Diabetes Care 2015;38:997-1007

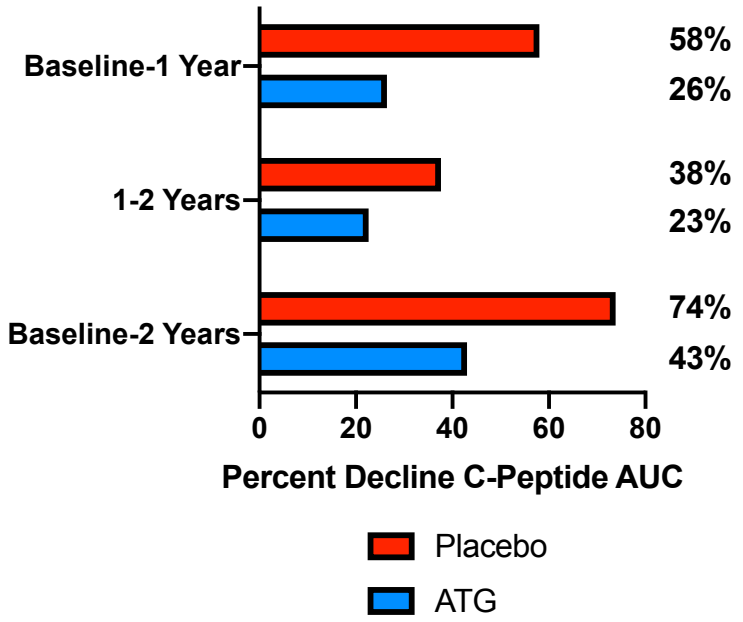
Low-Dose Anti-Thymocyte Globulin Preserves C-Peptide, Reduces HbA_{1c}, and Increases Regulatory to Conventional T-Cell Ratios in New-Onset Type 1 Diabetes: Two-Year Clinical Trial Data

Michael J. Haller,[1] S. Alice Long,[2] J. Lori Blanchfield,[2] Desmond A. Schatz,[1] Jay S. Skyler,[3] Jeffrey P. Krischer,[4] Brian N. Bundy,[4] Susan M. Geyer,[4] Megan V. Warnock,[4] Jessica L. Miller,[4] Mark A. Atkinson,[1] Dorothy J. Becker,[3,5] David A. Baidal,[3] Linda A. DiMeglio,[6] Stephen E. Gitelman,[7] Robin Goland,[8] Peter A. Gottlieb,[9] Kevan C. Herold,[10] Jennifer B. Marks,[3] Antoinette Moran,[11] Henry Rodriguez,[4] William E. Russell,[12] Darrell M. Wilson,[13] and Carla J. Greenbaum,[2] for the Type 1 Diabetes TrialNet ATG-GCSF Study Group*

Diabetes 2019;68:1267–1276 | https://doi.org/10.2337/db19-0057



ATG treatment reduces but does not fully prevent further decline in C-peptide AUC

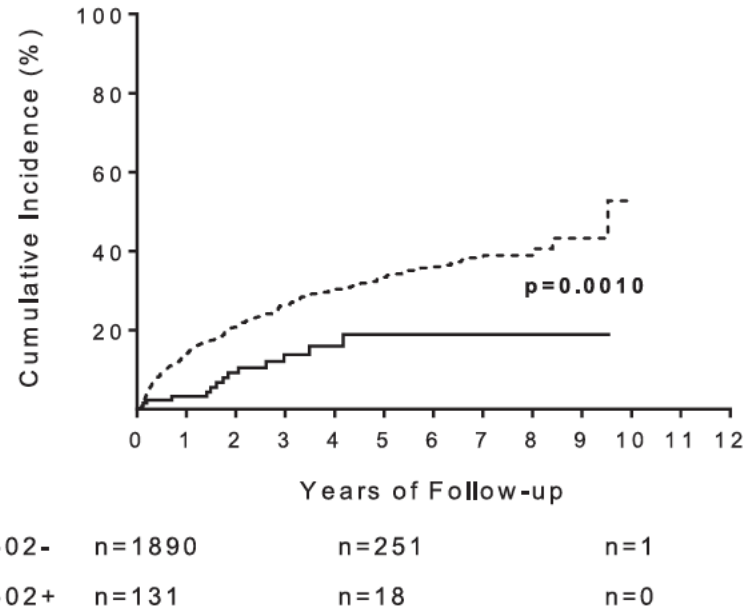


HLA-DRB1*15:01-DQA1*01:02-DQB1*06:02 Haplotype Protects Autoantibody-Positive Relatives From Type 1 Diabetes Throughout the Stages of Disease Progression

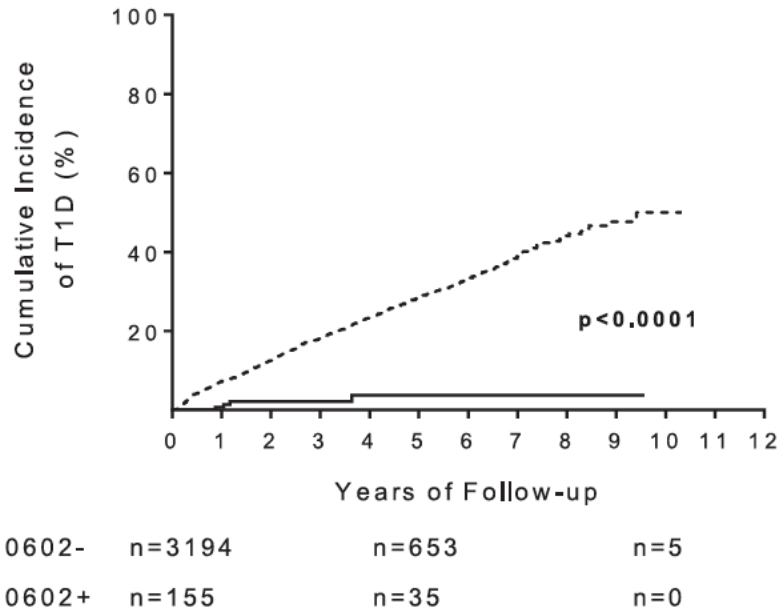
Diabetes 2016;65:1109–1119 | DOI: 10.2337/db15-1105

Alberto Pugliese,[1,2] David Boulware,[3] Liping Yu,[4] Sunanda Babu,[4] Andrea K. Steck,[4] Dorothy Becker,[5] Henry Rodriguez,[6] Linda DiMeglio,[7] Carmella Evans-Molina,[8] Leonard C. Harrison,[9] Desmond Schatz,[10] Jerry P. Palmer,[11] Carla Greenbaum,[12] George S. Eisenbarth,[4] Jay M. Sosenko,[1,13] and the Type 1 Diabetes TrialNet Study Group*

Conversion from single to multiple autoantibody positivity



Progression to T1D diagnosis



A Type 1 Diabetes Genetic Risk Score Predicts Progression of Islet Autoimmunity and Development of Type 1 Diabetes in Individuals at Risk

*Maria J. Redondo,[1] Susan Geyer,[2] Andrea K. Steck,[3] Seth Sharp,[4] John M. Wentworth,[5] Michael N. Weedon,[4] Peter Antinozzi,[6] Jay Sosenko,[7] Mark Atkinson,[8] Alberto Pugliese,[7] Richard A. Oram,[4] and the Type 1 Diabetes TrialNet Study Group**

https://doi.org/10.2337/dc18-0087

Diabetes Care, 2018

RESULTS

Higher T1D GRS significantly increased the rate of progression to T1D adjusting for DPT-1 Risk Score, age, number of positive autoantibodies, sex, and ethnicity (hazard ratio [HR] 1.29 for a 0.05 increase, 95%CI 1.06–1.6; *P* = 0.011). Progression to T1D was best predicted by a combined model with GRS, number of positive autoantibodies, DPT-1 Risk Score, and age (7-year time-integrated AUC = 0.79, 5-year AUC = 0.73). Higher GRS was significantly associated with increased progression rate from single to multiple positive autoantibodies after adjusting for age, autoantibody type, ethnicity, and sex (HR 2.27 for GRS >0.295, 95%CI 1.47–3.51; *P* = 0.0002).

CONCLUSIONS

The T1D GRS independently predicts progression to T1D and improves prediction along T1D stages in autoantibody-positive relatives.

