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Delaying Type 1 Diabetes – Early Antibody Screening and Use of Teplizumab in Children

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Disclosure Information

I have the following relationships with the manufacturer of commercial products discussed in this CME activity:

- Scientific Expert, Scientific Education Program – Sanofi

Learning Objectives

At the conclusion of the presentation, participants should be able:

- To understand the role diabetes autoantibody screening can play in those with and without family members who have type 1 diabetes
- Understand the stages of Type 1 Diabetes and the differences in management and monitoring throughout the different stages
- Understand the referral process to Children's National Hospital for possible early stage Type 1 Diabetes
- Understand the use of Teplizumab in children with Stage 2 Type 1 Diabetes

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Outline

- Current state of Type 1 Diabetes
- Diabetes autoantibody screening
- Stages of Type 1 Diabetes – monitoring and management
- Teplizumab in children with Stage 2 Type 1 Diabetes

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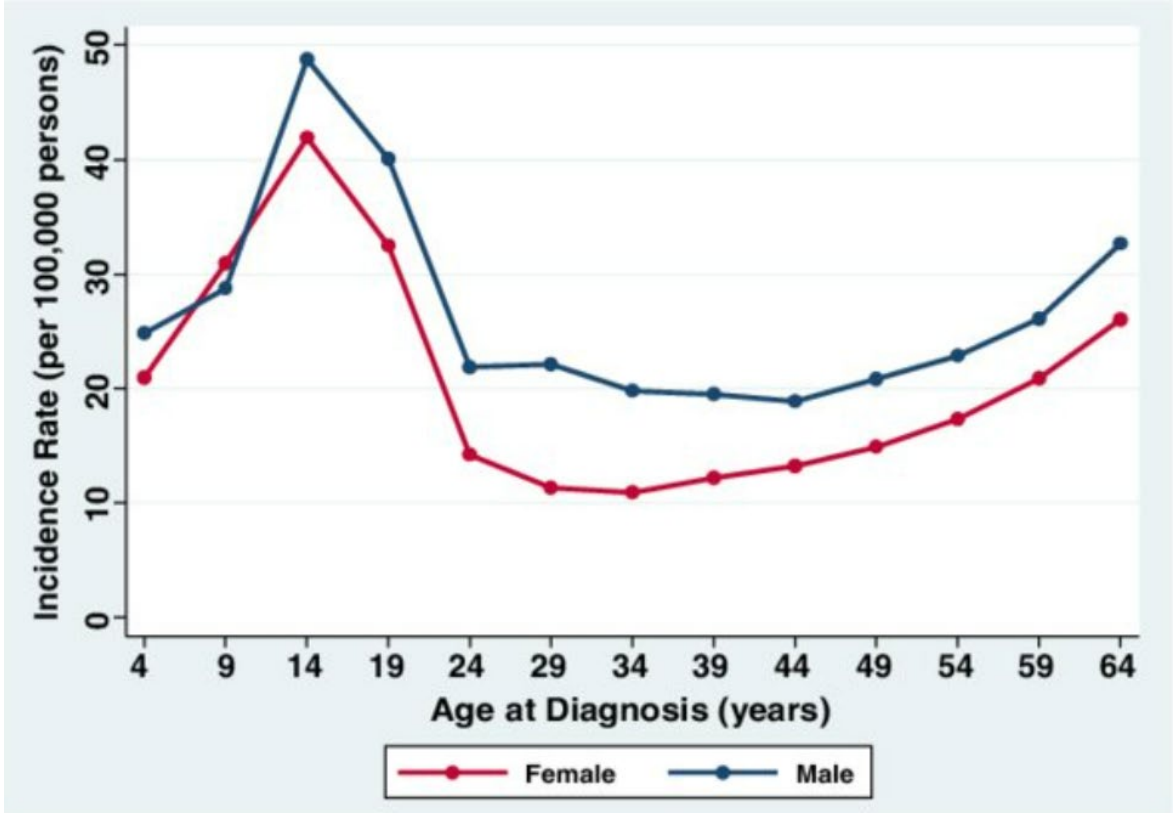
Current State of Type 1 Diabetes

