The TEDDY study – understanding diabetes in the young by combining big data and biobanking.

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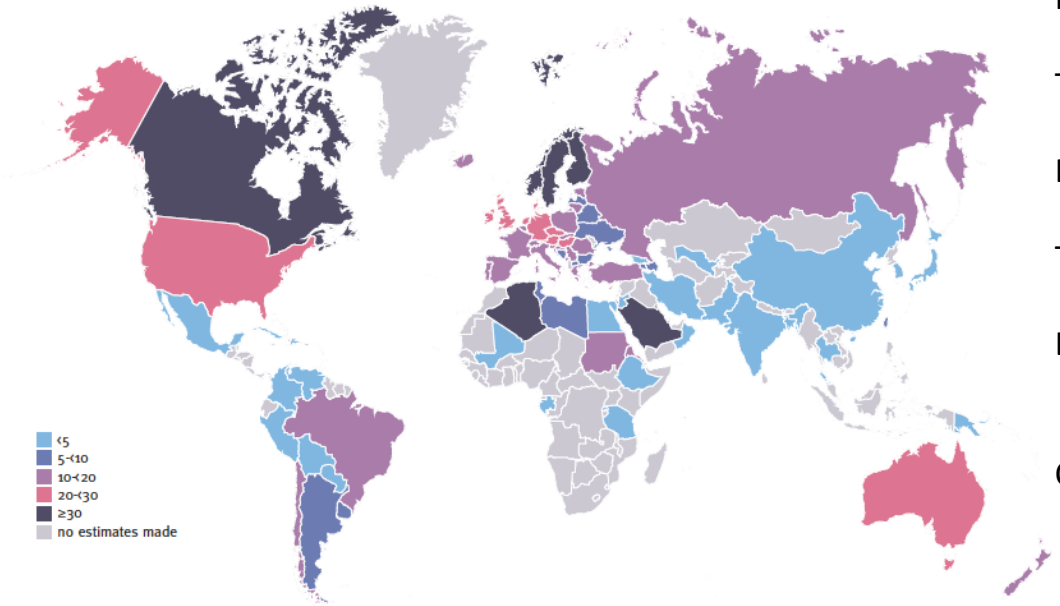
Nordic Biobank Conference 2022

Conflict of interest

Diamyd Medical AB, Stockholm, Sweden : member of the Scientific Advisory Board

Autoimmune type 1 diabetes incidence rate is increasing worldwide



Incidence rate for 1-14 year old children.

The disease may develop at any age.

Insulin dependent for life.

The prognosis is poor in developing countries.

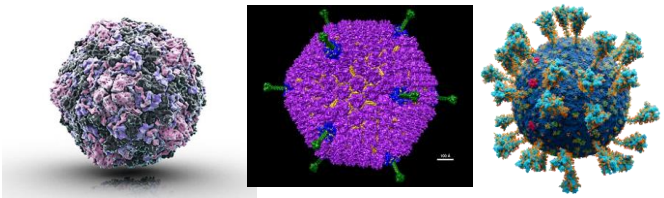
Life expectancy reduced by 10-15 years also in developed countries.

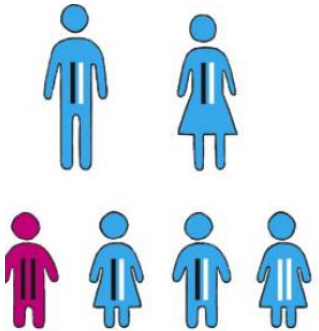
Complications are retinopathy, neuropathy, nephropathy and cardiovascular disease.

Cause and effect

Two events – one is the trigger - the other is the effect of the trigger

- ETIOLOGY - the cause or origin of disease
  - Genetic etiology
  - Environmental factors





- PATHOGENESIS – the natural progression of the disease.
- DIAGNOSIS - diabetes is a late endpoint after years of symptom-free disease eradicating the pancreatic beta cells.