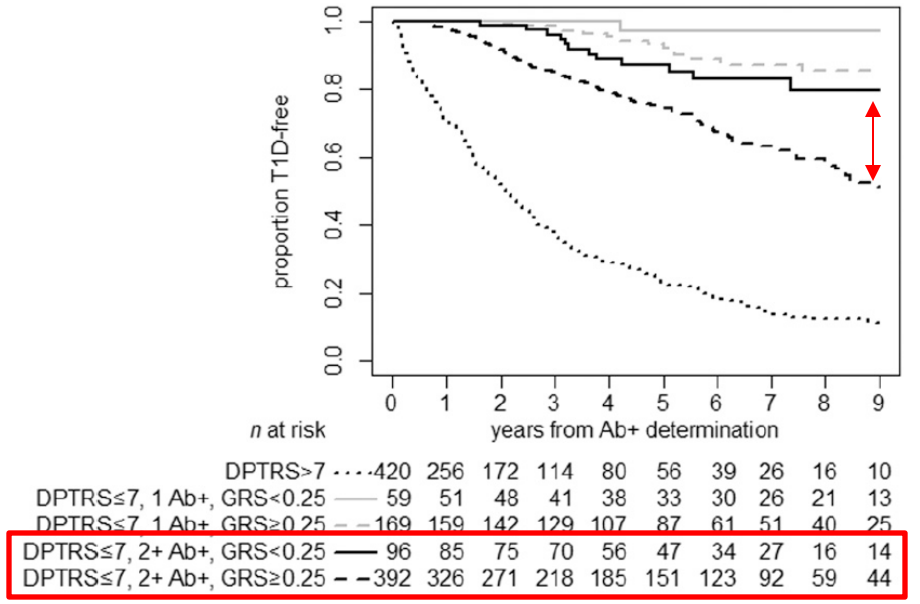


Figure 1—Time to T1D in patients' relatives who were initially without diabetes and islet autoantibody–positive (Ab+), by DPT-1 Risk Score (≤7 vs. >7), number of positive autoantibodies (i.e., single vs. multiple autoantibody positivity), and T1D GRS (<0.250 vs. ≥0.250) ($P < 0.0001$). While the T1D GRS did not further increase the predictive ability in the group with DPT-1 Risk Score >7, which already had high risk of T1D, it was able to stratify risk in individuals with DPT-1 Risk Score <7, with either single positive autoantibody or multiple positive autoantibodies. DPTRS, DPT-1 Risk Score.

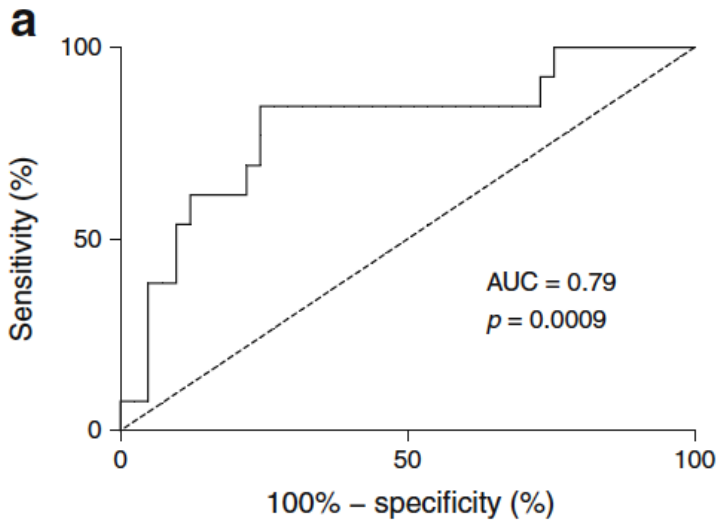
Association of serum microRNAs with islet autoimmunity, disease progression and metabolic impairment in relatives at risk of type 1 diabetes

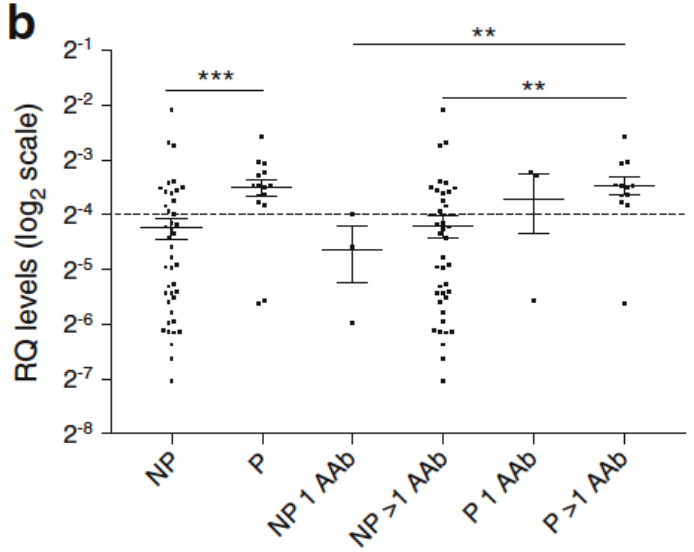
Isaac V. Snowhite[1] · Gloria Allende[1] · Jay Sosenko[1,2] · Ricardo L. Pastori[1,2] · Shari Messinger Cayetano[3] · Alberto Pugliese[1,2,4]

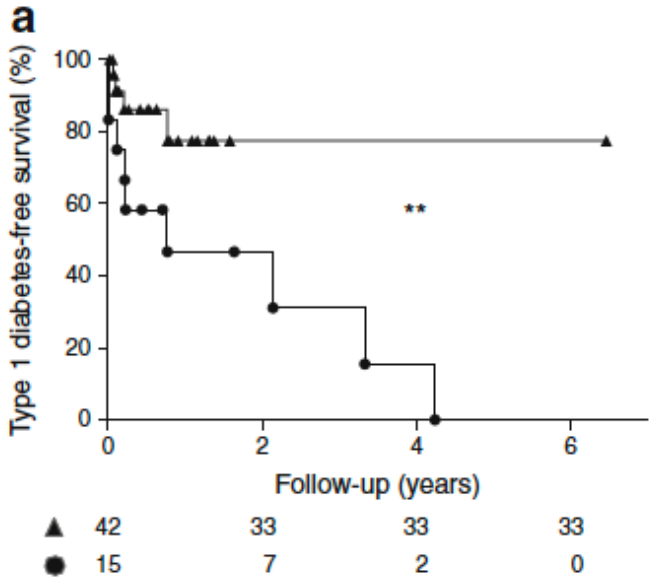
Diabetologia (2017) 60:1409–1422
DOI 10.1007/s00125-017-4294-3

Type 1 Diabetes TrialNet

Increased serum levels of miR-21-3p are associated with higher risk of progression to T1D among high-risk individuals with multiple autoantibodies







Multiple autoantibodies

miRNA	Progressors	Non-progressors	*p* value	RR	OR	PPV	NPV
miR-21-3p	7/12 (58.3%)	6/39 (15.4%)	0.006	3.8	7.7	0.58	0.84
miR-29a-3p	15/35 (42.8%)	21/102 (20.5%)	0.01	2.1	2.9	0.42	0.79
miR-424-5p	15/35 (42.8%)	19/103 (18.4%)	0.006	2.3	3.3	0.44	0.80

PPV, positive predictive value; NPV, negative predictive value

Rising Hemoglobin A_{1c} in the Nondiabetic Range Predicts Progression of Type 1 Diabetes As Well As Oral Glucose Tolerance Tests

Diabetes Care 2022;45:2342–2349 | https://doi.org/10.2337/dc22-0828

Kendra Vehik,[1] David Boulware,[1]
Michael Killian,[2] Marian Rewers,[3]
Richard McIndoe,[4] Jorma Toppari,[5]
Åke Lernmark,[6] Beena Akolkar,[7]
Anette-G. Ziegler,[8] Henry Rodriguez,[9]
Desmond A. Schatz,[10] Jeffrey P. Krischer,[1]
*and William Hagopian,[2] for the TrialNet Study Group and TEDDY Study Group**

TEDDY
The Environmental Determinants of Diabetes in the Young

Type 1 Diabetes TrialNet

An increase of ≥10% in HbA_{1c} from baseline is as informative as OGTT 2-hPG in predicting risk of stage 3 in youth with genetic risk and diabetes-associated autoantibodies.