Type 1 Diabetes

- Pancreatic beta-cell destruction → absolute insulin deficiency
  - Autoimmune condition
  - Diabetes autoantibodies
- Most common form of diabetes in US children
- Peak of onset is in childhood, but can develop in adulthood



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Type 1 Diabetes – Genetic Risk

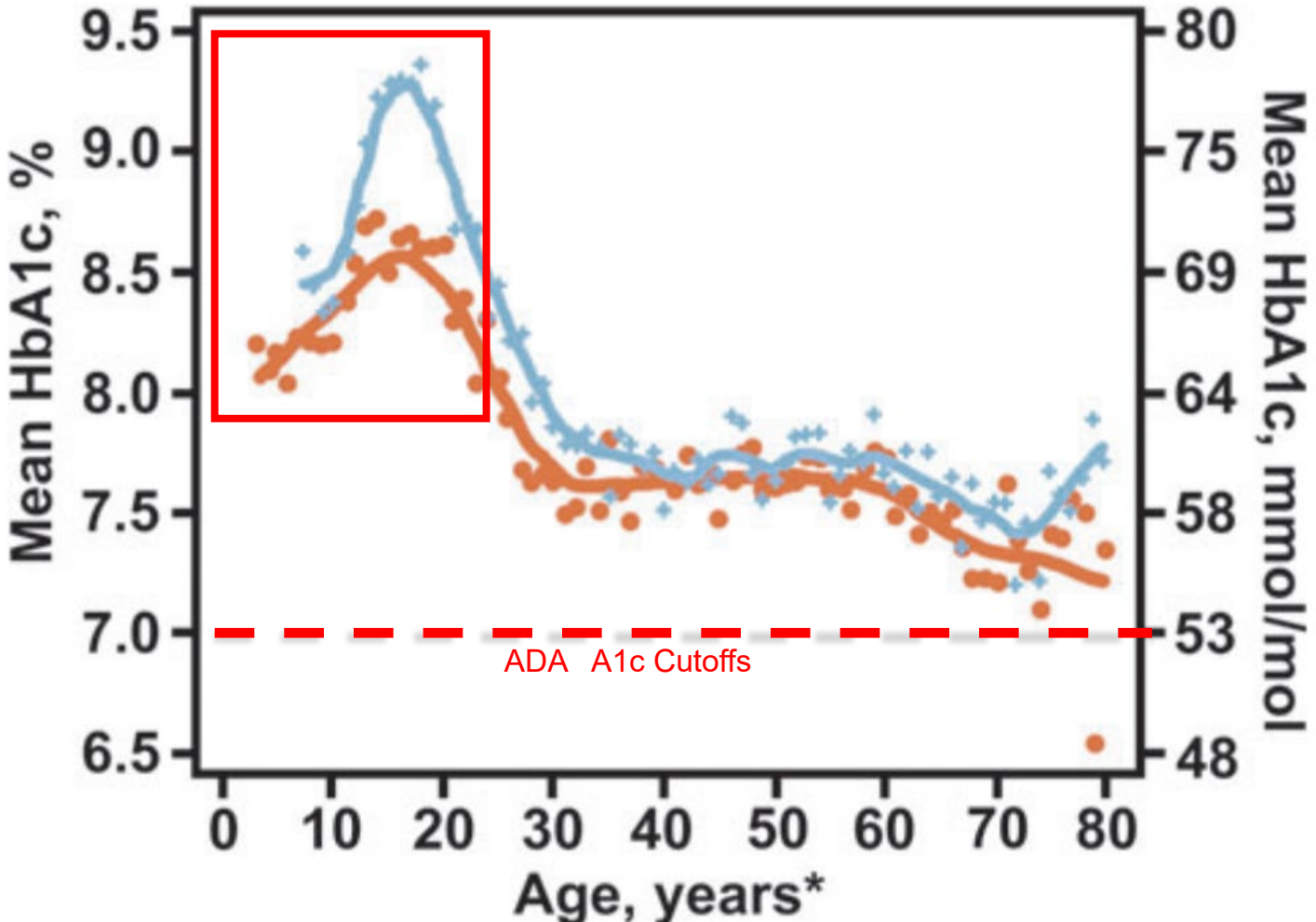
General population: ~0.4% (1:300 to 1:250)
Siblings: 3-6%

