UPDATES ON SCREENING AND PREVENTION EFFORTS IN T1D

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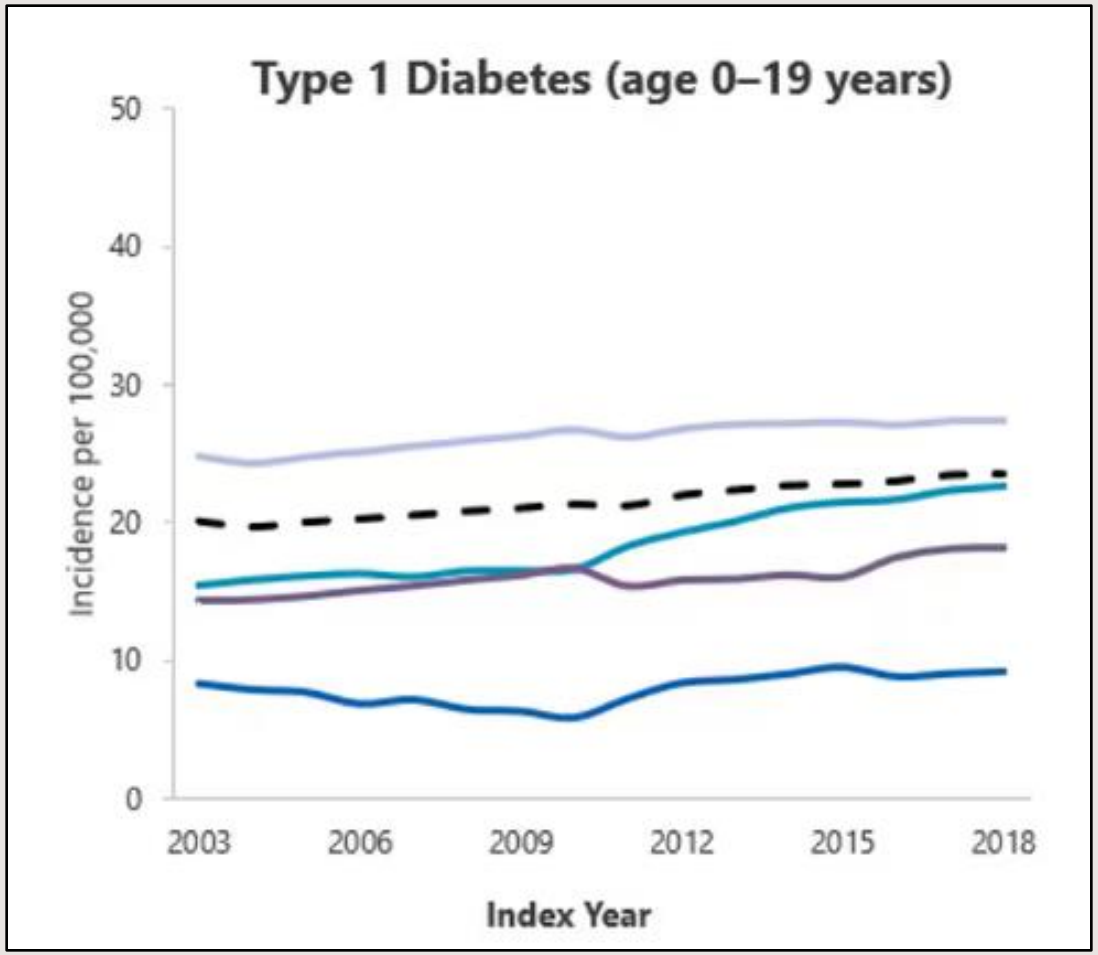
LEARNING OBJECTIVES

- Review the incidence and prevalence of T1D in the U.S. and globally
- Understand the genetic and environmental risk factors for type 1 diabetes (T1D)
- Know the risk of T1D for the general population and those with a family history
- Learn the proposed nomenclature for T1D disease “staging”
- Review available screening methods for T1D risk
- Learn about the FDA-approved medication, teplizumab, for delaying T1D

T1D EPIDEMIOLOGY



Estimated current U.S. T1D population:

- 72% NHW
- 9.3% NHB
- 15.7% Hispanic
- 2.4% Asian

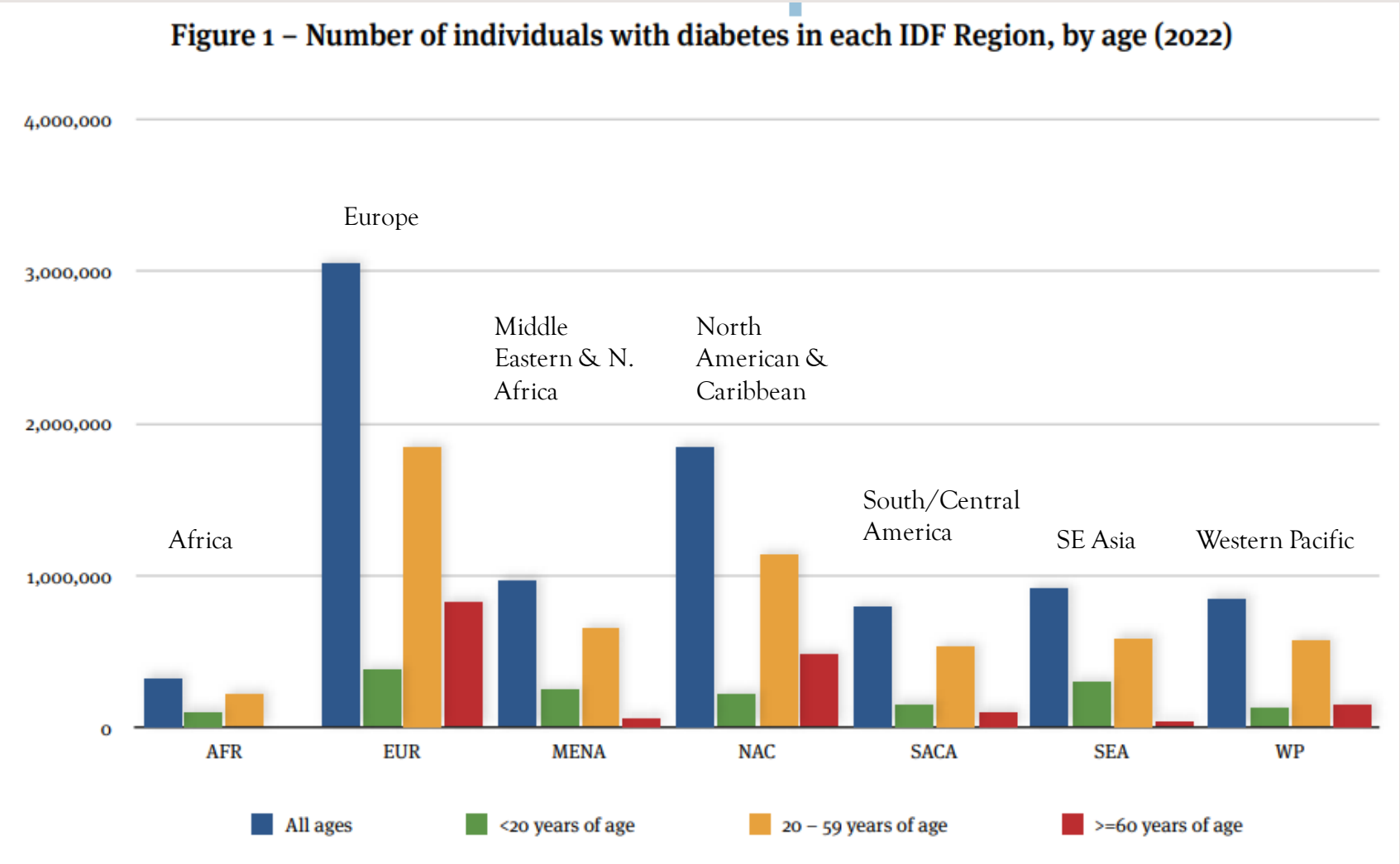
- Age at diagnosis follows a bimodal distribution
- Only autoimmune disease with slight male predominance

www.cdc.gov/diabetes/health-equity/diabetes-by-the-numbers.html; Lawrence et al, JAMA 2021; Dabelea JAMA 2014

T1D IS A GLOBAL CONDITION

IDF Diabetes Atlas

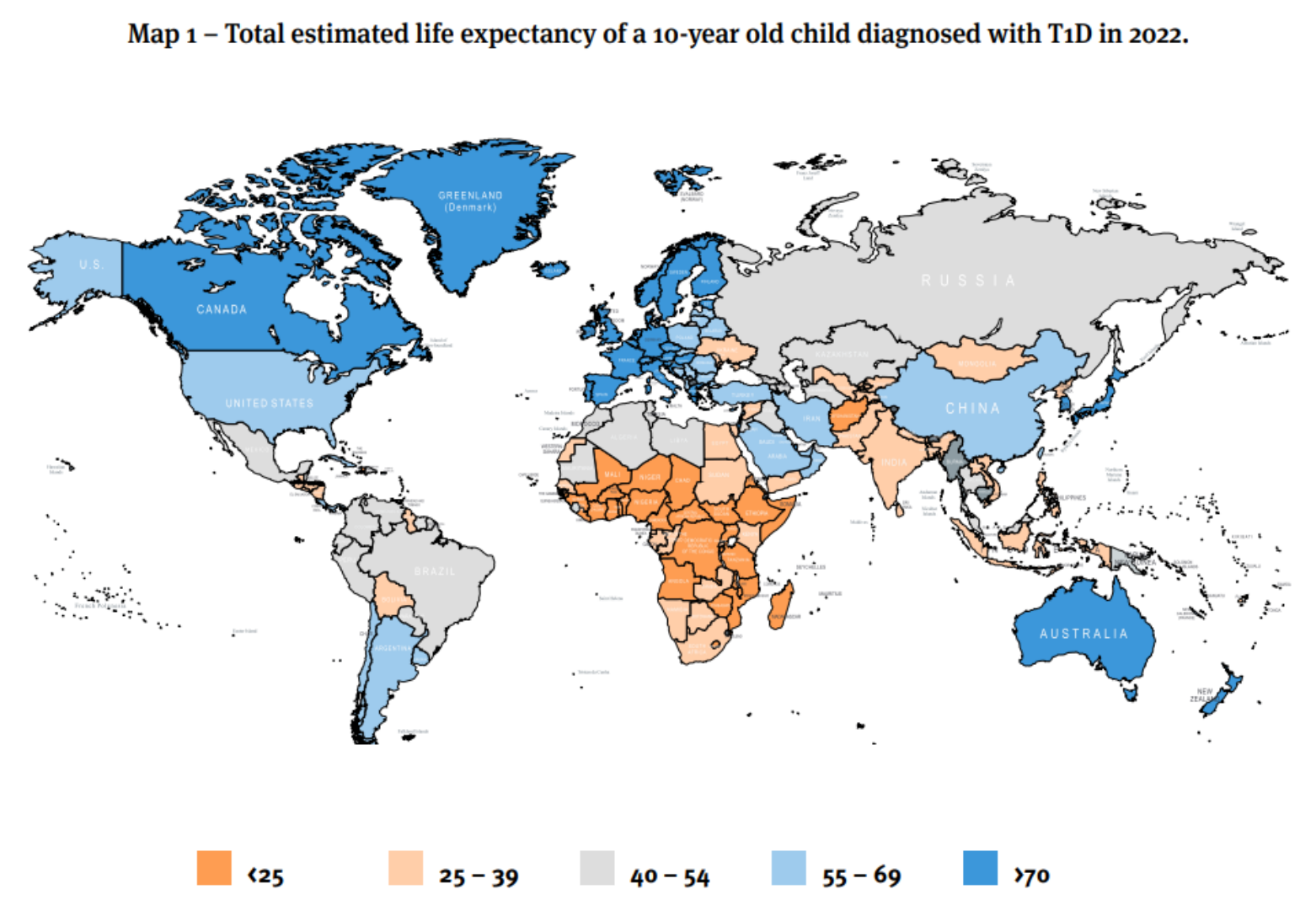
In 2022, 8.75 million individuals were living with T1D worldwide



