Type 1 Diabetes Mellitus: Diagnosis and Aggressive Management

Erica Kretchman DO, FACE

ACOi 2023 October 11-14
Tampa • Hybrid

Objective

- Discuss the stages of Type 1 Diabetes Mellitus
- Review use of teplizumab-mzwv new medical therapy to delay the onset of Type 1 Diabetes Mellitus
- Discuss how technology can impact the management of Type 1 Diabetes Mellitus

Conflicts of Interest

- Speaker: Novo Nordisk, Lilly, Boehringer Ingelheim, Mannkind, Medtronic, Abbott, AstraZenica
- Research: Novo Nordisk
- These have no impact on today's presentation

Diabetes Classification

- Type 1 diabetes (T1D) is characterized by marked insulin deficiency in the presence of hyperglycemia and positive autoantibody tests to glutamic acid decarboxylase (GAD65), pancreatic islet b cells (tyrosine phosphatase IA-2), and IA-2b zinc transporter (ZnT8), and/or insulin. The presence of immune markers and clinical presentation are needed to establish to establish the correct diagnosis and to distinguish between T1D and type 2 diabetes (T2D) in children or adults, as well as to determine appropriate treatment.

T1D is a Growing Problem

- In 2019, approximately **1.9 million** Americans were living with T1D[2]
- An estimated **300,000** people in the US are at risk for Stage 3 (clinical) T1D[3],*

Approximately **64,000** people are diagnosed with T1D each year[4]

T1D incidence **is increasing**[5]

Rate of increase:

White……..0.7%
Black……..2.7%
Hispanic …….. 4.0%
Asian/Pacific…….4.0%
Islander `

Overall increase 2% per year

Although type 1 diabetes can develop at any age, it is **one of the most common chronic childhood diseases**[1]

*Individuals with stage 1 or 2 T1D.

1. Scheiner G, et al. *ADCES Pract.* 2022;10(5):20-25; 2. Centers for Disease Control and Prevention.National Diabetes Statistics Report website. Accessed January 24, 2023. https://www.cdc.gov/diabetes/data/statistics-report/index.html. 3. Ward K, et al. Modeling the total economic value of novel type 1 diabetes (T1D) therapeutic concepts. Accessed January 24, 2023 https://t1dfund.org/wp-content/uploads/2020/02/Health-Advances-T1D-Concept-Value-White-Paper-2020.pdf; 4. Rogers MAM, et al. BMC Med. 2017;15(1):199; 5. Divers J, et al. *MMWR Morb Mortal Wkly* Rep. 2020;69(6):161-165.

- T1D accounts for 5% to 10% of all DM cases and occurs more commonly in children and young adults but can occur at any age
- Antibodies status
  - 90% of newly diagnosed persons with T1D have 1 or more antibodies.
  - The presence of >2 antibodies in a relative without diabetes of a person with T1D is highly predictive of developing T1D within 5 years.
  - Some forms of T1D have no evidence of autoimmunity and have been termed idiopathic.
- The clinical presentation and rate of b-cell destruction progression is variable, with higher rates of ketosis in children and slower progression in older adults.
- In some individuals with T1D in adulthood, the clinical presentation may follow a more indolent course (termed latent autoimmune diabetes in adults) with slower decline in b-cell insulin secretion.
- Worldwide epidemiological studies have reported that between 13% and 80% of individuals with T1D present with DKA

T1D is a Progressive and Chronic Autoimmune Disease

Multifactorial disease[1-3]

- Strong genetic component
- Variety of potential environmental triggers, including viral infections

T cell–mediated autoimmune activity damages insulin-producing beta cells[3]

Characterized as 3 progressive stages leading to irreversible loss of glycemic control[1]

Islet autoantibodies signal presence of disease before clinical symptoms appear

≥2 islet autoantibodies

constitutes a diagnosis of T1D[1-3*]

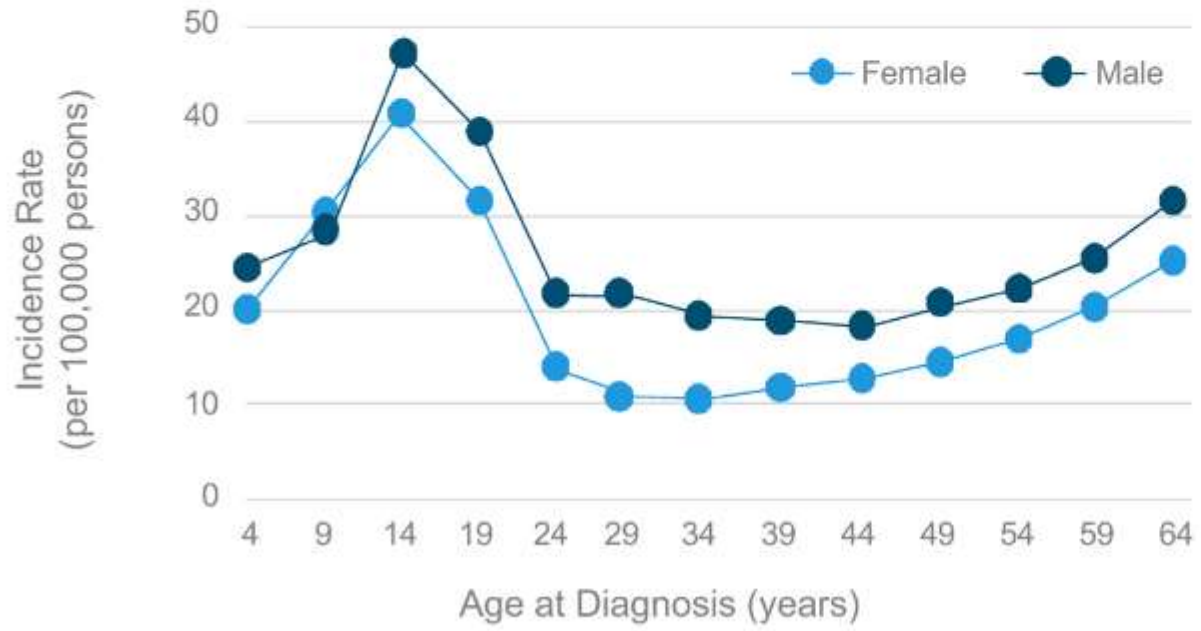
The detection of autoantibodies does not inform understanding of underlying disease progression.

*JDRF, Endocrine Society, and American Diabetes Association have defined T1D diagnosis as the presence of ≥2 autoantibodies to pancreatic beta cells.

1. Insel RA, et al. *Diabetes Care*. 2015;38(10):1964-1974; 2. American Diabetes Association. *Diabetes Care*. 2022;45:S17-S38; 3. van Belle TL, et al. *Physiol Rev*. 2011;91(1):79-118.