Children of affected parents:

- Affected mother: 1-4%
- Affected father: 3-8%

Most individuals diagnosed with type 1 diabetes have no family history of type 1 diabetes

Average Hemoglobin A1c level by year of age



Orange line = 2010-2012 cohort
Blue line = 2016-2018 cohort

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Diabetic Ketoacidosis (DKA)

- A state of absolute or relative insulin deficiency resulting in hyperglycemia, dehydration and the accumulation of ketone bodies in the blood
- Results in hospitalization

40-60% of newly diagnosed Type 1 Diabetes patient present in DKA

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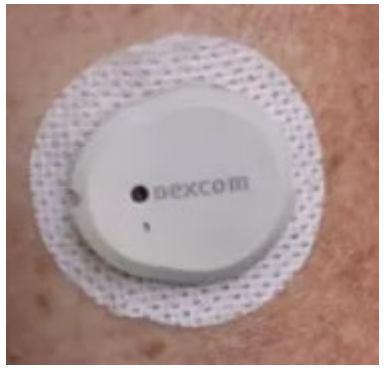

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Diabetes Autoantibody Screening

Diabetes Autoantibodies

Pancreatic autoantibodies :

- GAD65 (GADA) – Glutamic ac decarboxylase
- IA-2 – Insulinoma-associated antigens 2
- IAA – Insulin antibody
- ZNT8A - Zinc Transporter 8
- ICA – islet cell antibody

Type	Code	Description
CPT (Immunoassays for T1D-Related Autoantibodies[7])	86341	Glutamic acid decarboxylase autoantibodies (GADA)
		Islet tyrosine phosphatase 2 autoantibodies (IA-2A)
		Zinc transporter 8 autoantibodies (ZnT8A)
	86337	Insulin autoantibodies (IAA)
ICD-10-CM (Screening & Diagnosis)	E10.1-E10.9	Diagnosis for type 1 diabetes
	Z13.1*	Encounter for screening for diabetes mellitus
	Z13.9*	Encounter for screening, unspecified
	Z83.3*	Family history of diabetes mellitus
	Z83.49*	Family history of other endocrine, nutritional, and metabolic diseases
	E34.9	Endocrine disorder, unspecified

Timeline to Diabetes Onset

The presence of 2 or more autoantibodies is associated with
44% risk for Type 1 diabetes development within 5 years

70% risk within 10 years

84% risk within 15 years

~100% in their lifetime

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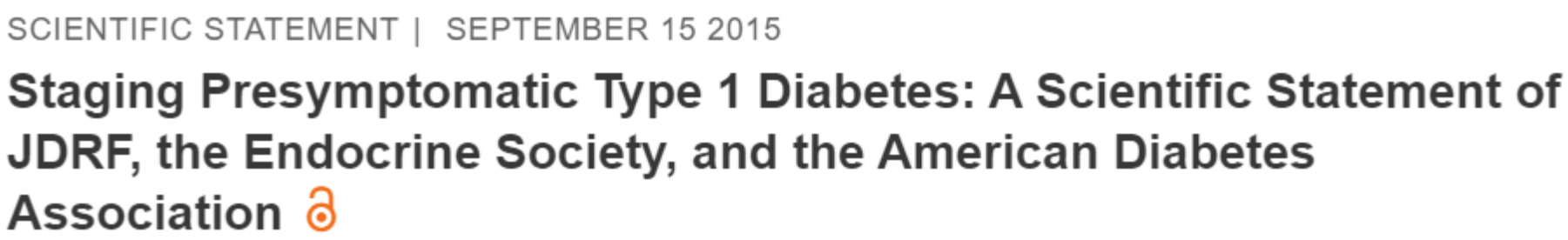
Why Screen?