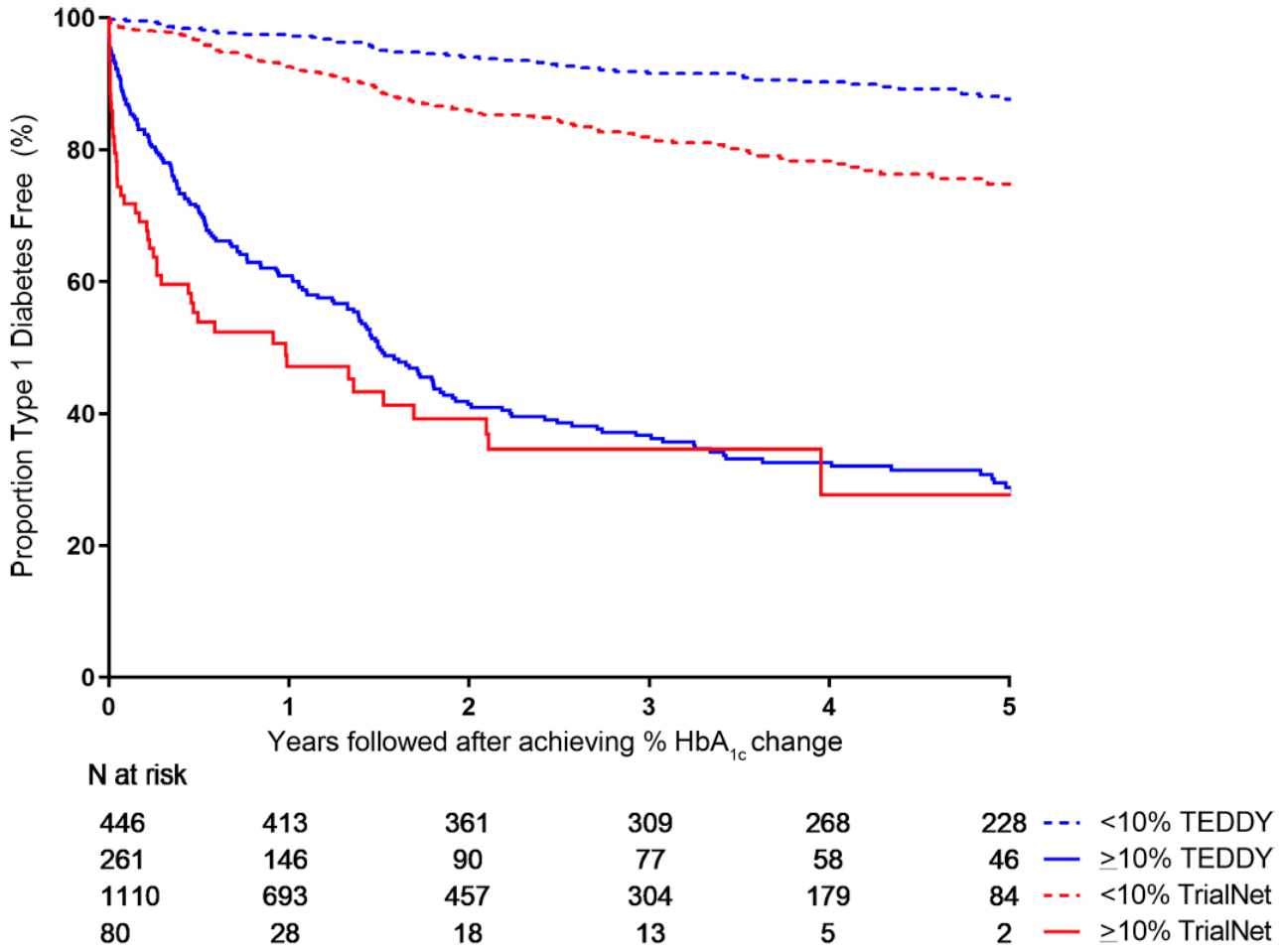


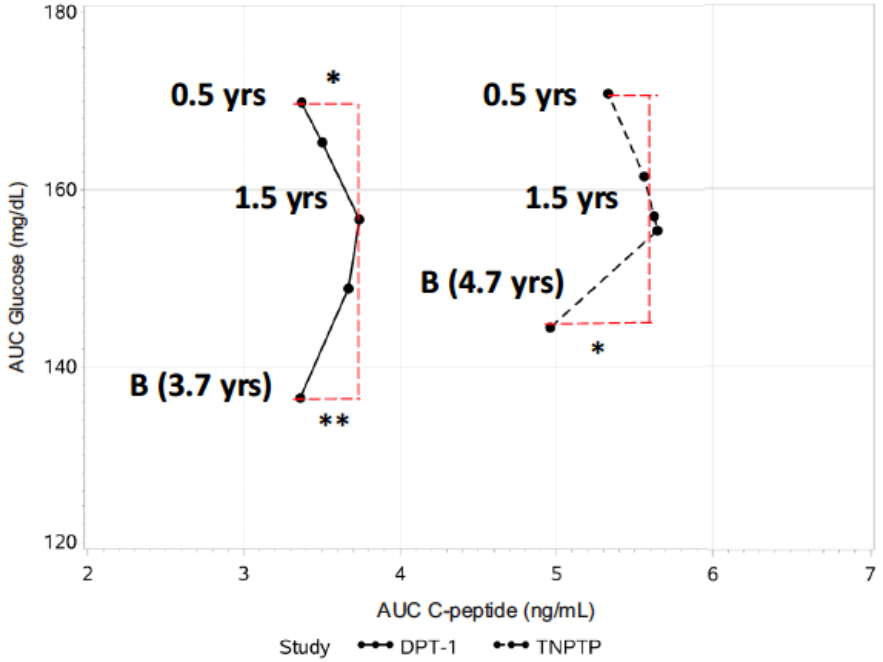
Figure 2—Multivariable Cox proportional hazards models evaluating ≥10% HbA_{1c} increase in TEDDY and TrialNet on progression to type 1 diabetes from time at ≥10% increase in HbA_{1c}. Reference is <10% HbA_{1c} increase. Models adjusted for age at HbA_{1c} baseline, HbA_{1c} baseline measure, number of autoantibodies at time of HbA_{1c} change, maximum rate of change from baseline, and genetic sex. A ≥10% increase in HbA_{1c} increases the risk of progression to type 1 diabetes in both the TEDDY (HR 12.74, 95% CI 8.7–18.6, $P < 0.0001$) and TrialNet (HR 5.09, 95% CI 3.3–7.9, $P < 0.0001$) studies.

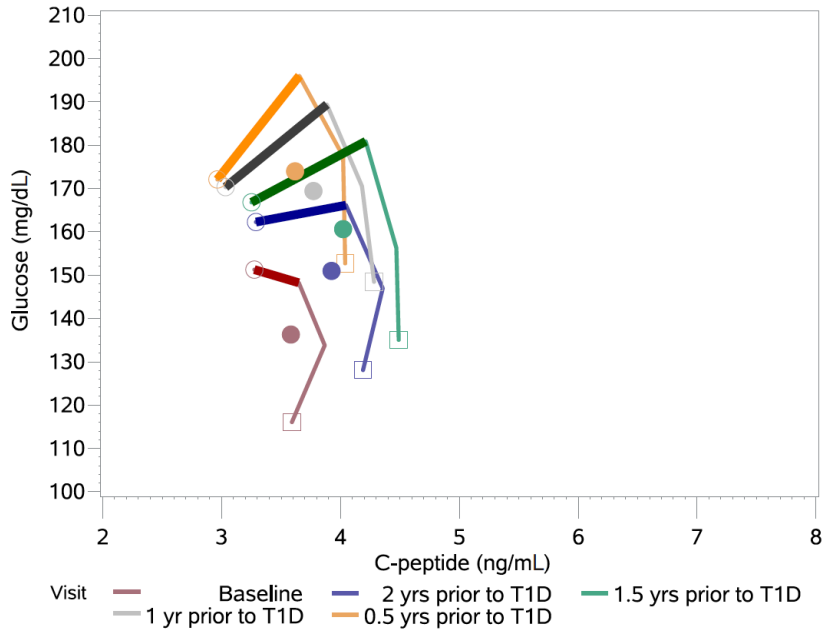
The Transition From a Compensatory Increase to a Decrease in C-peptide During the Progression to Type 1 Diabetes and Its Relation to Risk

Diabetes Care 2022;45:2264–2270 | https://doi.org/10.2337/dc22-0167

*Heba M. Ismail,[1] David Cuthbertson,[2] Stephen E. Gitelman,[3] Jay S. Skyler,[4] Andrea K. Steck,[5] Henry Rodriguez,[6] Mark Atkinson,[7] Brandon M. Nathan,[8] Maria J. Redondo,[9] Kevan C. Herold,[10] Carmella Evans-Molina,[1] Linda A. DiMeglio,[1] and Jay Sosenko,[4] on behalf of DPT-1 and TrialNet Study Groups**

A transition from an increase to a decrease in AUC C-peptide ~1.5 years prediagnosis was validated in two independent cohorts. The median Index60 value at that time point can be used as a pathophysiologic-based threshold for identifying individuals at high risk for T1D.