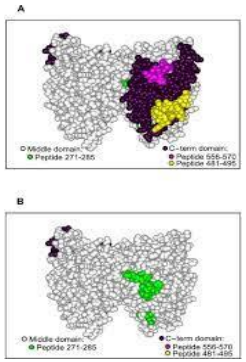
PREREQUISITE 1
GENETIC ETIOLOGY

SINCE THE 1990s:

HLA DR3-DQ2 OR DR4-DQ8 HAPLOTYPES ARE NECESSARY BUT NOT SUFFICIENT.
90% of newly diagnosed type 1 diabetes children
26% of the Scandinavian population

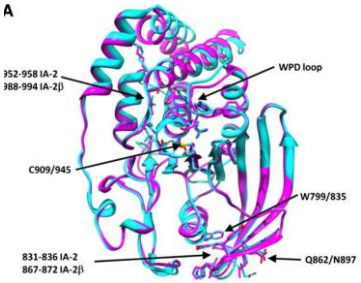
- The primary function of HLA molecules is **to present foreign antigens to elicit T helper cell responses**.
- HLA presentation of autoantigens may cause cell specific autoimmune disease.
- Self reactive CD4+, CD8+ T cells and B cells producing autoantibodies.

PREREQUISITE 2
AUTOANTIBODIES AS BIOMARKERS



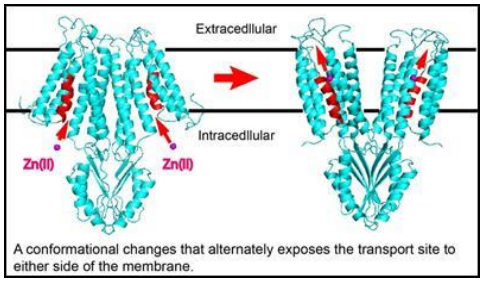
GAD65

GADA



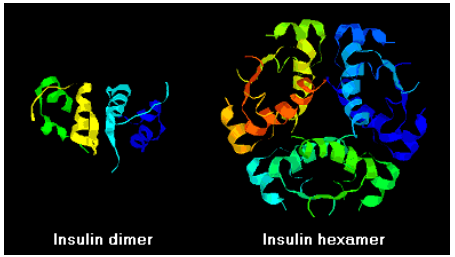
Islet Antigen-2

IA-2A



Zn Transporter 8

ZnT8A



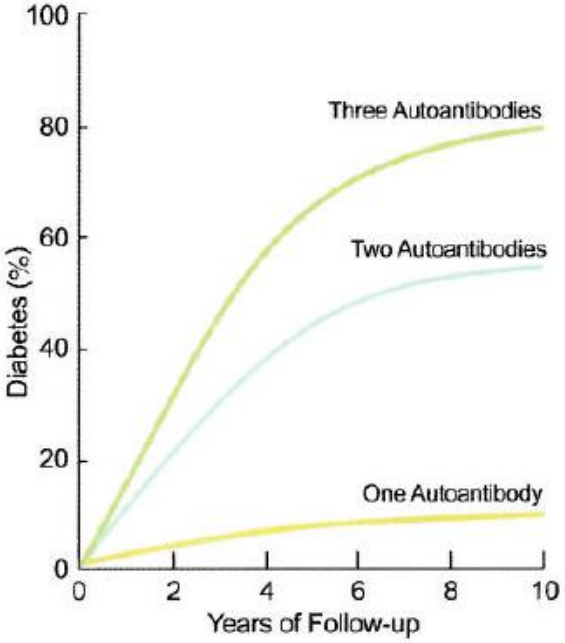
Insulin

IAA

Islet Autoantibodies as Enrichment Biomarkers for Type 1 Diabetes (T1D) Prevention Clinical Trials.
Start of public consultation November 2021.
Adopted by the Committee for Medicinal Products for Human Use March 2022.

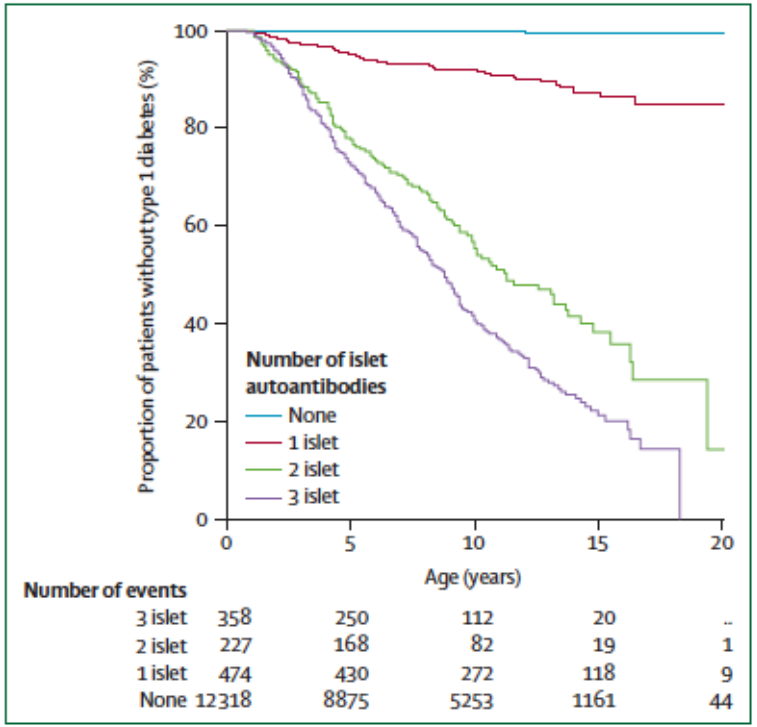
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