1. Guidelines for presymptomatic diabetes screening released from American Diabetes Association, International Society of Pediatric and Adolescent Diabetes, and the Endocrine Society


SCIENTIFIC STATEMENT | SEPTEMBER 15 2015

Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association

Why Screen?

2. Most individuals with type 1 diabetes do NOT have a family member with type 1 diabetes

    Family Members DO have an increased risk

    But, **Majority** (80-90%) do not have a family history

Additionally, symptoms of diabetes are general and can be mistaken for other illnesses

Why Screen?

3. Screening can decrease rate of Diabetic Ketoacidosis (DKA) at diagnosis

Diabetic Ketoacidosis is the leading cause of mortality in youth with Type 1 Diabetes
Studies have shown knowledge of diabetes antibody presence reduces rate of DKA at diagnosis from **40-60% to 3-6%**

DAISY

Autoimmunity Screening for Kids
ask
A SIMPLE TEST TO DETECT
Type 1 Diabetes (T1D) + Celiac

Frlda
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

TRIGR

TEDDY

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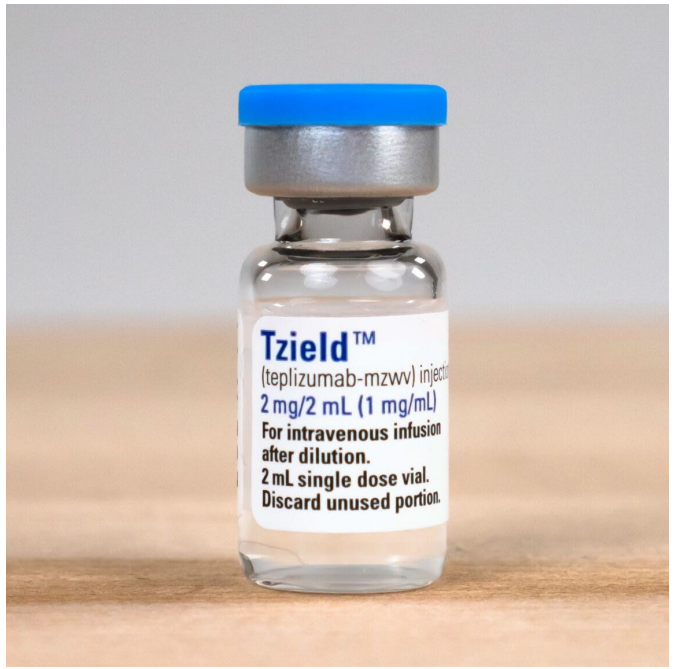
Why Screen?