Clinical Stage 3 T1D Requiring Exogenous Insulin Can Be Diagnosed Months to Years After the Development of Islet Autoantibodies[1,2]

Incidence peaks between 10 and 14 years of age[1]



In this longitudinal study, claims data were obtained from the Clinformatics Data Mart Database (N=61,795,350). Clinical (Stage 3) T1D requiring insulin developed in 32,476 individuals in the study cohort.[1]

1. Rogers MAM, et al. *BMC Med*. 2017;15(1):199. 2. Ziegler AG, Bonifacio E. *Diabetologia*. 2012;55(7):1937-1943.
Figure adapted from Rogers MAM, et al. *BMC Med*. 2017;15(1):199.

Relatives of Patients with T1D are at Increased Risk for Developing T1D

The risk of T1D is increased more than 10-fold if a person has a first-degree relative with T1D[1,2]

Second-degree relatives have a similar disease progression as first-degree relatives[3]

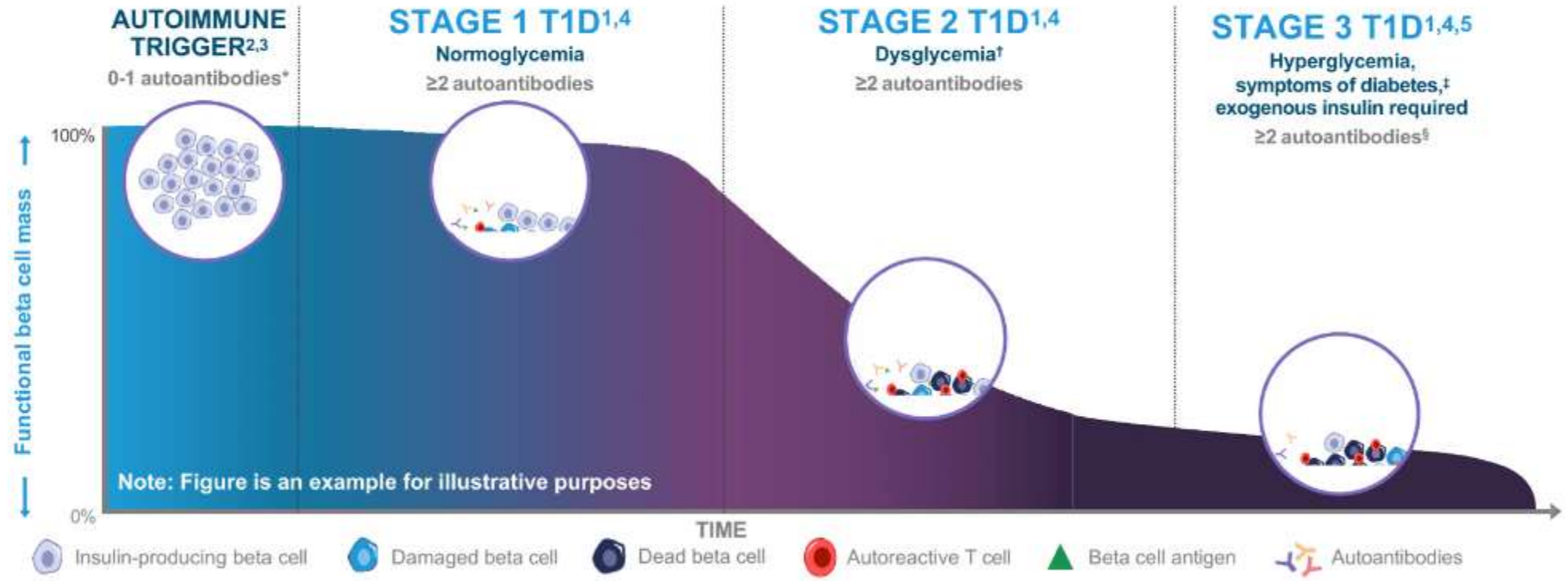
Approximately 80% of T1D cases are spontaneous with no family history[4]

FDR, first-degree relative

1. Maahs DM, et al. *Endocrinol Metab Clin North Am*. 2010;39(3):481-497.; 2. Bonifacio E. *Diabetes Care*. 2015;38(6):989-996.; 3. Ziegler AG, et al. JAMA. 2013;309(23):2473-9.; 4. Parkkola A, et al. *Diabetes Care*. 2013;36(2):348-354.

Figure adapted from Bonifacio E. *Diabetes Care*. 2015;38(6):989-996.

T1D Progresses in 3 Stages[1]



Glucose in Stages

Normoglycemia – Stage 1

Dysglycemia – Stage 2

- Fasting Glucose 100-125 mg/dL
- 2 Hour GTT 140-199 mg/dL
- A1c 5.7-6.5%

Overt Hyperglycemia – Stage 3

- Fasting Glucose ≥ 126 mg/dL
- 2 Hour GTT ≥ 200 mg/dL
- Random Glucose above 200 mg/dL with symptoms
- A1c ≥ 6.5%

Loss of Insulin Production Leads to Difficulty in Keeping Blood Glucose Levels in a Healthy Range and Results in Serious Acute and Chronic Complications[1-3]

Acute complications of Clinical Stage 3 T1D[3]

Diabetic ketoacidosis (DKA)

- DKA is the leading cause of mortality in youth with T1D[4]

Hypoglycemia

- Most people with T1D experience an average of

Episodes per week
of **symptomatic hypoglycemia**[5]

Episode per year
of **severe hypoglycemia** (requiring external assistance for recovery)*.[6]

Chronic complications of Clinical Stage 3 T1D[3]

Microvascular

Retinopathy/ cataracts

Nephropathy

Neuropathy

Macrovascular

Cerebrovascular disease

Heart disease

Extremity damage

Few individuals achieve adequate glycemic control to avoid long-term complications of hyperglycemia[2,3]

*Rate of severe hypoglycemia was 1.1 (median; range 0.3-3.0) episodes per patient-year in 28 retrospective studies including 25,765 unselected patients with T1D

1. Ward K, et al. Modeling the total economic value of novel type 1 diabetes (T1D) therapeutic concepts. Accessed July 8, 2022. https://t1dfund.org/wp-content/uploads/2020/02/Health-Advances-T1D-Concept-Value-White-Paper-2020.pdf; 2. Foster NC, et al. Diabetes Technol Ther. 2019;21(2):66-72; 3. Jiang J, Dutta S. Educational portal of: Research Collaboratory for Structural Bioinformatics Protein Data Bank. Diabetes mellitus: complications. Accessed December 21, 2020. https://pdb101.rcsb.org/global-health/diabetes-mellitus/monitoring/complications; 4. Gagnum V, et al. Diabet Med. 2017;34(1):56-63. 5. Frier BM, et al. Diabet Med. 2016;33(8):1125-1132. 6. Pedersen-Bjergaard U, et al. Curr Diab Rep. 2017;17(12):131.

proventionbio

DKA Occurs Due to a Critical Deficiency of Insulin and Can Have Lasting Negative Impacts[1]

~60% of youth in the US with T1D are **diagnosed as a result of a DKA event**[1]

DKA at diagnosis may have long-term impacts[2,3]

- **Brain changes** and detrimental neurocognitive outcomes
- **A sustained negative effect on glycemic control over time**, independent of other variables
- **Increased morbidity and mortality** that is associated with lifelong poor glycemic control

1. Alonso GT, et al. Diabetes Care. 2020;43(1):117-121; 2. Muñoz C, et al. Clin Diabetes. 2019;37(3):276-281; 3. Duca LM, et al. Diabetes Care. 2017;40(9):1249-1255.