KNOWN SINCE THE 1990s – autoantibodies predict clinical onset of diabetes.



Notkins & Lernmark J Clin Invest 2001

SCREENING OF FIRST DEGREE RELATIVES



Ziegler et al. JAMA 2013

CHILDREN WITH DR3-DQ2, DR4-DQ8, OR BOTH, FOLLOWED FROM BIRTH

ETIOLOGY

WHAT IS THE TRIGGER OF A FIRST APPEARING AUTOANTIBODY?

THE FIRST APPEARING AUTOANTIBODY IS THE ENDPOINT
IN INVESTIGATING THE ETIOLOGY OF TYPE 1 DIABETES.

SMALLER STUDIES HAVE TRIED (DIPP, BABY DIAB, DAISY, DIPIS, DEW-IT, PANDA)
BUT DID NOT HAVE THE STATISTICAL POWER

THE TEDDY (**THE ENVIRONMENTAL TRIGGERS OF DIABETES IN THE YOUNG**)
STUDY WAS DESIGNED TO PROVIDE SUFFICIENT POWER.

Funded by:

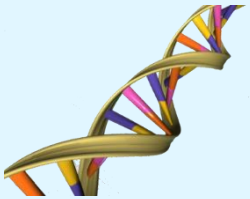
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Environmental Health Sciences (NIEHS)
- Centers for Disease Control and Prevention (CDC)
- JDRF

- Supported in part by the NIH/NCATS Clinical and Translational Science Awards to the University of Florida and the University of Colorado

Development of autoantibodies is the first primary endpoint in the TEDDY study

2004-201:
440,000 newborns screened
HLA DQ 2/2; 2/8;8/8, 4/8

Genetic susceptibility



→

Primary endpoint

Confirmed persistent islet autoimmunity:

GADA, IA-2A, IAA or ZnT8A
at least twice 3 months apart & confirmed in the second laboratory

→

Primary endpoint

Clinical diabetes

ADA / WHO

n=8667

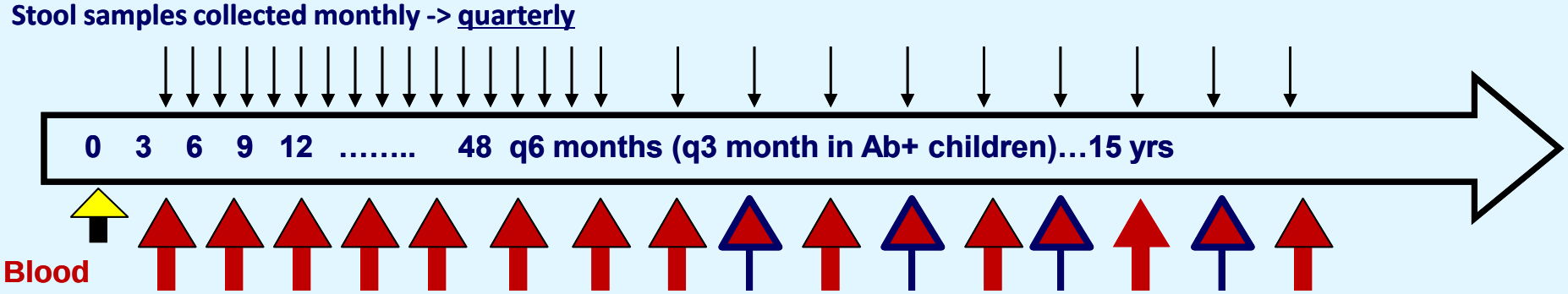
65% retention

n= 5707

Aged out:
1481 (17%)