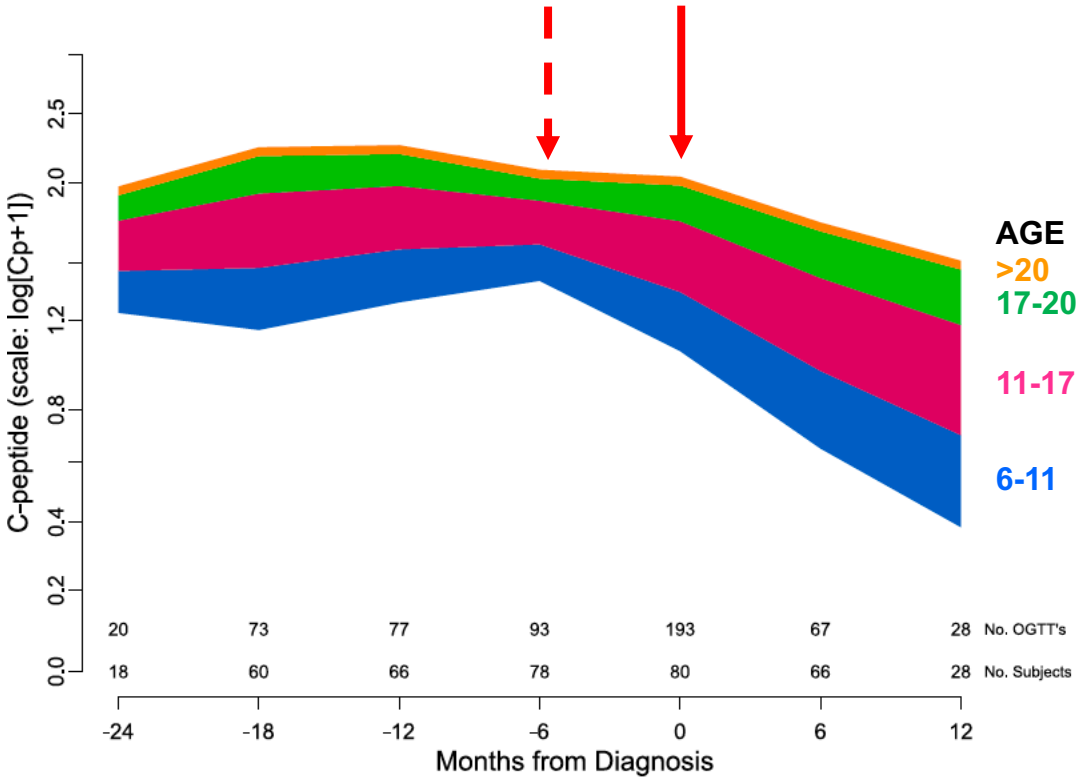


C-Peptide Levels in Subjects Followed Longitudinally Before and After Type 1 Diabetes Diagnosis in TrialNet

Magdalena M. Bogun,[1] Brian N. Bundy,[2] Robin S. Goland,[1] and Carla J. Greenbaum[3]

https://doi.org/10.2337/dc19-2288

Diabetes Care Publish Ahead of Print, published online May 26, 2020

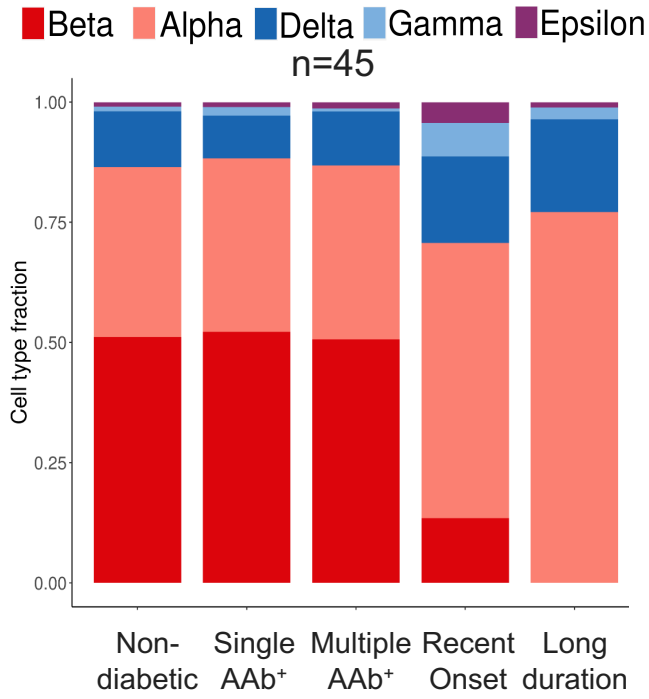


RESULTS

C-peptide did not change significantly until 6 months before the clinical diagnosis of type 1 diabetes and continued to decline postdiagnosis, and the rates of decline for the first 6 months postdiagnosis were similar to the 6 months prediagnosis. There were no significant differences in MMTT and OGTT C-peptide responses in paired tests postdiagnosis.

Assessment of Beta Cell Loss in nPOD Donors by Imaging Mass Cytometry

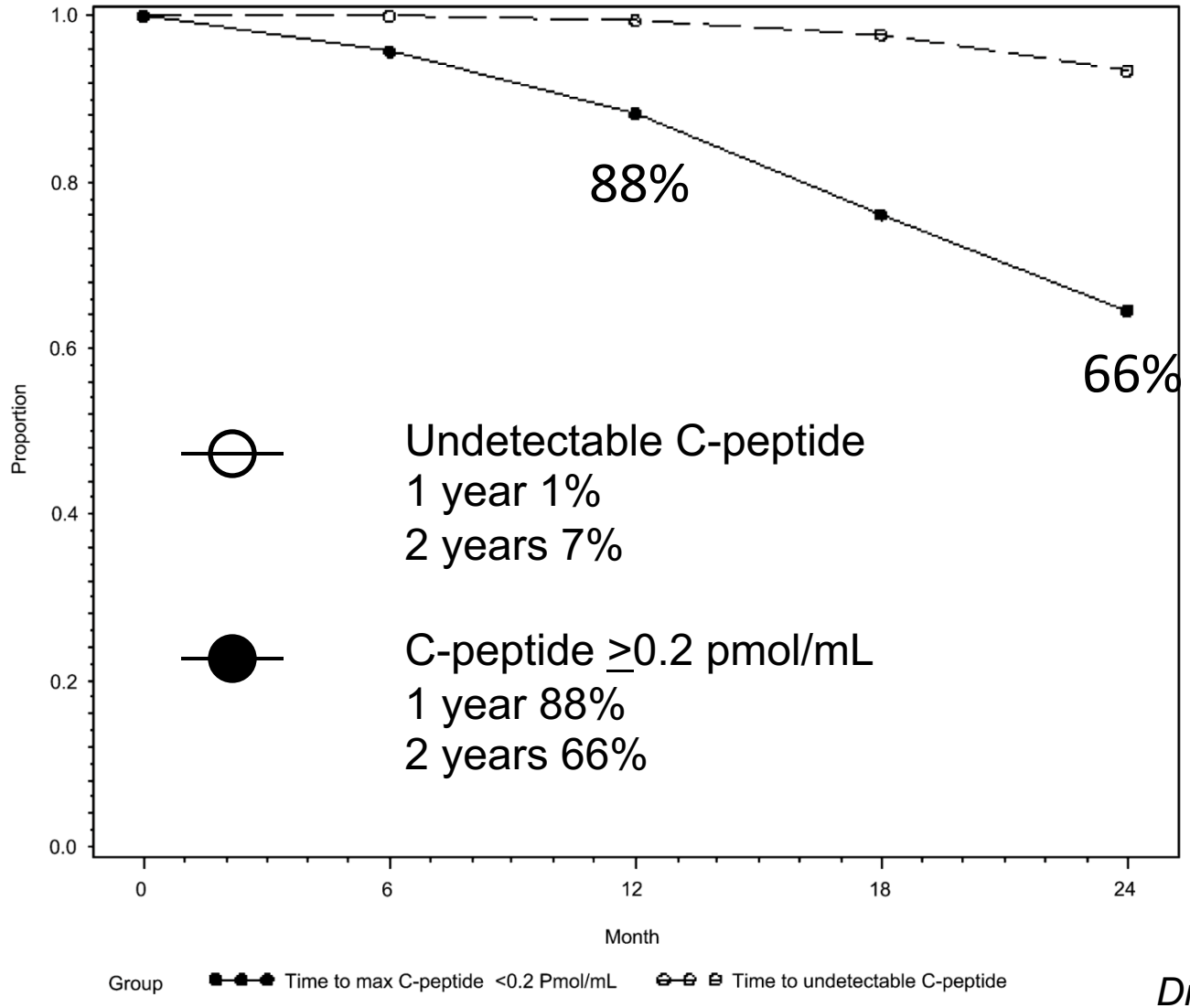
Nicolas Damond, Bernd Bodenmiller (unpublished)
Presented at the ADA 2022 by Mark Atkinson



- β cell loss only occurs at or near T1D onset (with high inter-donor variability)
- Increasing recognition that beta-cell mass at diagnosis is greater than previously thought
- Earlier studies estimated ~10% but more recent estimates suggest greater residual beta cell mass (30-50%), but this is impacted by age