Life Expectancy with T1D

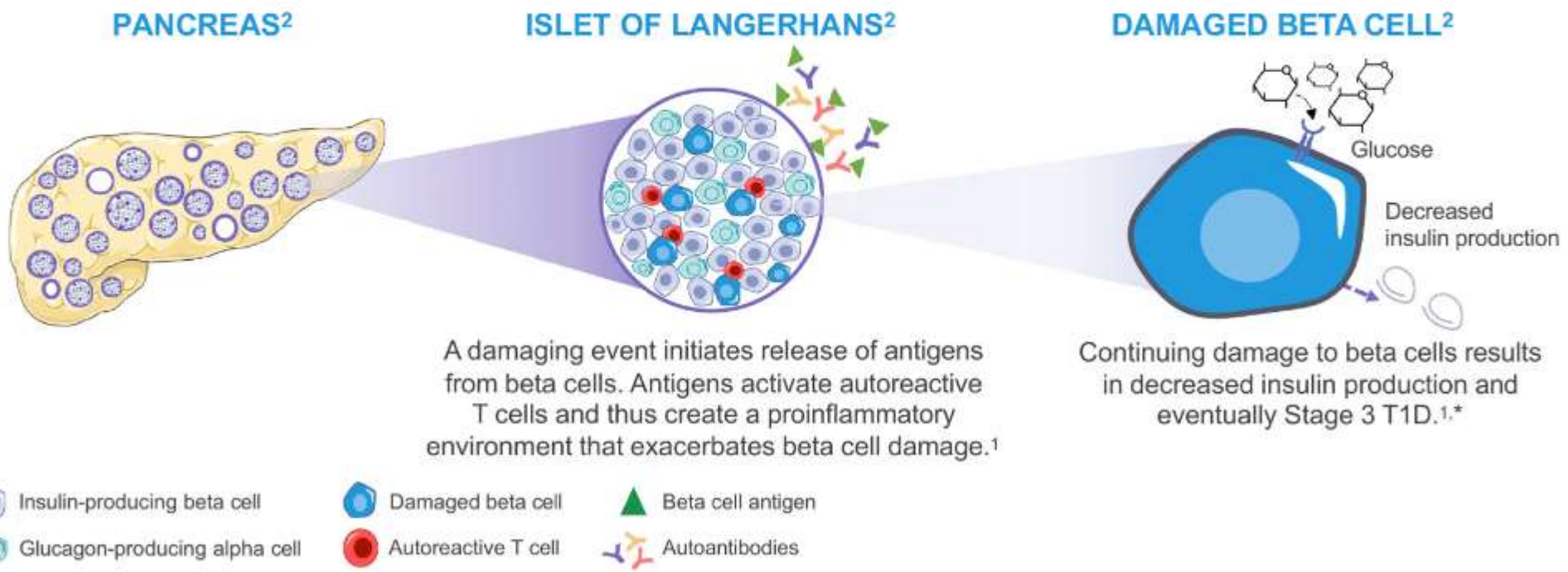
- Reduce life expectancy
  - If diagnosed by 10
    - 17.7 year reduction in women
    - 14.2 year reduction in men
    - 7-fold increase of cardiovascular death
  - If diagnosed after age 10 – 10 year reduction

Information was from individuals with T1D diagnosed at ≤30 years from the Swedish National Diabetes Register between January 1, 1998, and December 31, 2012 (n= 27,195), and matched controls without diabetes from the general population (n=135,178). Individuals diagnosed with T1D >20 years prior were excluded.

1. Rawshani A, et al. *Lancet*. 2018;392:477-486.

Autoimmunity Results in Beta Cell Dysfunction and Destruction, and the Need for Exogenous Insulin[1]

T1D

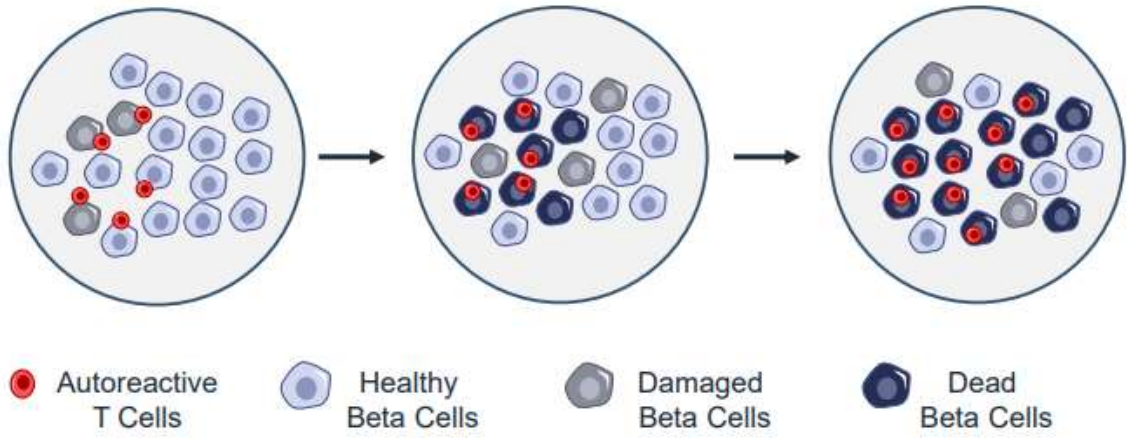


*Please see following slide for definition of Stage 3 T1D.

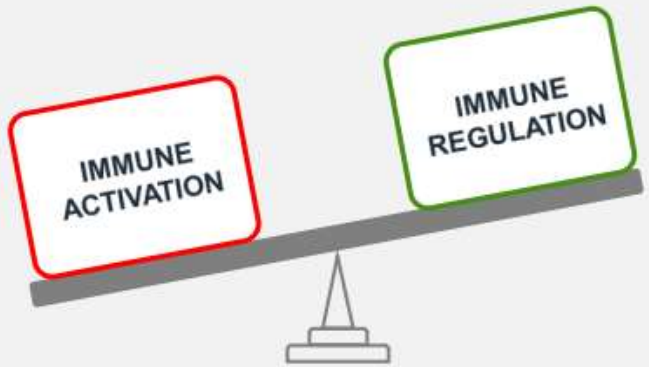
1. van Belle TL, et al. *Physiol Rev*. 2011;91(1):79-118. 2. Moede T, et al. *Diabetologia*. 2020;63(10):2064-2075.