LIFE EXPECTANCY VARIES GLOBALLY

Within the U.S. and elsewhere, T1D outcomes follow a social gradient, based on "**social determinants of health**":

- Race/ethnicity
- Insurance status
- Income level
- Health literacy
- Housing/food stability
- Social cohesion



IDF Diabetes atlas: https://diabetesatlas.org/idfawp/resource-files/2022/12/IDF-T1D-Index-Report.pdf

GENETIC RISK + ENVIRONMENTAL TRIGGERS

- Genetic risk (or protection) most strongly resides in the **class II HLA genes**
- Importance of HLA haplotype diminishes with age and in non-Caucasian populations
- Family-based and genome-wide association studies have identified > 70 other risk loci, which appear to have an additive effect on T1D risk

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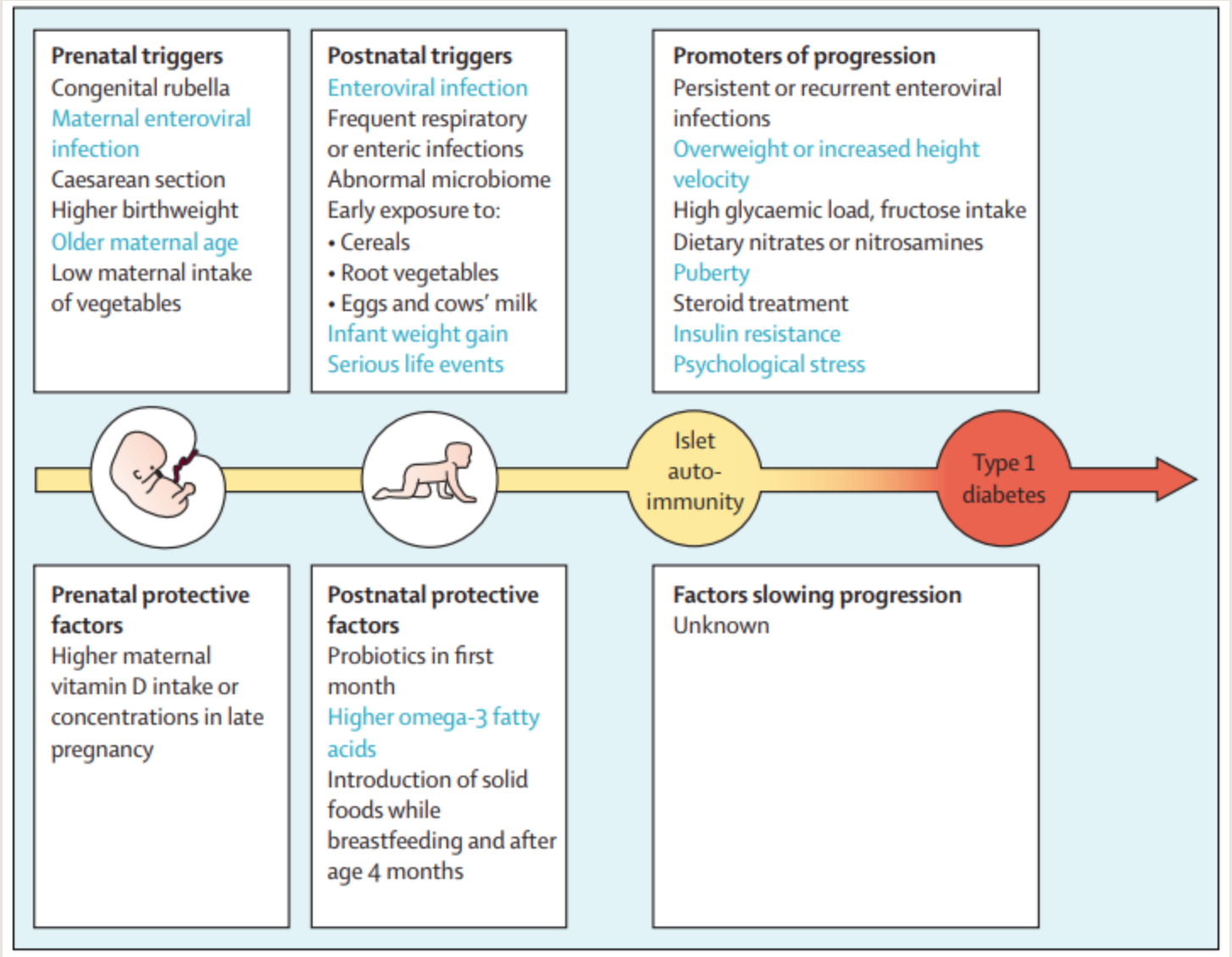