4. New therapy to help delay onset of Stage 3 (clinical) Diabetes



5. Opportunities to participate in research studies to delay/prevent type 1 diabetes

Type 1 Diabetes TrialNet

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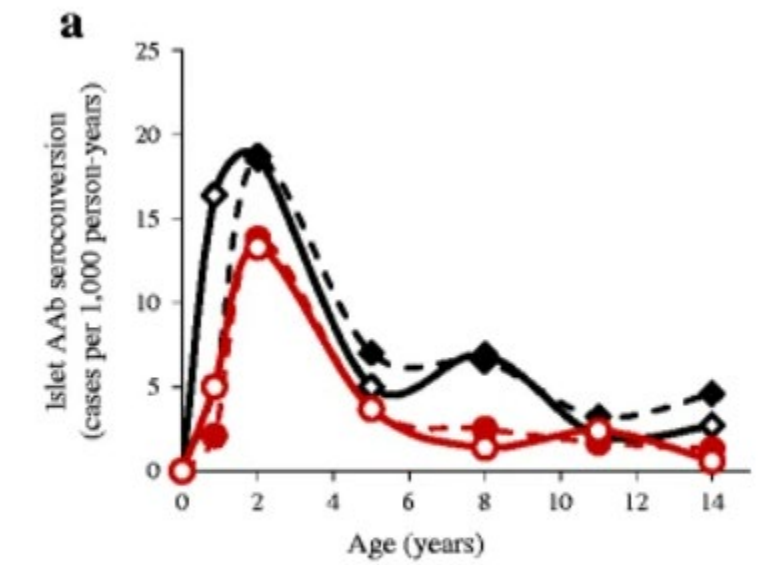
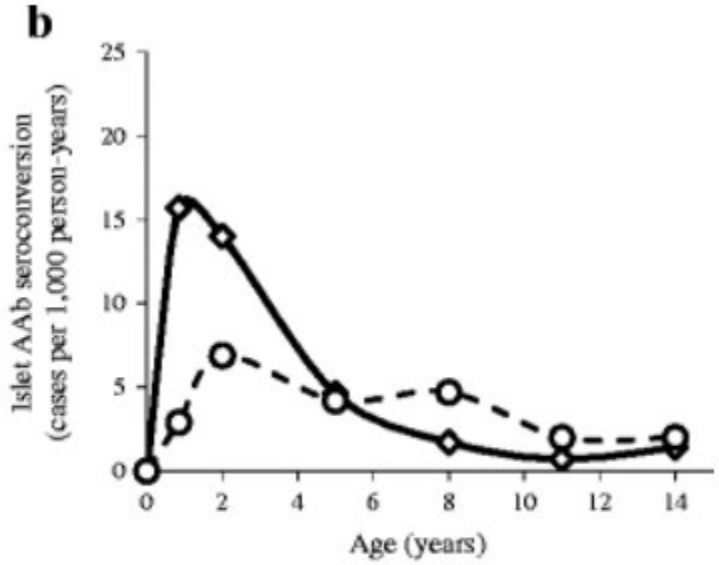
Islet antibody development at different ages



IAA	1,650	1,492	1,323	1,163	936	503
GADA	1,650	1,508	1,338	1,171	943	502
IA-2A	1,650	1,512	1,348	1,198	971	523
ZnT8-A	1,650	1,508	1,345	1,186	972	522



Multiple	1,650	1,489	1,316	1,143	960	483
Single	1,650	1,511	1,364	1,214	987	500

IAA solid black line
GADA dashed black line
IA-2A solid colored line
ZnT8 dashed colored line

Multiple antibodies- solid line
Single antibody – dashed line

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How to obtain diabetes antibodies

	Where do you LIVE to participate?	What AGES can be screened?	Screen for T1D	Screen for CELIAC	Requires ORDER from HCP
Research Based Screening Programs					
ASK	United States	1 to <18 yrs	✓	✓	No
CASCADE	Washington State	Newborn to 7 yrs	✓	✓	No
PLEDGE	South Dakota (must be Sanford Health patient)	Newborn to <6 yrs and 9 to <17yrs	✓	✓	No
TrialNet	United States	2.5 to 45 yrs and parent, brother/sister, or child with T1D — OR — 2.5 to 20 yrs with aunt/uncle, cousin, grandparent, niece/ nephew, or half-sibling with T1D	✓	⊗	No
Consumer Laboratory					
Enable Biosciences	United States (except NY and PA)	Over 1 yr	✓	⊗	No
Clinical Laboratory					
LabCorp	United States	ALL ages	✓	✓	Yes
Mayo Laboratories	United States	ALL ages	✓	✓	Yes
Quest	United States	ALL ages	✓	✓	Yes