T1D: Autoimmune Activation without Immune Regulation Leads to Loss of Tolerance

Immune attack by autoreactive T cells without proper immune regulation leads to progressive damage and destruction of beta cells



Loss of tolerance leads to imbalance in immune homeostasis



Current Guidelines Support Screening in Limited Settings

General population screening programs using islet autoantibody testing can identify high-risk children[1]

ISPAD
International Society for Pediatric and Adolescent Diabetes

INTERNATIONAL SOCIETY FOR PEDIATRIC AND ADOLESCENT DIABETES
AUGUST 2022

Islet autoantibody screening is currently recommended for research studies and **as an option for first-degree family members**[2]

American Diabetes Association.

AMERICAN DIABETES ASSOCIATION
JANUARY 2022

In the United States, free screening is offered to family members of T1D patients through the Type 1 Diabetes TrialNet.[3]

Type 1 Diabetes TrialNet

TYPE 1 DIABETES TRIALNET

1. Besser REJ, et al. Pediatr Diabetes. Published online August 30, 2022. doi:10.1111/pedi.13410. 2. American Diabetes Association Professional Practice Committee. Diabetes Care. 2022;45(Suppl1):S17-S38. 3.Type 1 Diabetes TrialNet. Pathway to Prevention. https://www.trialnet.org/our-research/risk-screening. Accessed April 16, 2020.

Potential Benefits of T1D Screening

- **Demonstrated to lower the rate of DKA in research and community settings**[1-3]
- **Opportunity to participate in research** (e.g., TrialNet, JDRF)
- **Creates opportunities to provide education and counseling to individuals and their families about the challenges they may face**[4]
  - Family counseling helps reduce anxiety and stress about the future diagnosis of T1D
- **May prompt closer monitoring and management**[4]
  - Follow-up visits
  - Awareness of the classic symptoms: polydipsia, polyuria, and weight loss

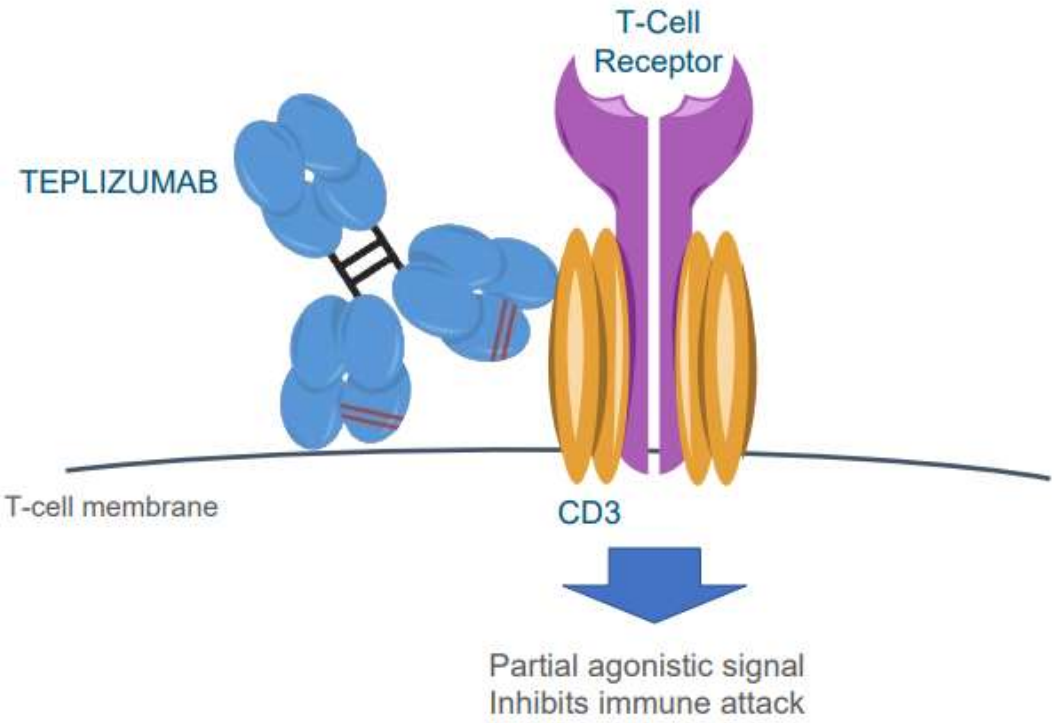
Early detection may allow people with diabetes and caregivers time to develop the skills they will need to sustain optimal glycemic management[4]

T1D Autoantibody Screening Options

T1D Autoantibody Testing Options	Blood Draw Location	Blood Draw	Autoantibodies Available	Cost±
Commercial lab	Local lab or healthcare provider's office	Blood draw	GAD IA-2 Insulin ZnT8*	Cost based on the individual lab
TrialNet (NIDDK)	TrialNet-sponsored event, health fair, or by mail to home	Blood draw or home finger poke blood test	GAD IA-2 Insulin ZnT8	Free if the individual meets the eligibility criteria†
Autoimmunity Screening for Kids (ASK)	Barbara Davis Center, Children's Hospital Colorado UC Health Laboratory Greenwood Pediatrics, At-home kit by mail	Blood draw or home finger poke blood test	GAD IA-2 Insulin ZnT8	Free if the individual meets the eligibility criteria‡
Enable Biosciences At-Home Test	Home	Home finger poke blood test	GAD IA-2 Insulin	$89 or $10 if the individual is unable to afford the full price cost±

Teplizumab: First Disease-Modifying Therapy in Humans to Delay Clinical T1D

- Humanized anti-human CD3 monoclonal antibody; does not cause depletion of T cells
- Delivers partial agonistic signal and inhibits immune attack on beta cells
- Increase in regulatory T cell function
- Induction of exhausted CD8+ T cells
  - Correlated with clinical response[1]
  - Linked to delayed progression to clinical T1D in natural course of disease[2]
- Partial agonistic signal leads to transient cytokine release responsible for mechanism-based side effects