N=867	***Nov. 2012***	***n=450***	***n=127***
	Nov. 2013	***n=520***	***n=169***
	Sep. 2015	***n=655***	***n=225***
	Mar. 2016	***n=675***	***n=241***
	Sep. 2022	***n=891***	***n=436***
Expected by age 15:		***n~800***	***n~428***

TEDDY STUDY – Methods



Clinic visits every 3 months (including ab+ children older than 4):

Blood for: GADA, IAA, IA-2A, ZnT8A; DNA, mRNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum; **urine** samples;

Nasal swabs, tap water, toenail clippings, and **salivary** cortisol.

Interviews: maternal pregnancy diet (FFQ of selected foods), infection and smoking; child's 24 hr recall, 3 day food record; negative life events, parental anxiety, depression, records of infections, medications, immunizations; family history, DNA from FDRs; Physical activity assessment; Re-enrollment of subjects lost

TEDDY – Outcome measures

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There are two primary outcome measures:

(1) the first appearance of one or more islet cell autoantibodies (GADA, IAA, IA-2A, ZnT8A), confirmed at two consecutive visits,

(2) development of T1D.

Additionally, there are two secondary outcome measures in TEDDY:

(1) celiac disease autoimmunity (CDA)(tTGA) and celiac disease (CD);

(2) Thyroid autoimmunity (TPOAb, TGAb) and autoimmune thyroid disease.

TEDDY OMICS ANALYSES AND DATA

Compressed data storage (as of October 2019): ~1 PB 10^{15}

- Activity Data – 73 variables (16 TB) 10^{12}
- Clinical Data – 9,943 variables (1.3 TB)

- Dietary Biomarkers – 42 biomarkers (10 MB) 10^{6}
- Exome chip – 641,241 variants (1 TB)
- Gene Expression – 47,231 probes (1 TB)
- HLA Sequencing – ~300 alleles (70 GB) 10^{9}
- ImmunoChip SNPs – 176,662 variants (400 GB)
- Inflammatory biomarkers – 92 proteins (3 GB)
- Metabolomics – 1,365 metabolites/lipids (105 TB)
- Microbiome/Metagenomics – 8,814 species & pathways (340 TB)
- Proteomics – 36,252 peptides (4 TB)
- RNA Sequencing – 23,000 genes (130 TB)
- Urinary Biomarkers – 41 analytes (2 MB)

- Whole Genome Sequencing – ~38 million variants (428 TB)

TEDDY – data is available to all

The TEDDY study group has published 145 peer-reviewed articles. More to come…….

Non-TEDDY investigators are beginning to publish:

- Zhang *et al.* Oklahoma University: Islet autoantibody seroconversion in type-1 diabetes is associated with metagenome-assembled genomes in infant gut microbiomes.

Nat Commun. 2022 Jun 21;13(1):3551.

OMICS data is uploaded to the NIDDK Central Repository free to download as the data has been quality controlled!