Rewers, Lancet 2016

T1D RISK STRATIFICATION BY FAMILY HISTORY AND GENETIC SUSCEPTIBILITY

Population	Risk of T1D (%)
Newborns (European/U.S. population)	0.4
Newborns with HLA high-risk genotypes*	4
Newborn first-degree relatives of people with T1D	5
First-degree relative + HLA high-risk genotype	10-20
Multiple affected first-degree relatives	20-25
Identical twin of a person with T1D	30-70
Multiple affected first-degree relatives + HLA high-risk genotype	50

*Most HLA at-risk individuals never develop T1D; **diabetes autoantibodies** are much better at detecting T1D risk

Adapted from Insel RA et al, Diabetes Care, 2015

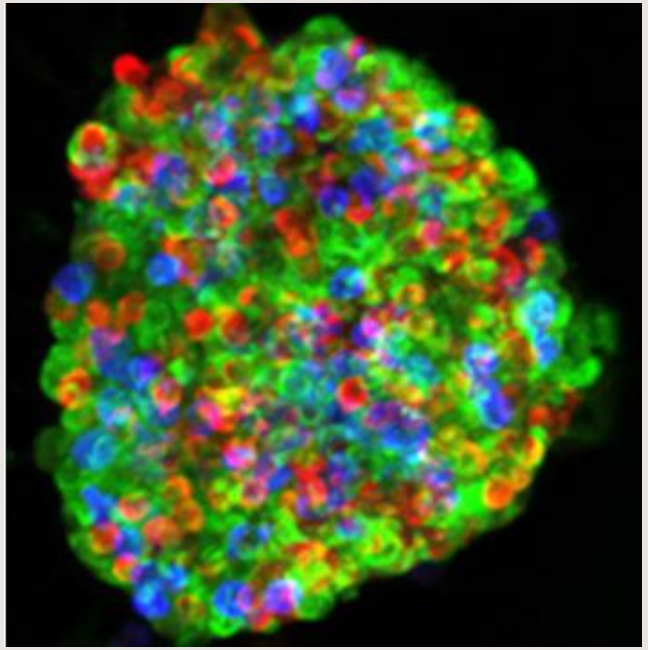
T1D RISK

88% of newly diagnosed persons with T1D have NO family history

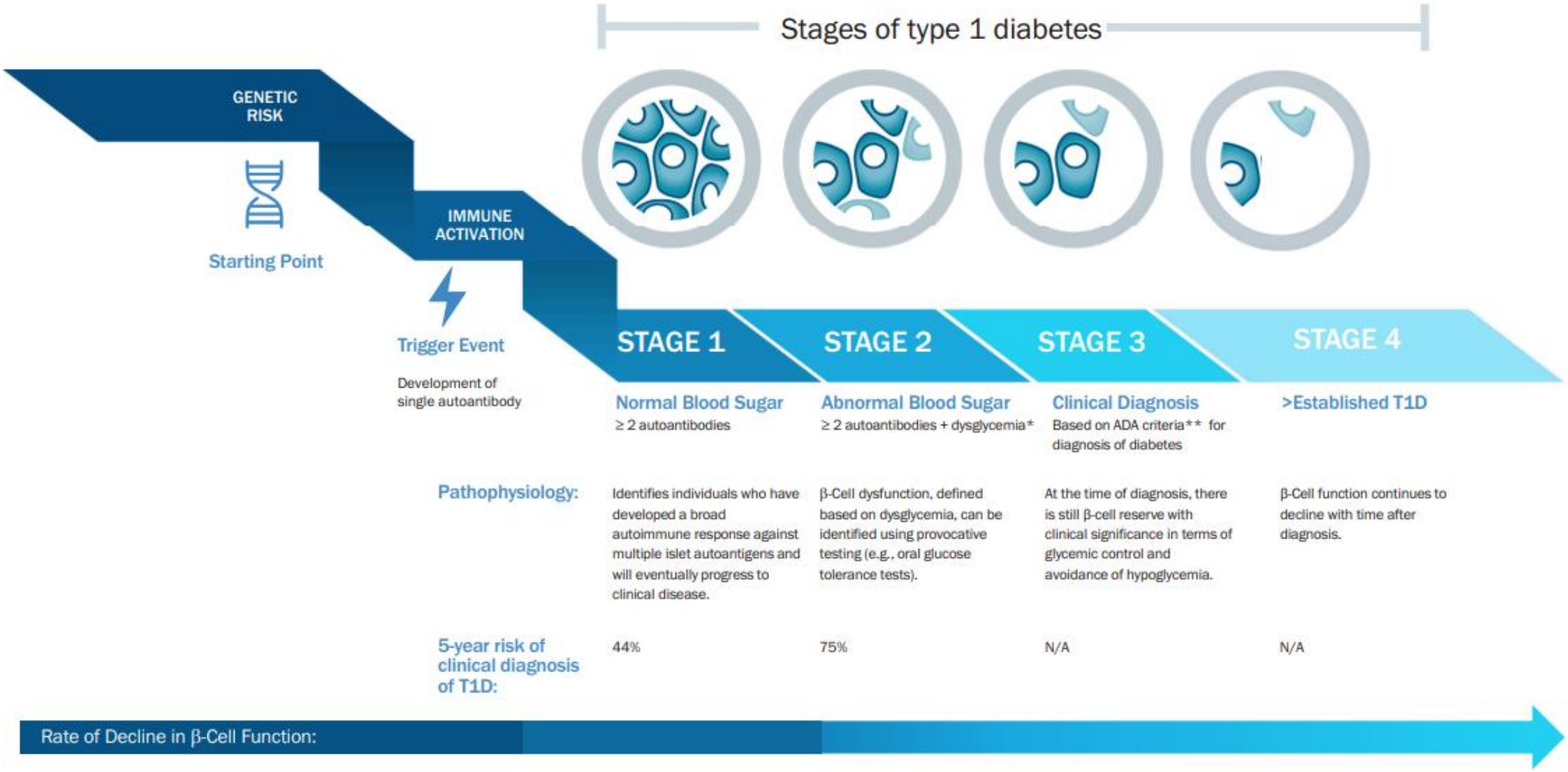
- **First-degree relatives of individuals living with T1D have a 10-15-fold increased risk compared to those without a relative with T1D**
  - Full siblings: 6-7% lifetime risk
  - Offspring of mothers: 1.3-4%
  - Offspring of fathers: 6-9%