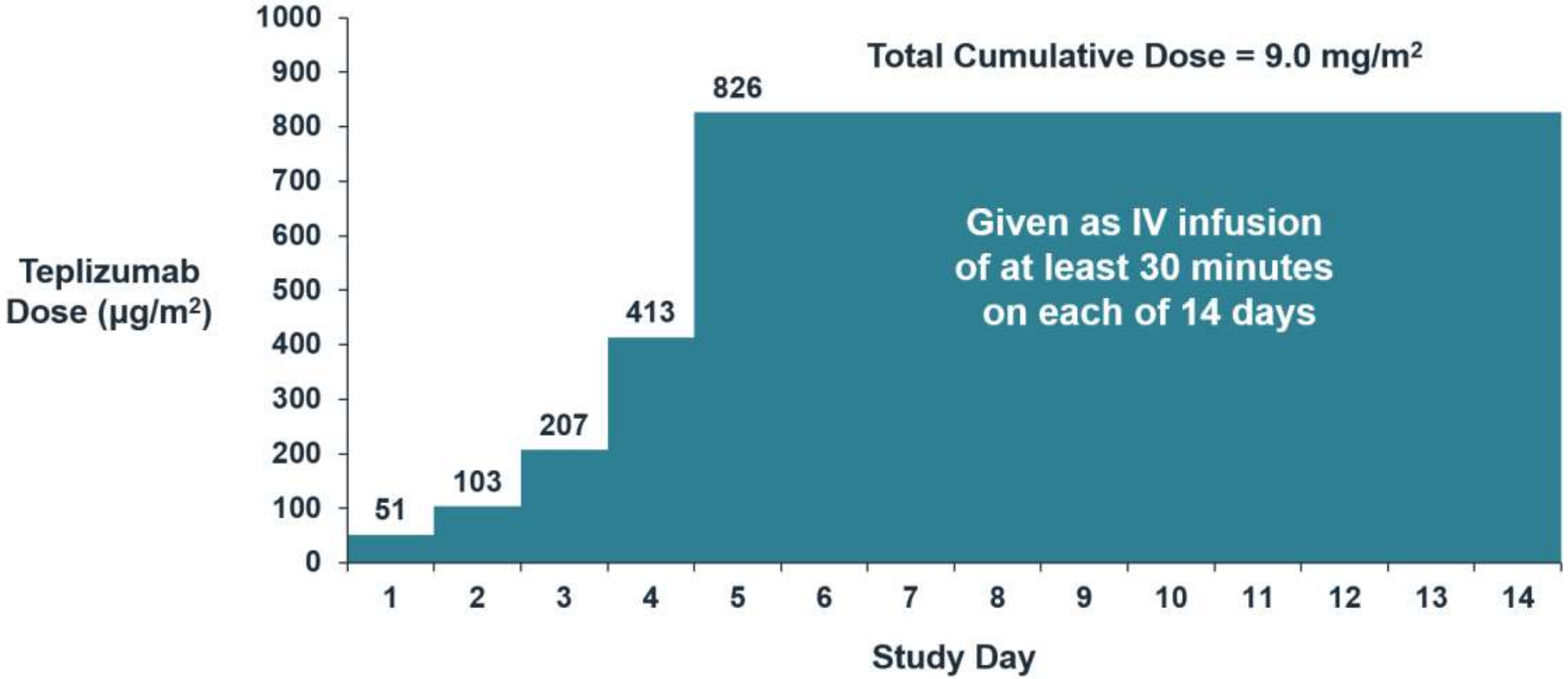


1. Long, 2016; Long, 2017; Herold, 2019; 2. Wiedeman, 2020
Figure adapted from Kuhn and Weiner, 2016; Chen and Flies, 2013

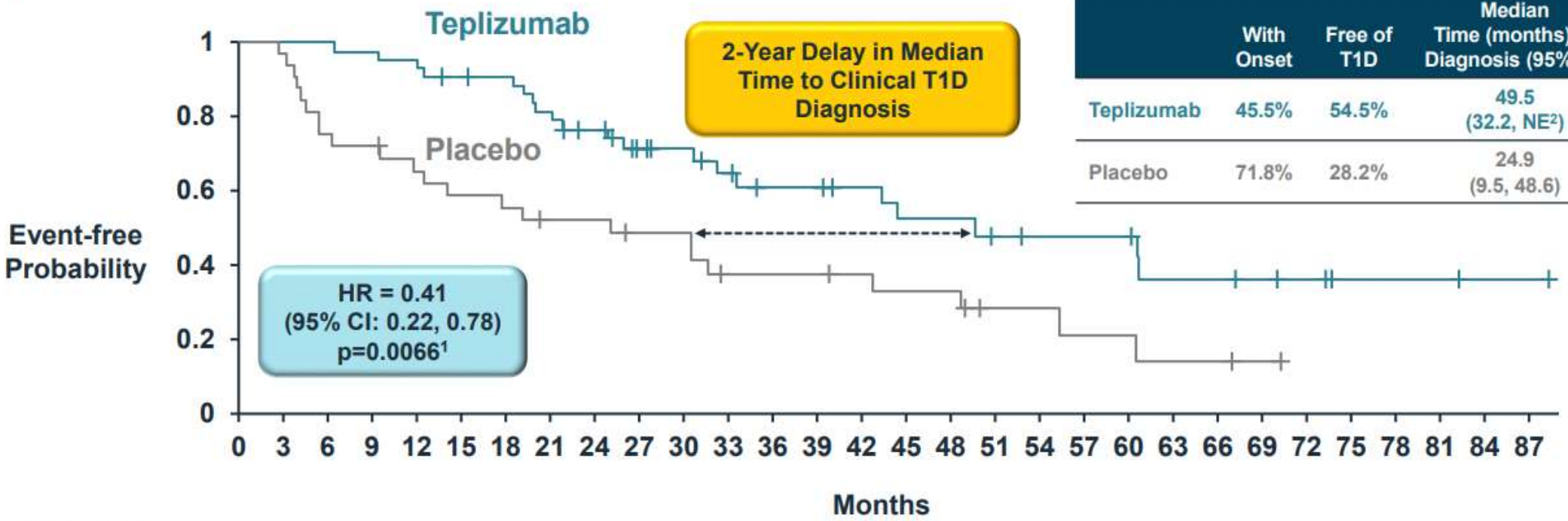
Study TN-10

- Randomized , double-blink, even driven Placebo controlled
  - 76 patients ages 8-49 with Stage 2 Type 1 Diabetes
    - 2 or more antibodies
    - Dysglycemia on glucose testing
- Received teplizumab-mzmw (TZEILD) vs placebo for 14 days of infusions.
- Time from randomization to the development of T1D

TN-10: Teplizumab or Matching Placebo Given IV in a Single 14-Day Treatment Course



Primary Endpoint Met - Teplizumab Significantly Delayed Onset of Stage 3 Clinical T1D vs Placebo



	With Onset	Free of T1D	Median Time (months) to Diagnosis (95% CI)
Teplizumab	45.5%	54.5%	49.5 (32.2, NE[2])
Placebo	71.8%	28.2%	24.9 (9.5, 48.6)

Number of Patients at Risk

Teplizumab	44	44	44	43	41	39	38	34	30	24	22	19	16	16	14	12	12	10	9	9	9	6	6	5	4	2	2	2	1	1
Placebo	32	31	24	23	20	18	17	15	15	13	13	9	9	9	8	7	7	4	4	3	3	2	2	1	0					

1. Cox Proportional Hazards model; 2. Not Estimable

TN-10: Most Common Adverse Events ≥ 10%

Preferred Term	Teplizumab N=44		Placebo N=32	
	n	%	n	%
Patients with ≥ 1 AE	43	98%	22	69%
Lymphopenia	32	73%	2	6%
Leukopenia	9	21%	0	0
Nasopharyngitis	7	16%	2	6%
Rash pruritic	7	16%	0	0
Rash	6	14%	0	0
Headache	5	11%	3	9%

Side Effects

- Cytokine Release Syndrome
  - Observed in 5% of TZEILD treated patients as compared to 0.8% of placebo
    - Fever, nausea, fatigue, eadache myalgia, increased LFT
    - Pretreated with antipyretics, antihistamines and antiemetics
    - Monitored liver enzymes and stopped if 5 times above the upper limit of normal
    - If CRS occurred paused treatment for 1-2 days then would return on treatment to complete 14 day course.