C-peptide decline after diagnosis

Proportions of patients with peak stimulated C-peptide ≥0.2 pmol/mL



Diabetes 2012

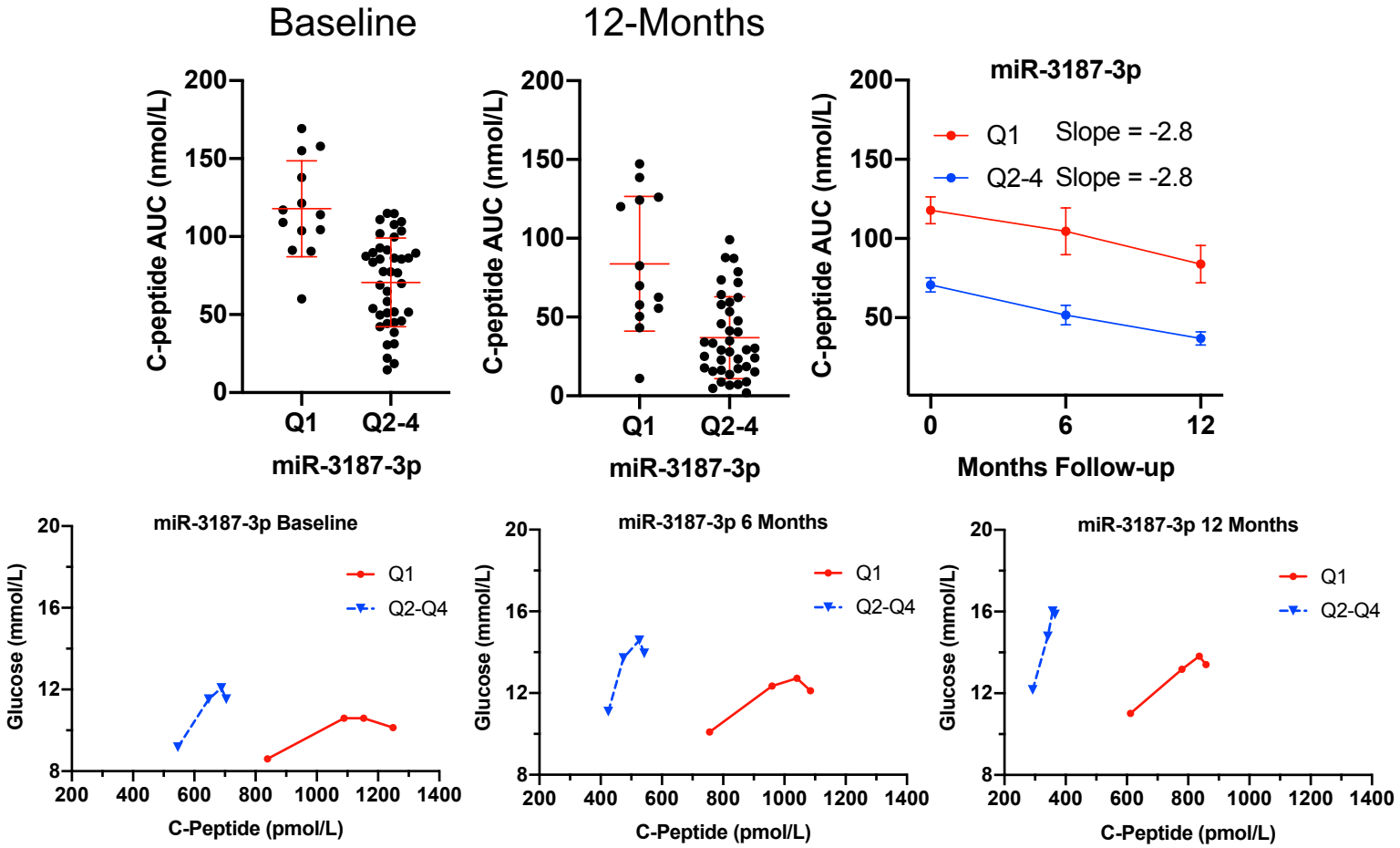
FIG. 1. Percent of individuals with detectable C-peptide and C-peptide ≥0.2 pmol/mL over time.

Baseline Assessment of Circulating MicroRNAs Near Diagnosis of Type 1 Diabetes Predicts Future Stimulated Insulin Secretion

- A set of circulating miRNAs is associated with C-peptide AUC at baseline and predict its future loss
- Many associated miRNAs are predicted to impact insulin and TCR signaling pathways

Isaac Snowhite,[1] Ricardo Pastori,[1,2] Jay Sosenko,[2] Shari Messinger Cayetano,[3] and Alberto Pugliese[1,2,4]

Diabetes 2021;70:638–651 | https://doi.org/10.2337/db20-0817

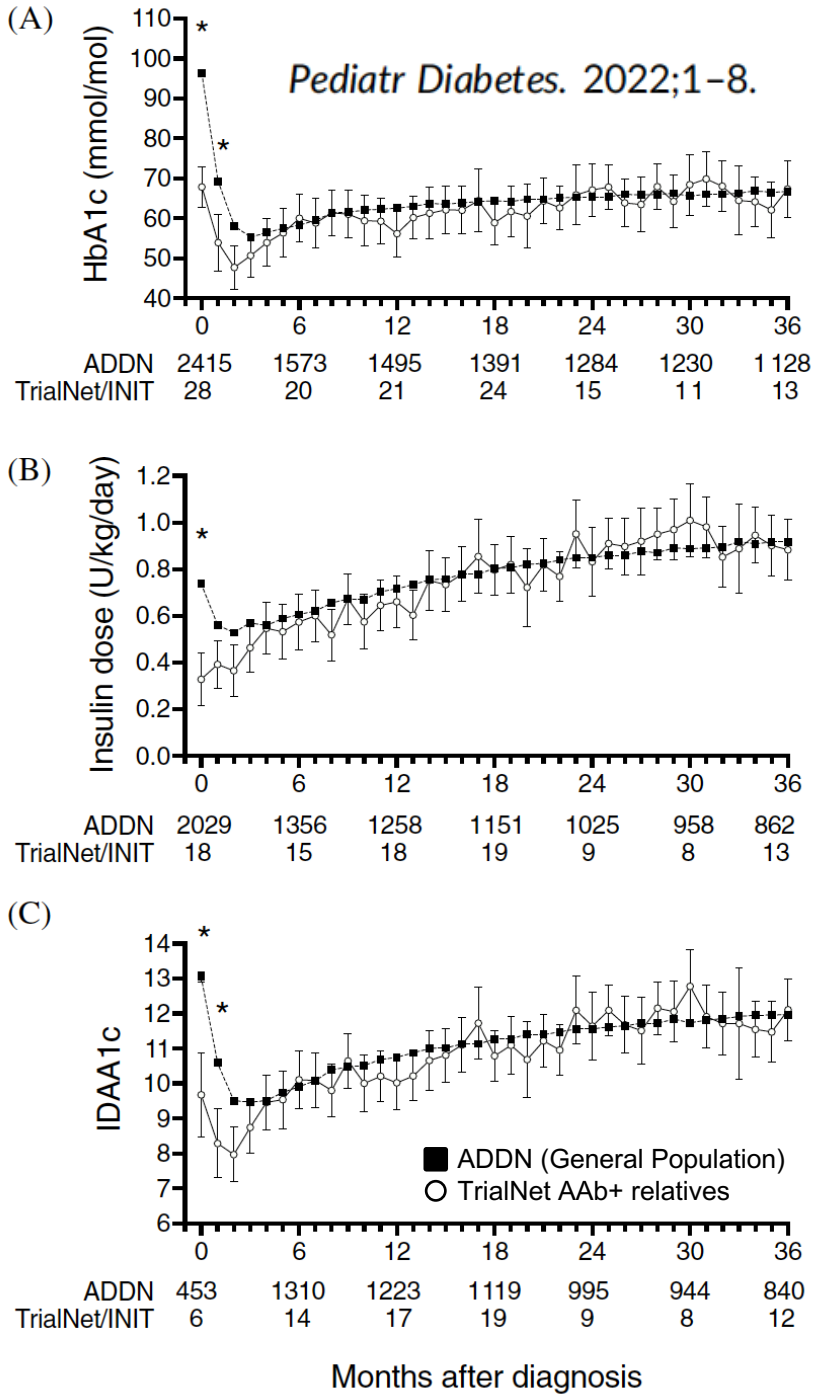


C-peptide AUC at baseline and 12 months, and its decline (top) and Glucose/C-peptide Ratio curves for patients separated by levels of miR-3187-3p at baseline (bottom). Patients with lower (Q1) circulating levels of this microRNA have better preservation of C-peptide at baseline and on follow-up, and the Glucose/C-peptide Ratio curves are flatter, lower and more to the right, indicating less severe hyperglycemia and better insulin secretion during the MMTT at baseline, 6 and 12 months.