DIABETES AUTOANTIBODIES

- Released by the inflamed islet cells, detectable in the blood
- "Seroconversion" proceed symptomatic T1D by years
- Rate of progression to symptomatic T1D can be predicted by:
  - Age at seroconversion (progression more common if seroconversion occurs before age 5 yrs)
  - Number of AAs present
    - **85% of people with 1 AA do not progress within 10 yrs**
    - **If ≥ 2 autoantibodies, lifetime risk of T1D > 85%**
  - Titer (the higher the titer, the worse)
  - Type (ZnT8A and IA2A are associated with faster progression)



- Insulin autoantibody (IAA)
- Glutamic acid decarboxylase autoantibody (GAD65A)
- Zinc transporter 8 autoantibody (ZnT8A)
- Islet cell autoantibody (ICA512A or IA2A)



Sims EK, Diabetes 2022

Stage 1

Two or more autoantibodies can be identified, but blood sugar levels are normal, and the person has no symptoms.

Stage 2

Two or more autoantibodies can be identified, and blood sugar levels are not normal, but most people still have no symptoms.

Stage 3

Two or more autoantibodies can be identified, blood sugar levels are high, and the person typically has symptoms.

Symptoms of type 1 diabetes include:

Frequent Urination

Extreme Thirst

Dry Mouth

Fatigue and Weakness

Increased Appetite

Unexplained Weight Loss

Slow Healing Cuts

WHY EARLY DETECTION?

- Enables access to medical expertise to discuss results and provide clinical education and monitoring strategies
- Reduce incidence of diabetic ketoacidosis (DKA) at diagnosis
- Identify individuals for T1D prevention or disease modifying therapy research studies
- Peace of mind (95% will be found to not be at risk!)

REDUCE DKA AT DIAGNOSIS

- 25-62% of youth in the U.S. experience DKA during their T1D diagnosis
  - *negatively affects cognitive function and alters brain development*
  - *portends higher overall lifetime glucose levels*

Mild or Moderate DKA

HbA1c is 0.87% higher on average

Severe DKA

HbA1c is 1.35% higher on average

- Early identification reduces DKA at diagnosis to 4-6%, with potential impact to reduce HbA1c and long-term complication risk

Duca LM, 2017; Semenkovich, 2016; Ghetti, 2020; Aye 2019; Alonso GT, 2020; Winkler C, 2012

RISKS OF EARLY DETECTION

- Risk of negative psychological impact
  - *Anxiety and worry are commonly reported*
  - *Diabetes risk is difficult to effectively communicate (predictions, probability, etc)*
- Post-diagnosis adjustment for participants diagnosed through screening and monitoring compares favorably to those diagnosed with clinical symptoms
- Individuals and families may elect to not pursue further monitoring and/or prevention trials/therapies (perceive risk exceeds benefit) so benefits of screening are lost

Johnson SB, Curr Diab Rep, 2011; Smith LB, Ped Diabetes, 2018; Sims EK, Diabetes Care 2019

T1D RISK ASSESSMENT IS BASED ON DECADES OF RESEARCH AND REMAINS ON-GOING

Birth (Universal) Cohorts vs Targeted Screening

BIRTH COHORTS

- Based on genetic risk score (high risk HLA alleles)
- **TEDDY (The Environmental Determinants of Diabetes in the Young)**
  - *>8,000 HLA genetically at-risk newborns, 90% without a known relative with T1D*
  - *Followed for 15 years for appearance of AAs or T1D diagnosis*
  - *Environmental factors that may contribute to disease are closely monitored*
- **DIPP (The Type 1 Diabetes Prediction and Prevention Study)**
  - *>250,000 infants screened in Finnish hospitals since 1994, capturing 25% of all newborns in Finland*
  - *10% screened by cord blood found to have HLA-conferred susceptibility for T1D*
  - *Followed for 15 years for T1D diagnosis*
- **BABYSCREEN (The Newborn Screening for Genetic Susceptibility to T1D and Celiac Disease and Prospective Follow-up Study)**
  - *>9,000 screened for HLA alleles conferring high risk for T1D and celiac disease*
  - *Followed for 3 years with AAs*

Steck AK, Diabetes Care 2015; Pollanen PM, JCEM 2020

U.S. GENERAL POPULATION SCREENING

Program	Population screened	Location	Screening site(s)	Number screened	Screening material	Screening assay(s)	Rate(s) of positive screens	Comment(s)
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

GRS = Genetic Risk Score, incorporating multiple genetic loci
RBA = radiobinding assays for autoantibodies

Sims EK, Diabetes 2022

TRIALNET PATHWAY TO PREVENTION

- Initiated in 2004, screening 1st and 2nd degree relatives of persons with T1D
- In 2022, incorporated screening of at-risk individuals (AA+) from the general population
- Goal: identify participants for clinical trials
- > 220,000 relatives screened to date
- ~5% relatives have at least 1 autoantibody; 50% of which have multiple autoantibodies
- Children's Wisconsin/MCW is an affiliate site of Indiana University

AUTOANTIBODY SCREENING AFTER THE NEWBORN PERIOD: IS UNIVERSAL SCREENING COST-EFFECTIVE?