Thoughts

- Treatment was shown to decrease risk of Stage 3 T1D presenting with DKA
- Need the screening to impact disease state
- Would there be an impact on life expectancy/complications.
- Other factors/considerations

The Role of Technology in Type 1 Diabetes

ADA Standards of Care 2023
"There is no one size fits all approach"

- Continuous Glucose Monitoring
  - Robust education, training and support are required for optimal CGM device implementation and ongoing use.
  - When used properly, real-time CGM in conjunction with MDI or CSII are a useful tool to lower and/or maintain A1C levels and/or reduce hypoglycemia in adults and youth with diabetes.
- Insulin pumps
  - Insulin pump therapy may be considered as an option for all adults and youth with type 1 diabetes who are able to safely manage the device.
  - Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and youth with diabetes to prevent/mitigate episodes of hypoglycemia. .
  - Automated insulin delivery systems may be considered in youth and adults with type 1 diabetes to improve glycemic control

T1D EXCHANGE DATA (2018)

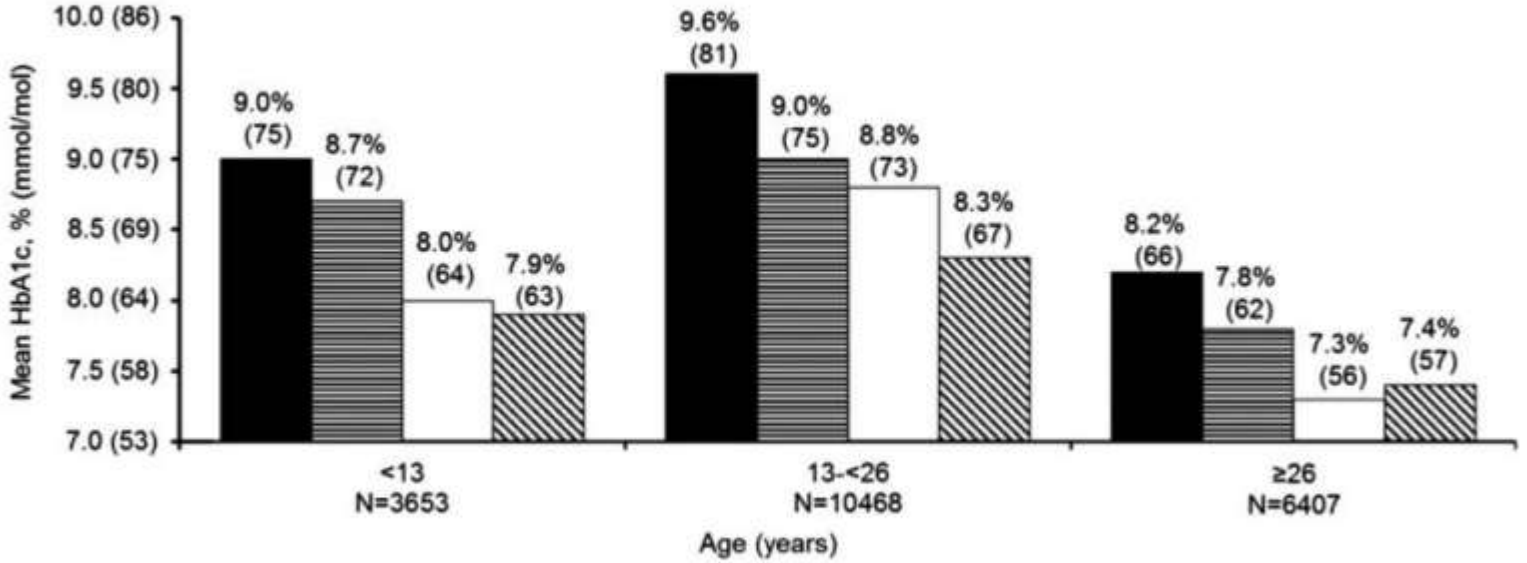
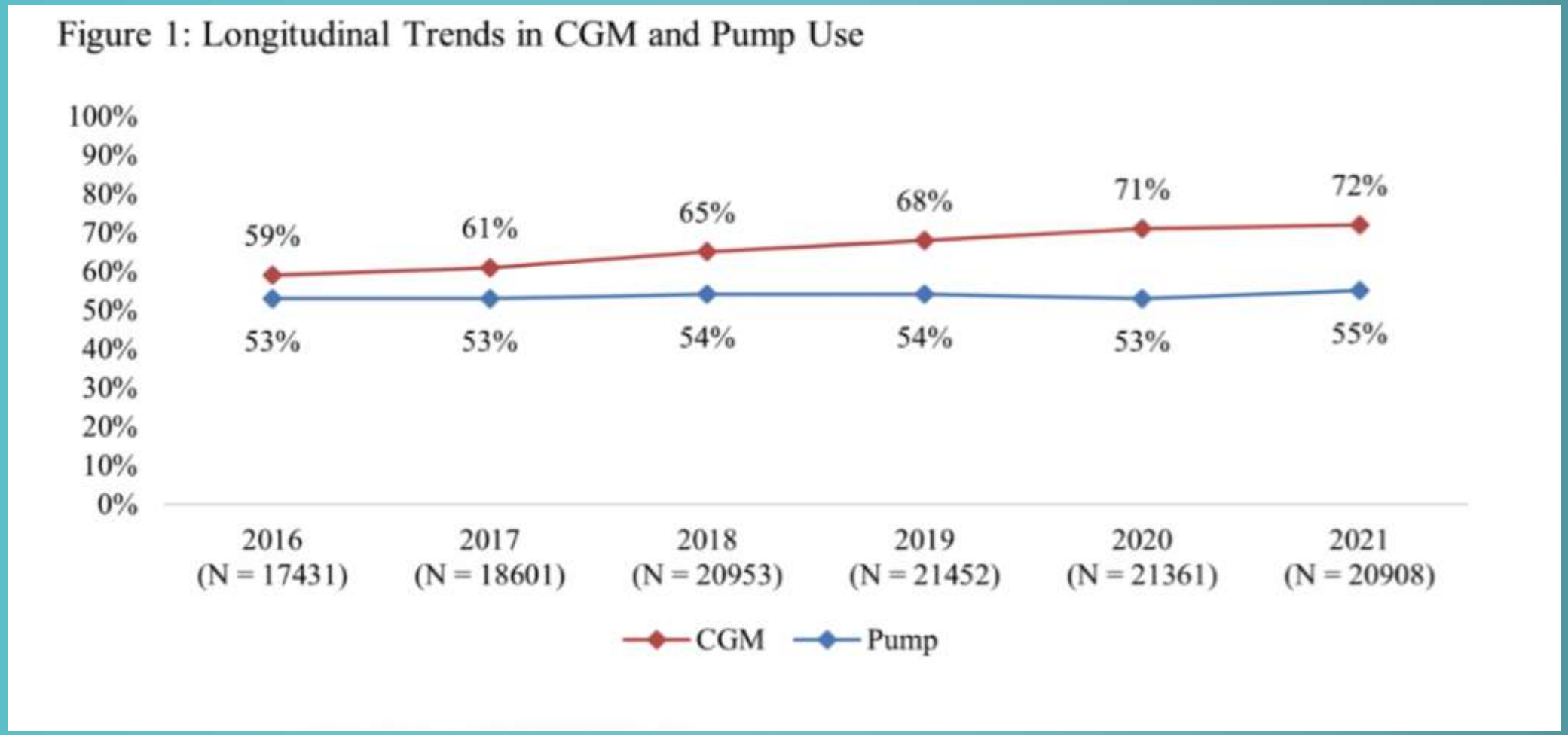