Decreased occurrence of ketoacidosis and preservation of beta cell function in relatives screened and monitored for type 1 diabetes in Australia and New Zealand

John M. Wentworth[1,2,3] | Helena Oakey[4] | Maria E. Craig[5,6,7] | Jennifer J. Couper[8] | Fergus J. Cameron[9] | Elizabeth A. Davis[10] | Antony R. Lafferty[11] | Mark Harris[12] | Benjamin J. Wheeler[13,14] | Craig Jefferies[15] | Peter G. Colman[2] | Leonard C. Harrison[1,3]

After adjustment for age of diagnosis and sex, the risk of DKA remained markedly lower at 5.4% compared to 30.7% in the general population, or a decrease in DKA frequency of 82% ($p < 0.001$).



Type 1 Diabetes TrialNet

As T1D risk increases, the proportion of people at risk decreases - implications for prevention

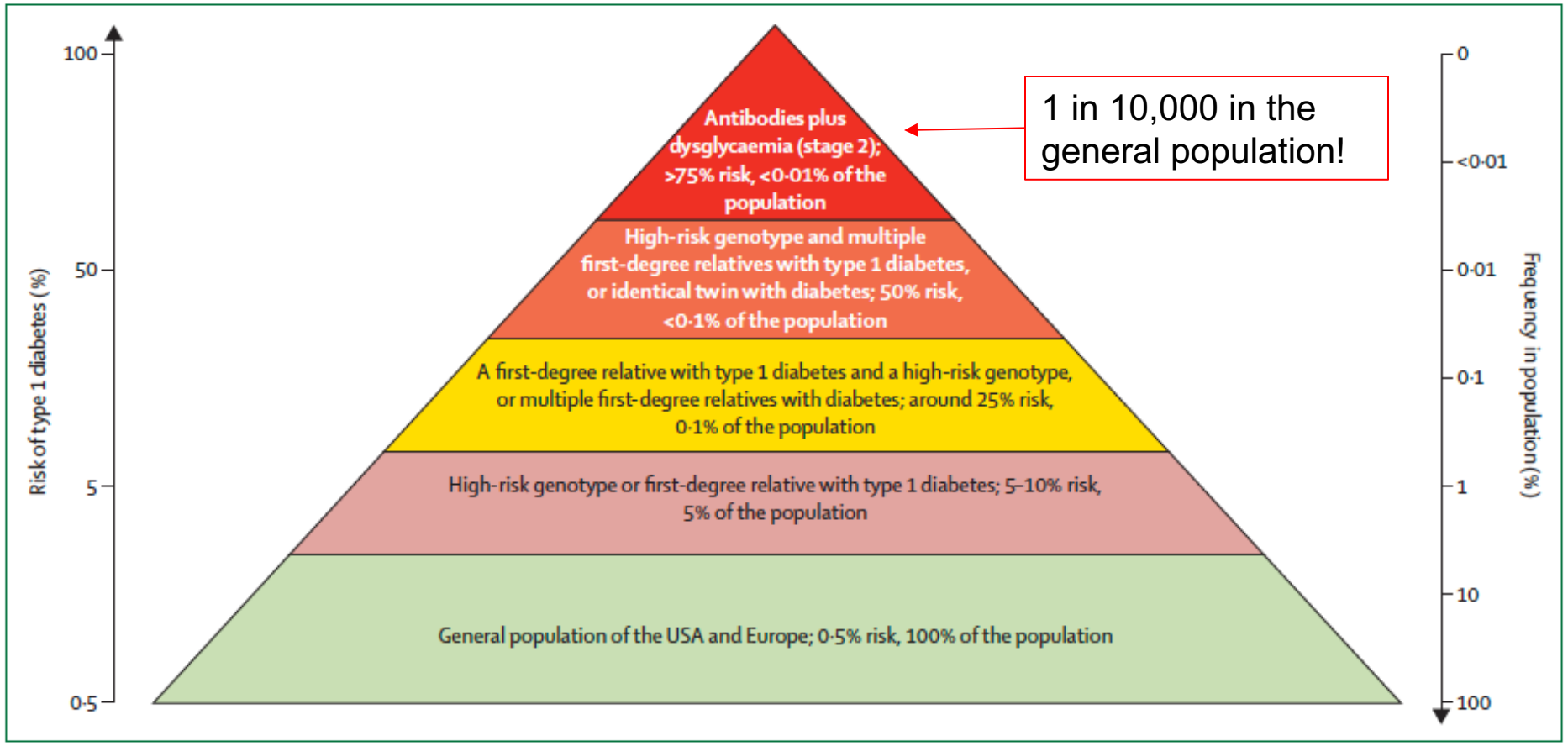


Figure 2: **Lifetime risk of developing type 1 diabetes versus prevalence of that level of risk in the population**
Left hand scale shows lifetime risk of type 1 diabetes. Right hand scale shows proportion of the population that have this level of risk or greater. Individuals in the top area have more than a 75% risk of developing diabetes, but less than 0·01% of the population have this level of risk, so 10 000 people in the general population would need to be screened to find one person with this level of risk.[26]

C. Dayan et al. Lancet 2019

Screening for Type 1 Diabetes in the General Population: A Status Report and Perspective

Emily K. Sims,[1] Rachel E.J. Besser,[2,3] Colin Dayan,[4] Cristy Geno Rasmussen,[5] Carla Greenbaum,[6] Kurt J. Griffin,[7] William Hagopian,[8] Mikael Knip,[9–11] Anna E. Long,[12] Frank Martin,[13] Chantal Mathieu,[14] Marian Rewers,[5] Andrea K. Steck,[5] John M. Wentworth,[15] Stephen S. Rich,[16] Olga Kordonouri,[17] Anette-Gabriele Ziegler,[18,19] and Kevan C. Herold,[20] for the NIDDK Type 1 Diabetes TrialNet Study Group*