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
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

LESSONS LEARNED ON **WHEN** TO SCREEN

- Peak rates of seroconversion occur at age 1.5 years, with most seroconverting by 2-3 years of age
- Most genetically high-risk young children who convert from single to multiple autoantibodies do so within 2 years of initial seroconversion
- Possible Take Home Autoantibody Screening Strategies:
  - *Initial screen around 2-3 years of age*
  - *In those with single autoantibody positivity, rescreen 2-3 years later (~ 5-7 years of age)*
- No consensus on frequency of re-screening individuals with negative autoantibodies

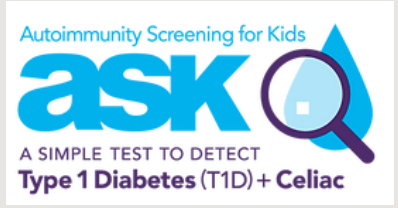
Parikka V, Diabetologia 2012; Chmiel R, Diabetologia 2015; Bonfacio, Diabetes Care, 2021

AVAILABLE AA SCREENING METHODS

- **Commercial Lab (Quest, Mayo, LabCorp)**, using insurance
  - *Quest Laboratories: IA-2, GADA, and IAA panel (test code 10584) + ZnT8A (test code 93022)*
- **Enable Biosciences** (type1testing.enablebiosciences.com)
  - *≥ 1 yr, dry blood spot testing*
  - *Tests for GADA, IAA, and IA2A (detected or not detected, no titer)*
- **TrialNet Pathway to Prevention** (trialnet.org)

  - *≥ 2.5 - 45 yrs with family history, on-line consent and either home capillary test kit or take venous sample kit to Quest or LabCorp*
  - *GADA and IAA with expansion to IA2A and ZnT8A if either are positive*
  - *If negative, cannot be screened again; If 1 AA, can be rescreened in 1 yr; If 2+ AA, can have an OGTT/HbA1c*
- **ASK (Autoimmunity Screening for Kids)** (askhealth.org)

  - *Age 1-17, on-line consent, at-home screening kit (finger poke)*
  - *GADA, IAA, IA2A, ZnT8A + tissue transglutaminase IgA*



MANAGEMENT OF SCREENING RESULTS

# of positive autoantibodies	Action
0	• If < 3 yrs, repeat autoantibody screen in 2-3 years • If > 3 yrs, rescreen around 11 years of age • **STOP if no autoantibody after 13 years old**
1	• Obtain glucose and HbA1c • Assure all 4 autoantibodies are checked if not done so with screening modality • Consider enrollment into TrialNet Pathway to Prevention • **Retest annually; if no more autoantibodies within 4 years, STOP testing**
≥2	• Obtain glucose and HbA1c • Assure all 4 autoantibodies are checked if not done so with screening modality • Referral to a local diabetologist for counseling and diabetes staging • If no local resources or poor insurance coverage, recommend enrollment into TrialNet • Provide education about symptoms of hyperglycemia

DIABETES STAGING

- For those with ≥ 2 autoantibodies, risk depends on whether dysglycemia is present or not
- Oral glucose tolerance test (OGTT) or HbA1c can be done clinically or through TrialNet Pathway to Prevention
- No standards for optimal and most cost-effective metabolic follow-up

Glucose tolerance	Risk	Action
Normal **(Stage 1)**	• **44% 5-year risk** • >85% lifetime risk	• Repeat OGTT in 6 months, then annually (clinically or TrialNet) • Discuss symptoms of hyperglycemia, when to call
Intolerant/ pre-diabetes **(Stage 2)**	• **75% 5-year risk** • >85% lifetime risk	• Glucometer with fasting and 2-hr post-prandial glucose (infrequently) • Discuss symptoms of hyperglycemia, when to call • OGTT every 6 months (clinically or TrialNet) • Discuss **teplizumab** or other active prevention trials