FIG. 3. Mean HbA1c by technology use in 2016–2018. Solid black represents injection only. Horizontal stripes represent pump only. Solid white represents injection+CGM. Diagonal stripes represent pump+CGM.

Foster et al. Diab & Technol & Therapeutics, 2019;21(2):66-72. DOI: 10.1089/dia.2018.0384

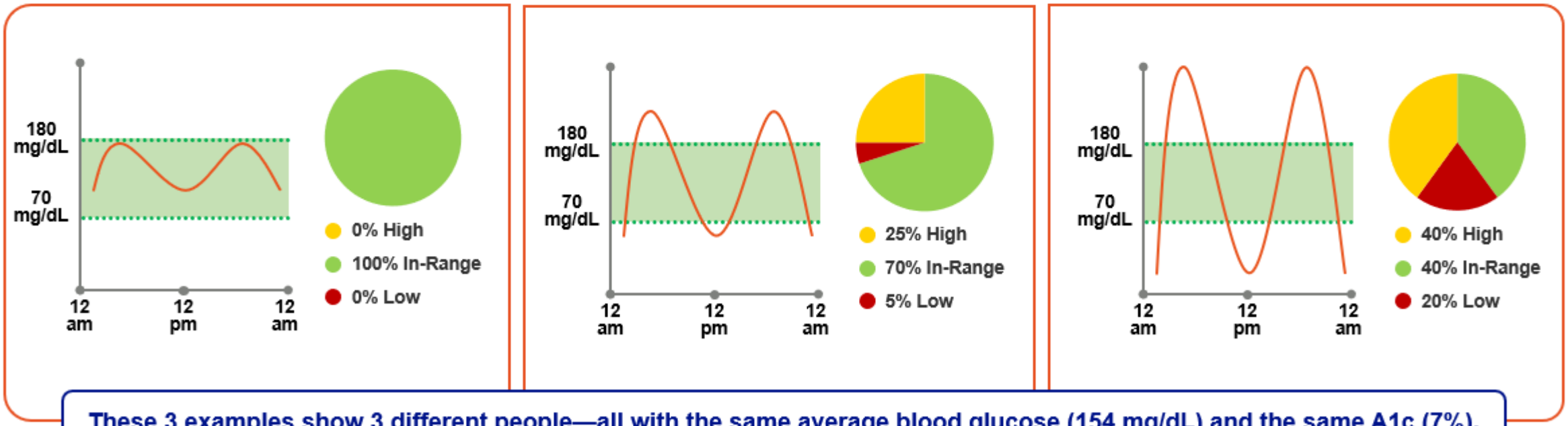


Longitudinal Trends in CGM and Pump Use: Real-World Data from the T1D Exchange QI Collaborative

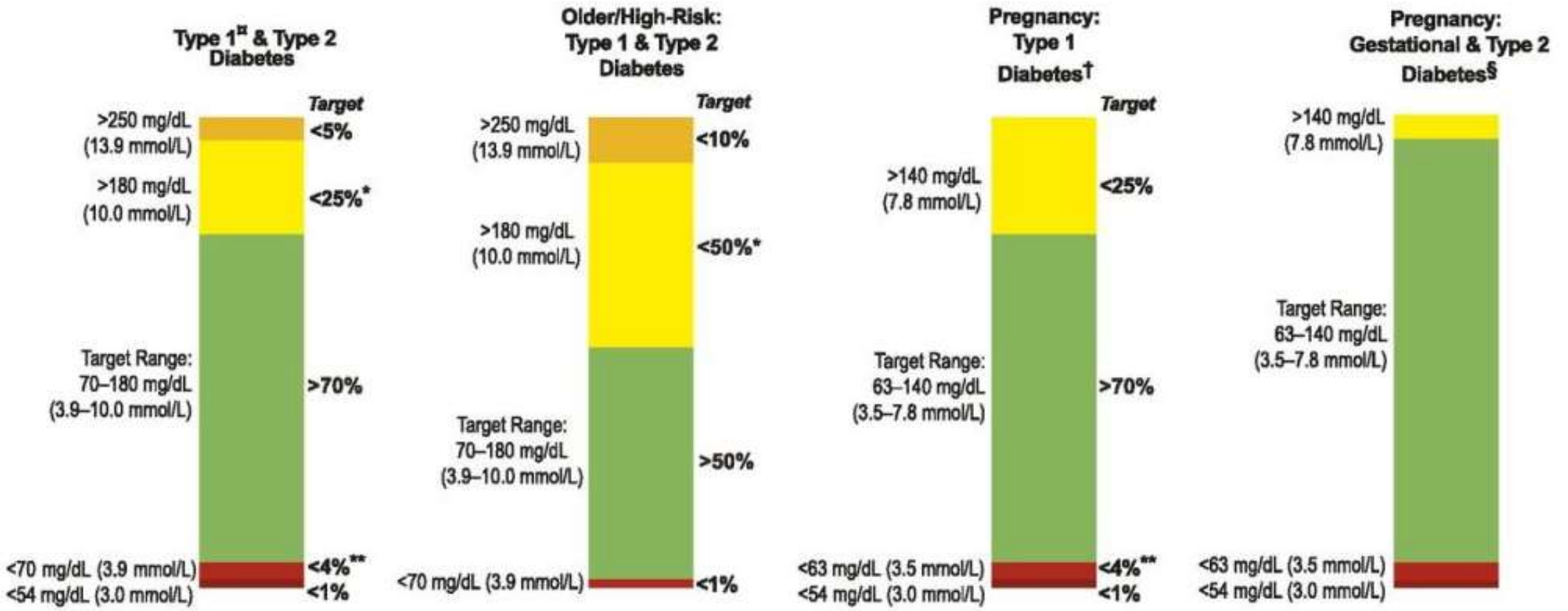
Though A1c is the primary metric for assessing glycemic control, relying on A1c alone may not provide a complete assessment[1,2]

While it reflects 3-month glucose averages, A1c doesn't track glycemic excursions or hypoglycemia, so patients with an acceptable level (<7%) may still not be in control[1,3,4]

For educational purpose only, not actual patients



These 3 examples show 3 different people—all with the same average blood glucose (154 mg/dL) and the same A1c (7%).