Diabetes 2022;71:610–623 | https://doi.org/10.2337/dbi20-0054

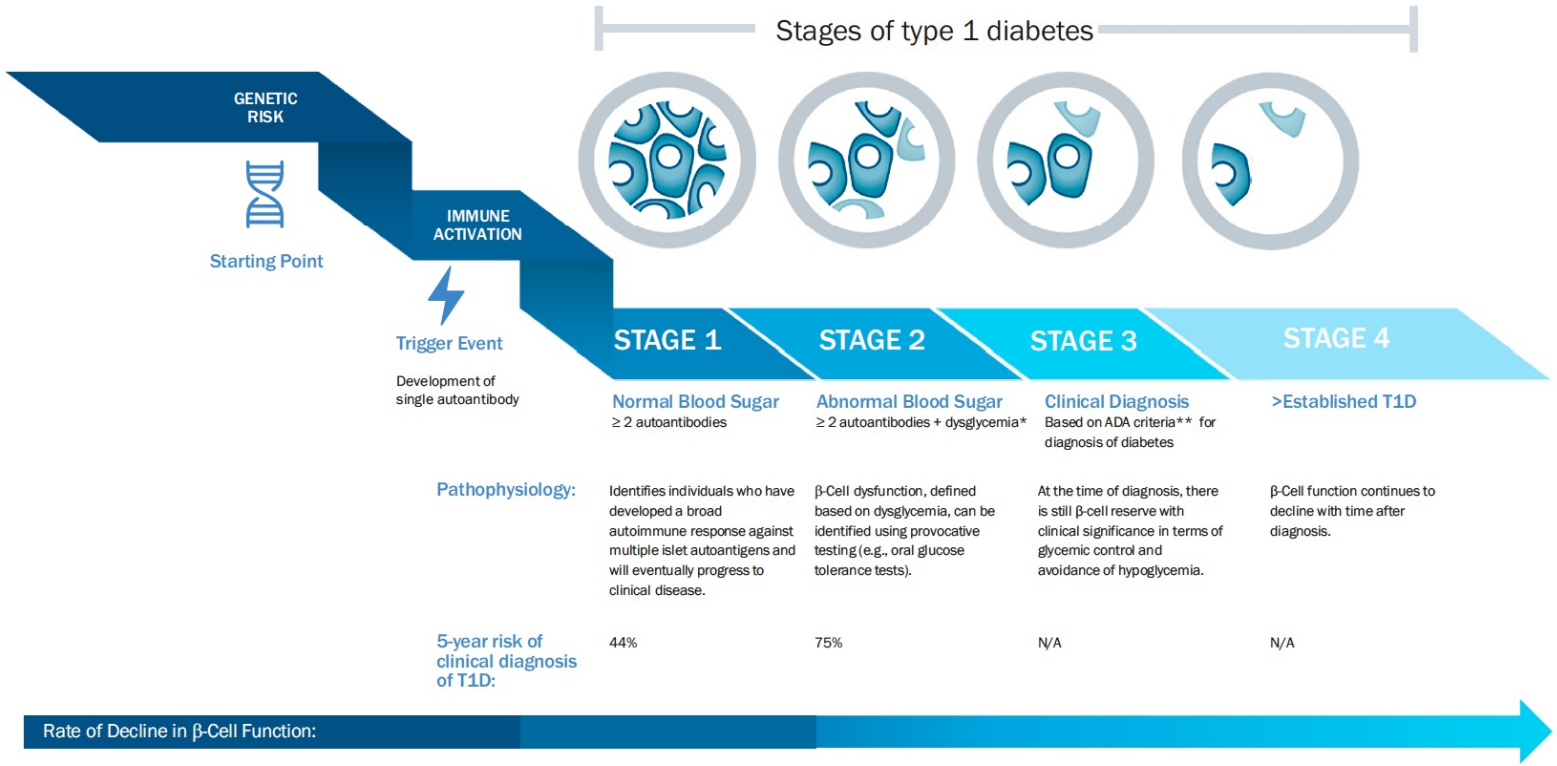


Table 2—Ongoing screening programs

A: Selected type 1 diabetes screening programs using screening of relatives for eligibility to participate in clinical studies

Program	Population screened	Location	Screening site(s)	Number screened	Screening material	Screening assay(s)	Rate(s) of positive scree(s)	Comment(s)
TrialNet Pathway to Prevention (TN01)	Relatives aged 3–45 years	U.S., Canada, Europe, Australia	TrialNet centers and affiliates	>250,000	Serum or capillary sample	RBA: IAA and GADA, followed by IA-2A, ZnT8A, and ICA if positive	AA+: 5% • ≥2 AA+: 2.5%	Objective is to identify participants eligible for clinical trials Monitors nonrelatives identified through other programs
INNODIA	Relatives and general population	Europe	Academic sites	>4,400	Serum	RBA	AA+: 379 • 1 AA+: 6.0% • >2 AA+: 1.0% • 3 AA+: 0.9% • 4 AA+: 0.8% • ≥2 AA+: 2.6%	Of AA+ • IAA: 184 (49.9%) • GADA: 242 (65.2%) • IA-2A: 81 (21.8%) • ZnT8A: 94 (25.1%)
Bart's Oxford (BOX) Family Study	Relatives	U.K.	Diabetes clinics/ at home	6,000	Capillary blood since 2015	RBA: IAA, GADA, IA2A, ZnT8A	470 AA+: • 1 AA+: 6% • ≥2 AA+: 2%	Family members are recruited at diagnosis of a proband (<21 years old) in the study area
Type1Screen	Relatives aged 2–30 years	Australia and New Zealand	Community collection centers and in-home collection	>700	Capillary or venous blood	IAA: RBA or ADAP; GADA, IA-2A, ZNT8A, ELISA, or ADAP	AA+: 34 (5%) • 1 AA+: 13 (1.9%) • ≥2 AA+: 21 (3.9%)	Family members recruited by health professionals, emails, and social media Of AA+: • IAA 3 (9%) • GADA 25 (74%) • IA-2A 18 (53%) • ZNT8A 22 (65%)

B: General population screening programs

Program	Population screened	Location	Screening site(s)	Number screened	Screening material	Screening assay(s)	Rate(s) of positive screens	Comment(s)
Genetic prescreening with follow-up for AA								
DIPP	Age 0.25–15 years with high-risk HLA genotypes	Finland	Three university hospitals	>250,000	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A	~10% of screens with high-risk HLA ≥2 AA+: • by 2 years: 2.2% • by 5 years: 3.5% • by 15 years: 5.0%	All newborns with parental consent (~25% of birth cohort) receive cord blood HLA screening; guardians of ~19,000 at-risk infants have agreed to follow-up AA screening at 3- to 12-month intervals up to age 15 years

Continued on p. 615

Table 2—Continued

B: General population screening programs

Program	Population screened	Location	Screening site(s)	Number screened	Screening material	Screening assay(s)	Rate(s) of positive screens	Comment(s)
BABY-SCREEN	Newborns to 3 years with high-risk HLA for type 1 diabetes and/or celiac disease	Helsinki, Finland	University hospital	Target for HLA screening: 30,000; >9,000 tested	Serum	HLA genotyping followed by RBA: IAA, GADA, IA-2A, ZnT8A, tTGA	By 1 year: • 1 AA+: 5.3% • ≥2 AA+: 1.8% By 2 years: • 1 AA+: 6.5% • ≥2 AA+: 3.7%	HLA screening from cord blood followed by AA screening at age 1, 2, and 3 years Type 1 diabetes in first-degree relative in 3.1%
GPPAD	Infants <1 month of age	Germany, U.K., Poland, Belgium, and Sweden	Around delivery or PCP visits	>275,000 (1.72% first-degree relatives)	Capillary blood spots	47-SNP GRS to identify those with >10% risk of ≥2 AA+ by age 6 years	1.1% with increased genetic risk	Guardians of at-risk infants are offered participation in a primary prevention trial
PLEDGE	Age <6 years	North and South Dakota and Minnesota, U.S.	Integrated health system clinics and laboratories	Target = 33,000	Capillary blood spot for GRS, serum for AA	GRS, RBA	N/A	GRS with newborn screen or study entry; AA testing at ~2 and 5 years Uses EHR for tracking/communication
CASCADE	Age ≥1 year	Northwest U.S.	Newborn screens and elementary schools	Target = 60,000	Serum	GRS, RBA: GADA, IAA, ZnT8A, tTGA; LIPS for IA2A	N/A	Initial GRS screen, at-risk infants followed for type 1 diabetes and celiac disease
PRiMeD	Age 2–16 years	Virginia, U.S.	Pediatric clinics	3,477	Saliva for GRS, serum for AA	82-SNP GRS, RBA: IAA, GADA, IA-2A, ZnT8A	461 (1.3%) with high GRS (10× over expected) AA testing in progress	AA screening offered to those with high GRS, ≥2 AA+ invited to contact TrialNet or obtain CGM locally
Screening for AA								
Fr1da	Age 1.75–10.99 years	Bavaria, then Lower Saxony, Hamburg, Saxony, Germany	PCP clinics	>150,000	Capillary blood	ELISA: GADA, IA2A, ZnT8A/ LIPS: IAA; confirm with RBA: IAA, GADA, IA-2A, ZnT8A	≥2 AA+: 0.3%	Positive screens invited for metabolic staging by OGTT; >80% of these with stage 1

Continued on p. 616

Table 2—Continued

B: General population screening programs

Program	Population screened	Location	Screening site(s)	Number screened	Screening material	Screening assay(s)	Rate(s) of positive screens	Comment(s)
Fr1dolin	Age 2–6 years	Lower Saxony and Hamburg, Germany	PCP clinics	>15,000	Capillary blood	ELISA: GADA, IA-2A, ZnT8A; confirm with RBA: IAA, GADA, IA2A, ZnT8A	≥2 AA+: 0.35%	Combined screening for type 1 diabetes risk and familial hypercholesterolemia Positive screens invited for staging with OGTT
T1Detect (JDRF)	Age ≥1 year	Most U.S. states	At home	Up to 2,000/ month	Capillary blood spot	ADAP: GADA, IA-2A, IAA	Nonrelatives • 1 AA+: 12% • ≥2 AA+: 5.4% Relatives • 1 AA+: 12% • ≥2 AA+: 5.7%	Direct access to participants through the JDRF website Of the first 800 tests, 203 (25.4%) were from the general population
ASK	Age 1–17 years	Colorado, U.S.	PCP and hospital specialty clinics, emergency departments	25,738	Serum	RBA with ECL confirmation: IA-2A, GADA, IAA, ZnT8A, tTGA	AA+: 3.4% • ≥2 AA+: 0.52% • Single high-affinity AA+: 0.58%	Screening for type 1 diabetes, celiac disease, and SARS-CoV-2 Ab 4.84% with first-degree relative with type 1 diabetes
Screening programs in development								
T1Early	Preschool age: 3.5–4 years	U.K.	Preschool vaccination PCP visit	N/A	Capillary blood	LIPS: GADA, IA-2A, ZnT8A	N/A	Positive screens using the LIPS assay will undergo metabolic staging
ADIR	Age 9–18 months and 5 years	Israel	PCP visit with hemoglobin screening	Target of up to 50,000	Capillary or venous blood	ADAP: GADA, IA-2A, IAA	N/A	Due to start October 2021
JDRF Australia General Population Screening Pilot	Newborns, infants, and 2–6 years	Australia	Maternity hospitals, general population	Target of 3,000 in each cohort	Capillary blood and saliva	GRS, ADAP for IAA,GADA, IA-2A, ZNT8A	N/A	Starting in 2022; will compare GRS approach to cross-sectional AA screening in older children

ECL, enhanced chemiluminescence; EHR, electronic health record; LIPS, luciferase immunoprecipitation; N/A, not applicable.