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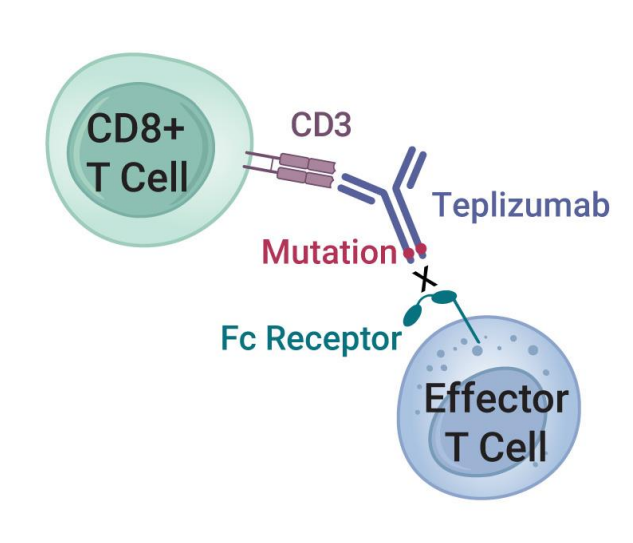
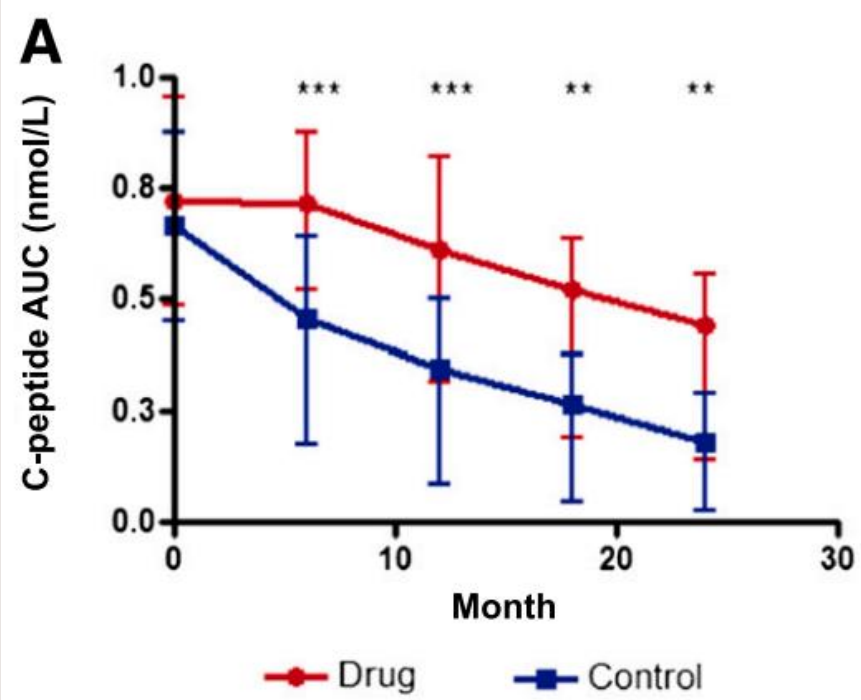
An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

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*

TEPLIZUMAB ("TZIELD"): BACKGROUND

- Anti-CD3 monoclonal antibodies that modify CD8+ T lymphocytes
- Previously shown to reduce the loss of C-peptide 2 years after treatment in new onset T1D





Herold KC, Diabetes 2013

TEPLIZUMAB: STUDY DESIGN

- Participants identified through TrialNet Pathway to Prevention
- Conducted July 2011 – Nov 2018 in US, Canada, Australia, Germany
- ≥ 8 years old with ≥ 2 diabetes AA x 2 samples within 6 months
- Oral glucose tolerance test confirmed Stage 2 T1D
- 14-day course of daily IV teplizumab or saline (placebo)
  - *Increasing dose course days 0-3, then full dose days 4-13*
- Primary endpoint: elapsed time from randomization to clinical diagnosis of diabetes
- OGTTs performed at 3 and 6 months and every 6 months thereafter

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Teplizumab (N=44)	Placebo (N=32)
Age — yr		
Median (IQR)	14 (12–22)	13 (11–16)
Range	8.5–49.5	8.6–45.0
Age <18 yr — no. (%)	29 (66)	26 (81)
Male sex — %	57	53
Relationship to person with type 1 diabetes — no. (%)		
Sibling†	28 (64)	16 (50)
Offspring	6 (14)	6 (19)
Parent	6 (14)	3 (9)
Sibling and another first-degree relative	2 (5)	3 (9)
Second-degree relative	2 (5)	3 (9)
Third-degree relative or further removed	0	1 (3)
Autoantibodies — no. of participants positive (%)‡		
Anti-GAD65, harmonized	40 (91)	28 (88)
Micro insulin	20 (45)	11 (34)
Anti–IA-2, harmonized	27 (61)	24 (75)
ICA	29 (66)	28 (88)
Anti-ZnT8	32 (73)	24 (75)
Median glycated hemoglobin level (IQR) — %	5.2 (4.9–5.4)	5.3 (5.1–5.4)

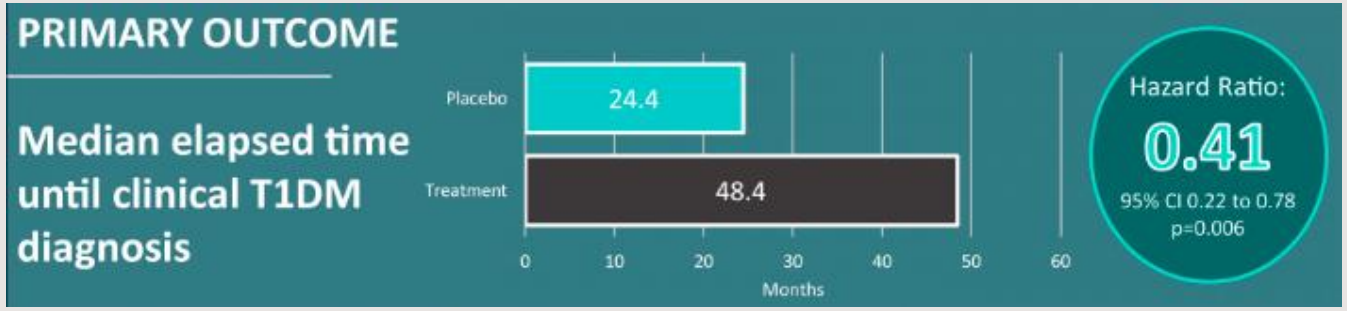
- Median follow-up duration was 745 days (range, 74-2683)
- T1D was diagnosed in 42 participants (55%)

TEPLIZUMAB: ADVERSE EVENTS

- Lymphopenia:
  - *Lymphocyte count decreased to a nadir on day 5 and resolved in all but 1 by day 45*
- Spontaneously resolving rash occurred in 36% teplizumab participants
- Rates of infection similar in both groups
- Cytokine release syndrome is a **rare** but significant concern (fatigue, fever, nausea, headache, myalgia, arthralgia)
- Teplizumab caused EBV reactivation in 8 of the 16 patients with EBV antibodies at entry (mild URTI Sx)