TEDDY – Biobanking

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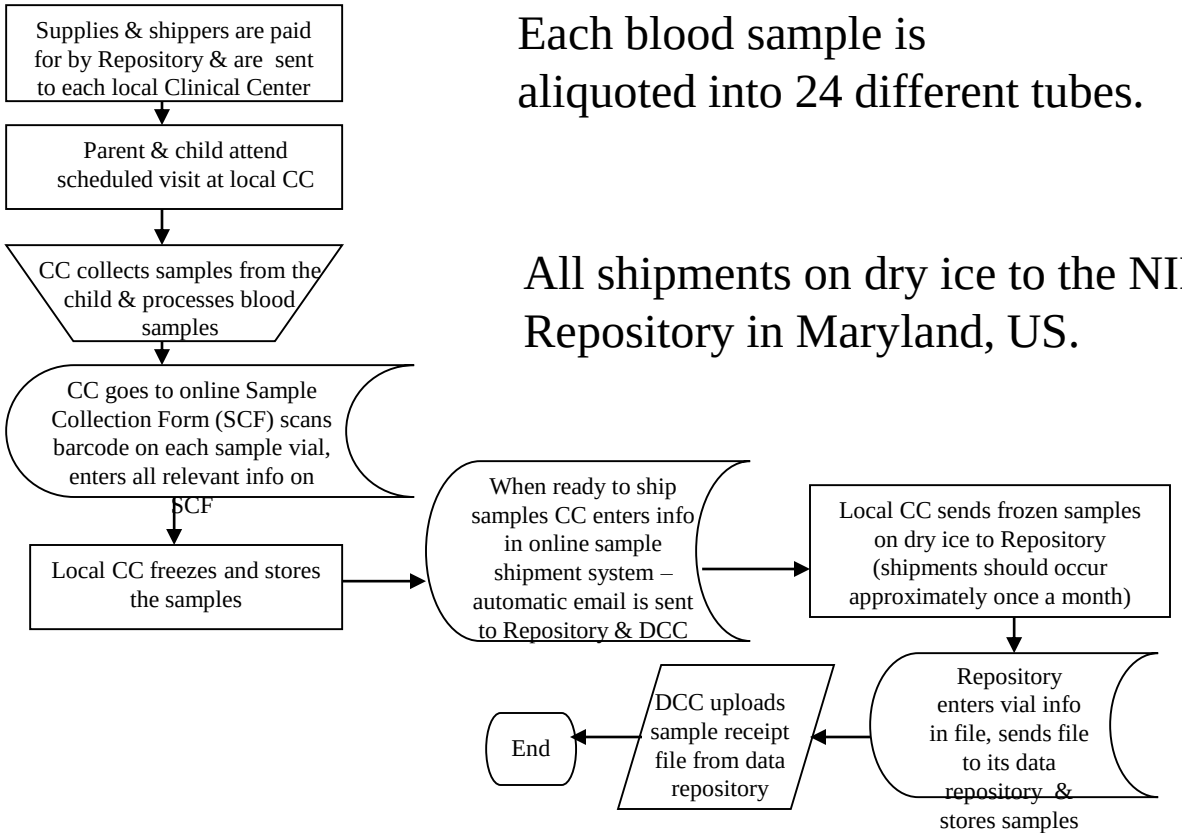
- Data request - available through: https://repository.niddk.nih.gov/studies/teddy/

- Biospecimen requests available through collaboration – ancillary investigation - with the TEDDY study: https://teddy.epi.usf.edu/research/#datacollect

Blood, Water & Toenail Samples from Local Clinical Centers to Repository



Each blood sample is aliquoted into 24 different tubes.

All shipments on dry ice to the NIDDK Central Repository in Maryland, US.

TEDDY – samples available in 2022

NORDIC Biobank Conference

• Plasma	1,728,125	Tap water	155,395
• Serum	1,175,592	Nasal Swabs	135,529
• RNA	1,124,853	RBC	113,084
• PBMC	243,825	Buffy coat	60,666
• Stool	199,035	Saliva	36,221
• Urine	179,715	Nail clipping	32,624
• DNA	173,939	Primary tooth	1, 349

These 14 examples are followed by 6 additional items.

The last TEDDY child is turning 15 years of age in March 2025.

NIDDK Central Repository

The National Institute of Diabetes and Digestive and Kidney Diseases

FISCHER BIOSERVICES
MORGANTOWN , MD

TEDDY

TEDDY NIDDK Central Repository

TEDDY
The Environmental Determinants
of Diabetes in the Young

SAMPLES ARE BEING USED!

- TEDDY NIDDK CENTRAL LABORATORIES ARE CONTACTED BY THE DATA COORDINATING CENTER (DCC) IN TAMPA, FL FOR SAMPLE RETRIEVAL. COMES AT A COST.
- WATCH OUT FOR NIH TEDDY RFA (Request For Applications)
- LATEST RFA: **RFA-DK-22-021**

https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-021.html

- **Collaborative Research Using Biosamples from TEDDY**
- **Foreign applicants are welcome**

TEDDY
The Environmental Determinants of Diabetes in the Young

TEDDY – what have we learned?

- Insulin autoantibodies–IAA-appeared during the first two years of life, may be associated with enterovirus infection presence and persistence.
- GAD65 autoantibodies–GADA –appeared later and attainted a steady incidence rate –signals indicating an association with viral infections require more study to elucidate.
- About 60% of first autoantibody positive children developed a second autoantibody within one year.
- About 70% of children with two or more autoantibodies progress to clinical onset within 10 years.
- Similar pattern of disease etiology and pathogenesis for Celiac disease and autoimmune thyroid disease.

Thank you!

TEDDY

The Environmental Determinants
of Diabetes in the Young

Thank you!

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