¤ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)

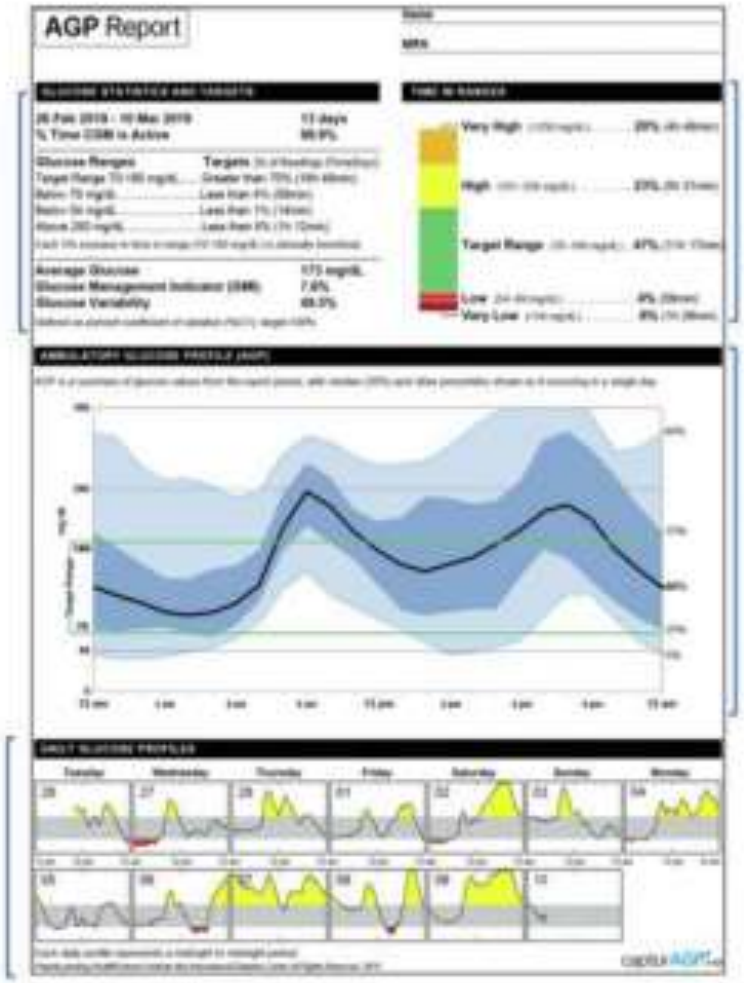
† Percentages of time in ranges are based on limited evidence. More research is needed.

§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.

* Includes percentage of values >250 mg/dL (13.9 mmol/L).

** Includes percentage of values <54 mg/dL (3.0 mmol/L).

- **Glucose Ranges** provide statistics regarding percentage of time within, above, and below target range.
- **Glucose Management Indicator (GMI)** indicates the average A1C level that would be expected based on mean glucose measured in a large number of individuals with diabetes.
- **Glucose Variability** is reported as the percentage of coefficient of variation
- **Daily Glucose Profiles** present a glucose profile for each day covered.



- **High (Level 1 Hyperglycemia) and Very High (Level 2 Hyperglycemia)** indicate percentage of time above range (TAR) for each of the high glucose levels.
- **Target Range** indicates the percentage of time in range (TIR) within a person's with diabetes target glucose range.
- **Low (Level 1 Hypoglycemia) and Very Low (Level 2 Hypoglycemia)** indicate percentage of time below range (TBR) for each of the low glucose levels.
- **The Ambulatory Glucose Profile (AGP)** combines daily profiles to create a 1-day (24-hour) graphic. The black line indicates the median glucose level at all day parts. The dark and light blue shaded areas graphically depict the degree of glycemic variability (SD or %CV), which in this case is well above the recommended goal of ≤36%.

Benefits of CGM

- DIAMOND trial demonstrated that the use of rtCGM in persons with T1D treated with MDI compared with SMBG resulted in lower A1C levels (-1.0% vs 0.4%, P < .001), with significant reductions in time spent at 250 mg/ dL (-78 vs 78 min/d, mean difference 156 min/d, P < .001)
- 2020 real world, nonrandomized trial showed significant and sustained reductions in A1C over 3 years, with increases in the %TIR and reductions in percentage of TBR in adults with T1D treated with MDI or SAP therapy using rtCGM compared with SMBG.
- Less episodes of DKA and hospital stays for hyper and hypoglycemia

Insulin Delivery Technology

- Smart Pen
- Patch Pump
- Sensor Augmented Pump therapy
- Automated Insulin Delivery Systems

ADCES SURVEY: POTENTIAL ROLE OF TECHNOLOGY IN INSULIN DELIVERY[1, 2]

Conducted in 2020 in >700 people taking insulin

62%

report being too busy to/or forgetting to log insulin dose details

80%

believe devices that assemble data automatically and display all data in one place would help

"Connected device" would provide:

- **Personalized understanding of their diabetes (79%)**
- **Make tracking insulin less time consuming (78%)**
- **Feel more empowered to manage diabetes (75%)**

Comparing Systems

Traditional Insulin Pens	Smart Insulin Pens	Smart Insulin Pump Systems
▪ More accurate, convenient, less painful insulin delivery relative to vial and syringe ▪ No data recording or sharing	▪ Automatically records insulin doses; differentiates therapy doses from prime doses ▪ Tracks active insulin ▪ Share integrated diabetes data (glucose, meals, dose) reports with the care team on demand ▪ Provides missed dose, insulin age and quality alerts ▪ Provides dose calculation support based on individualized insulin therapy settings	▪ Set various basal rates including temporary basal rates ▪ Use extended bolus doses ▪ Minimize hypo- and hyperglycemia ▪ Automatically records insulin doses; differentiates therapy doses from prime doses ▪ Tracks active insulin ▪ Share integrated diabetes data (glucose, meals, dose) reports

DATA

- Most studies are short lived
  - Show a modest improvement in A1c
    - AID systems have also shown to have increased TIR
  - Significant reduction in hypoglycemia in AID
    - 3.6% at baseline to 2.6%
    - Improved exercise induced control/less hypoglycemia
  - Reduces diabetes burden

ADA Standards of Care 2023


THANK YOU!
American Diabetes Association.
Connected for Life

Question 1

1. There are three stage to Type 1 Diabetes
    a. True
    b. False

Question 2

2. Teplizumab-mzwv has FDA approval to prevent the diagnosis of Stage 3 Type 1 Diabetes Mellitus

a. True

b. False

Question 3

3. Stage 2 Type 1 diabetes is defined by At least two positive pancreatic islet cell autoantibodies and Dysglycemia without overt hyperglycemia

a. True

b. False

Question 4

4. A goal for Time in Range (glucose between 70-180 mg/dL) is greater then 80%

a. True

b. False

Question 5

5. Systems with automated insulin delivery have been shown to reduce the rate of hypoglycemia while improving A1c.

a. True

b. False