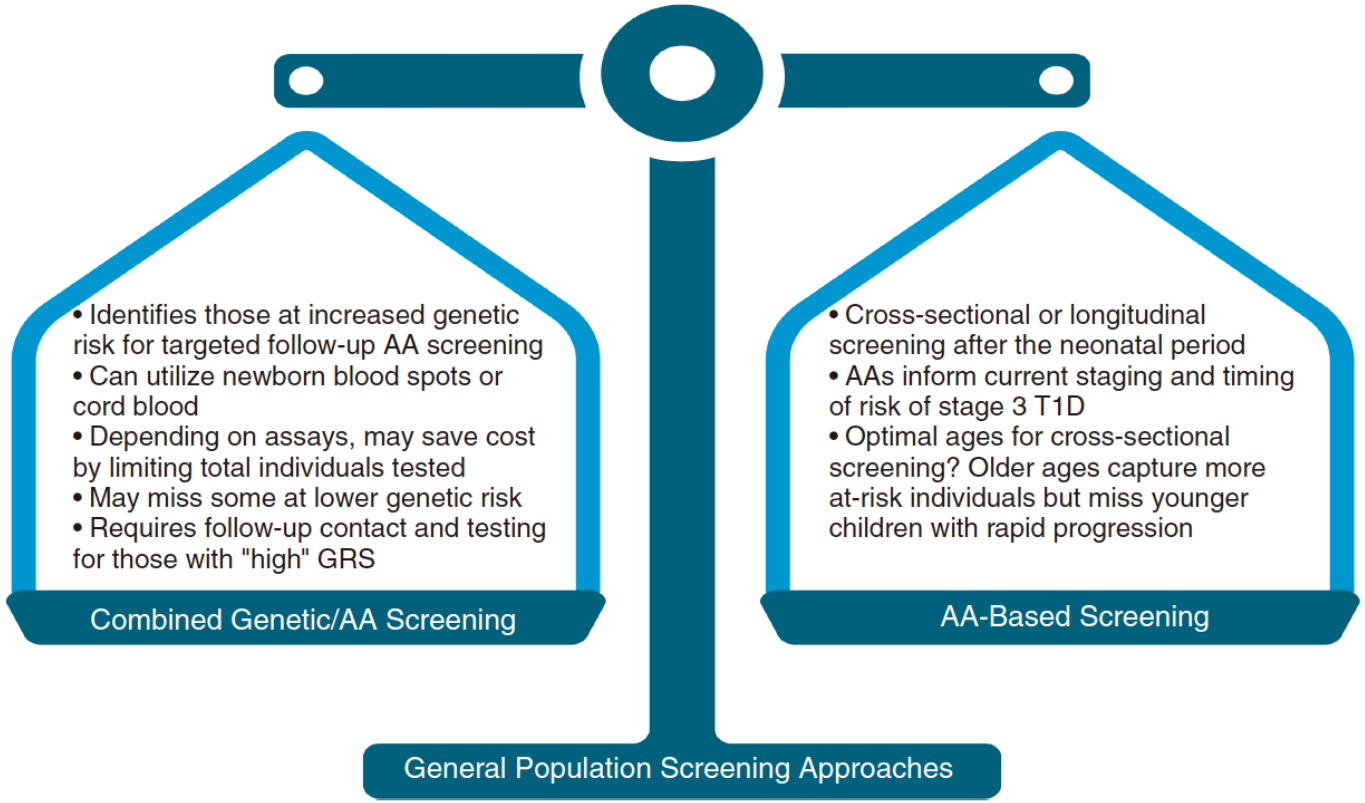


Figure 2—Considerations for approaches to general population screening: combined genetic/AA-based screening versus an AA-based approach. T1D, type 1 diabetes.

Table 4—Wilson and Jungner's guidelines for screening as applied to type 1 diabetes

Principle	Application to screening for type 1 diabetes
1. Identify an important health problem	Type 1 diabetes is one of the most common and consequential chronic illnesses of children but also affects individuals of all ages.
2. There should be an accepted treatment for the condition	Teplizumab was shown to delay the diagnosis of individuals at risk. Other agents are under evaluation.
3. Facilities for diagnosis and treatment are available	Diagnosis and treatment can be done in medical offices.
4. There should be a recognizable latent or early symptomatic period	Stages of progression of type 1 diabetes in those at genetic risk have been defined. High-risk individuals (stage 2) have a 75% risk of diagnosis within 5 years.
5. There should be a suitable test or examination 6. The test should be acceptable to the population	AAs can define risk. Newer technologies to improve prediction are under study. AAs can be measured in many laboratories.
7. The natural history of the condition should be understood	Although many specifics remain uncertain, results from immune therapy trials indicate that type 1 diabetes is due to immune-mediated killing of β-cells.
8. There should be an agreed policy on whom to treat as patients	Children and adolescents, during developmental years, have the highest unmet need.
9. The cost of case finding should be economically balanced in relation to expenditure on medical care as a whole	The lifetime costs for type 1 diabetes after onset in childhood are great, even without the additional costs associated with disease-related complications.
10. Case finding should be a continuing process	Projects across the globe are piloting strategies for case identification.

Guidelines are as described by Wilson and Jungner (64).

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An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group*

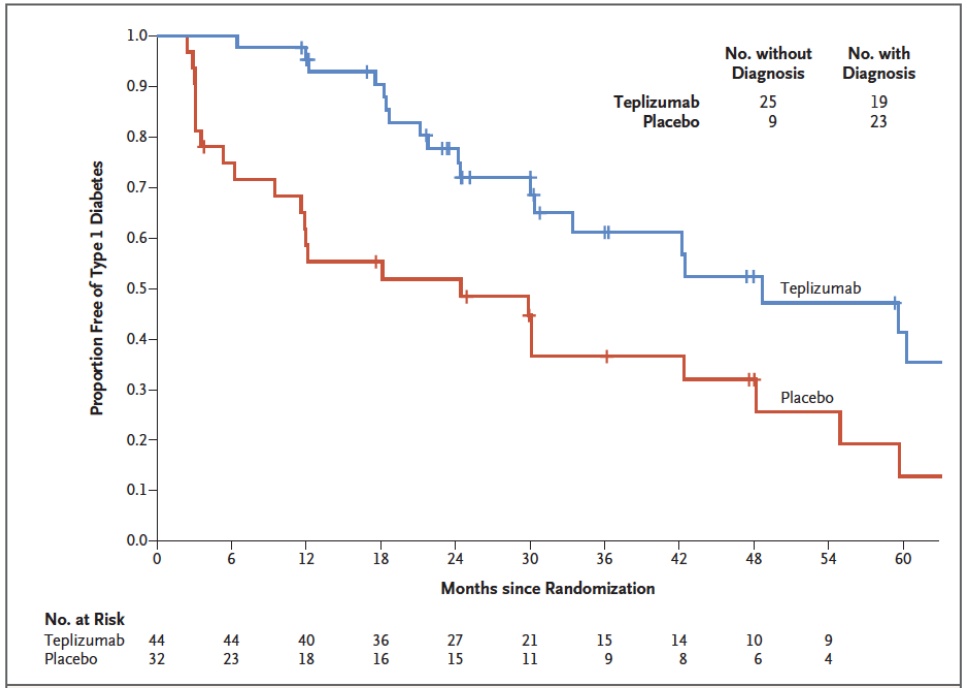

Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes.

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.

- Median time to the diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 24.4 months in the placebo group
- T1D developed in 43% of treated participants vs 72% of those who received placebo
- The hazard ratio T1D (teplizumab vs. placebo) was 0.41 (95% CI, 0.22 to 0.78; P = 0.006 by adjusted Cox proportional-hazards model
- The annualized rates of diagnosis of diabetes were 14.9% per year in the teplizumab group and 35.9% per year in the placebo group

The Impact of Team Science efforts in T1D research

- The examples of Team Science efforts described today illustrate how these have been instrumental in advancing type 1 diabetes research at multiple levels
- Further advancing prevention and treatment strategies will continue to require team science approaches and well-organized consortia, partnerships with the biomedical industry, private and governmental agencies, and participation from patients and their family members
- Collaboration and flow of communication within and across consortia is essential for progress
- Studies have advanced our ability to identify those at risk in the general population
- Implementation of screening strategies in the general population and early diagnosis have important benefits for prevention and better control of morbidities

THANK