TEPLIZUMAB SIGNIFICANTLY DELAYED PROGRESSION TO STAGE 3 DIABETES

- Annualized rate of T1D diagnosis 14.9% in teplizumab vs 35.9% in placebo group



- Largest effect of treatment was found in 1st year (7% teplizumab group diagnosed vs 44% placebo within 12 months)

FDA APPROVAL: TZIELD

- After 3-year process, TZIELD received FDA approval on 11/17/22
- Approval met with flurry of phone calls from diabetes clinic patients and families
- Mixed thoughts on the clinical importance of this therapy among providers and famlies
  - *Risk vs benefit assessment must be made by each family/patient, with best information possible from a knowledgeable provider*
- First therapy to delay T1D is a game-changer and 1st step towards complete prevention! **We are not stopping here**.
- Moves diabetologists into the world of disease-modifying therapies

TEPLIZUMAB: TREATMENT COURSE

- Daily intravenous infusion x 14 days (including the weekend!)
- Children's Wisconsin developed a therapy plan Spring 2023, aligned with many other institutions
- Before infusions start, must assure no active infections or illnesses
- Initial infusions in the Children's Wisconsin Infusion Clinic for close supervision/monitoring, then transfer care to an outpatient infusion center or home nursing
- Close lab monitoring required
- Pre-treatment with acetaminophen or ibuprofen, ondansetron, and diphenhydramine

POST-TEPLIZUMAB FOLLOW-UP

- Hopefully this phase goes on for a long, long time!
- However, at increased risk of progressing to Stage 3 T1D
- Provide patient with glucometer for testing periodically or PRN symptoms
- Contact clinic if fasting POC glucose consistently ≥ 126 or random > 200 mg/dL
- Follow-up in CW Diabetes Clinic at 3 months, 6 months, 12 and 24 months; then annually (?)
  - *HbA1c, POC glucose values, and symptoms*

ONGOING PREVENTION TRIALS

- TrialNet: ATG Prevention Study (STOP-T1D)
  - Randomized 1:1 placebo-controlled clinical trial of low dose of the immunotherapy drug anti-thymocyte globulin (ATG) in Stage 2 diabetes
  - Ages 12-35 years
- Clinicaltrials.gov
- JDRF.org/clinicaltrials

POST-TZIELD APPROVAL EFFORTS

- JDRF launched T1Detect program
- Education and awareness program on T1D risk screening and monitoring
  - Goal: global universal screening
  - Immediate goal: expand familial screening
- Help people understand why screening matters, how to get screened, and what to do after they are screened

https://www.jdrf.org/t1d-resources/t1detect/

Children's Wisconsin (V)EST1D Clinic

- Children's Wisconsin Diabetes Program launched the (Very) Early Stage Type 1 Diabetes Clinic
- Moving from research-based screening to clinical screening strategies and management
- Clinic for those with Stage 1 or Stage 2 T1D, focused on counseling, education, and monitoring for T1D progression
  - *Ordering oral glucose tolerance tests, HbA1c, and repeat diabetes autoantibodies*
  - *Ordering testing supplies PRN*
  - *Establishes the at-risk child into the CW Diabetes Clinic program*
- Developing educational material for primary care providers and diabetes care providers on screening and interpretation of diabetes autoantibody results

CHILDREN'S WISCONSIN/T1DETECT PILOT

Children's Wisconsin
Kids deserve the best.

- Screening of family members should be a routine part of outpatient diabetes care, delivered by knowledgeable, trusted, and compassionate diabetes care team members
- **Clinical implementation pilot to integrate family-based autoantibody screening (Enable Biosciences dry blood spot testing kit) into our routine diabetes clinical care services**
- **Phase 1**: diabetes care provider education
- **Phase 2**: family outreach/education (Milwaukee and Kenosha clinics first)
- **Phase 3**: implementation (up to 500 kits)
  - Screening Days
  - Rolling in-clinic screening
- **Phase 4**: sustainability (workflow, clinical billing, reporting/managing results)

OTHER T1DETECT INITIATIVES

- **Community education**
- **Pilots to reach historically underrepresented groups**
- **Clinical Trial Education Program**
  - 0.2% of patients are referred to research
  - Health care providers rarely refer due to inability to access clinical trial information, lack of time to evaluate and confidently discuss clinical trial options
  - Proximity to research activity and previous involvement in research positively correlate with research referrals
  - **Jdrf.org/clinicaltrials**
- **Participant Advisory Council**
  - Volunteers to inform study design

TAKE-HOME POINTS

- Individuals with a family member with T1D have a 10-15-fold increased risk of developing T1D
- Screening reduces risk of DKA and opens doors for monitoring and preventive therapies/trials
- Autoantibody screening can be done several ways (TrialNet, ASK, Enable Biosciences, commercial laboratory testing)
- Stage 1 vs Stage 2 assessment requires dysglycemia testing and can be done through TrialNet or clinically
- Teplizumab is FDA approved to delay T1D in those aged 8+ with Stage 2 diabetes – a critical and important first step in full prevention of T1D!
- Everything discussed in this talk is based on individuals participating in clinical trials – never underestimate the power of research participation!!

THANK YOU!

- Children's Wisconsin Diabetes Program
  - *Milwaukee*
  - *Appleton*
  - *New Berlin*
  - *Kenosha*
- Diabetes Leadership Team (Jackie Allen, Chelsey Thompson)
- University of Wisconsin (American Family) Diabetes Team
- Cabrera Clinical/Translational Type 1 Diabetes Team
- Participants and their families in our own clinical trials – THANK YOU!
- Funding: JDRF, ADA, NIH, Children's Foundation