ASKhealth.org

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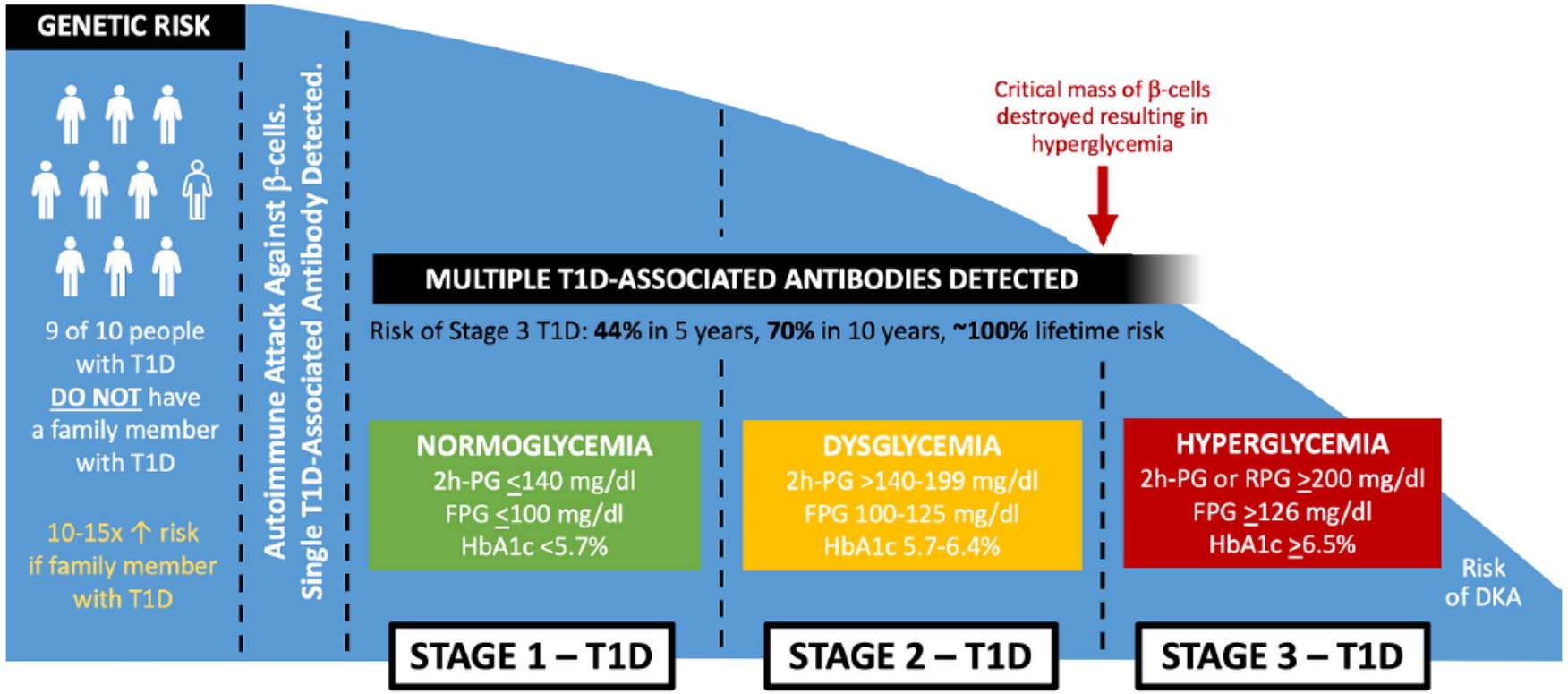
Stages of Type 1 Diabetes – Monitoring and Management

Stages of Type 1 Diabetes



TREATMENT:

- **STAGE 1 – T1D**
  - Metabolic Monitoring
  - Clinical Research Trials
- **STAGE 2 – T1D**
  - Metabolic Monitoring
  - Clinical Research Trials
- **STAGE 3 – T1D**
  - Diagnosis by ADA criteria*
  - Routine Clinical Care Including Insulin Treatment
  - Clinical Research Trials

ASKhealth.org

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What happens when they see the diabetes team @ Children's National Hospital – *The T1Delay Program*

- Assess for symptoms of diabetes, history of autoimmune diseases
- Assess for family history of diabetes, monogenic diabetes
- Check A1c level via point of care
- Check diabetes antibodies (consider checking thyroid levels, thyroid antibodies, celiac antibodies based on likelihood of type 1 diabetes)
- Teach glucometer and have them monitor blood sugars for 2 weeks
  - Fasting and 2 hours after dinner
- Provide follow-up and monitoring

Referral for possible early stage type 1 diabetes:

- **Any patient <18 years of age with:**
- **Positive autoantibodies**
- **A1c 5.7%-6.4% (BMI <85% or with family history of type 1 diabetes) can be referred to Children's National Hospital Endo/Diabetes**

Questions? Contact: T1DelayProgram@childrensnational.org

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Referral for Early Stage Type 1 Diabetes

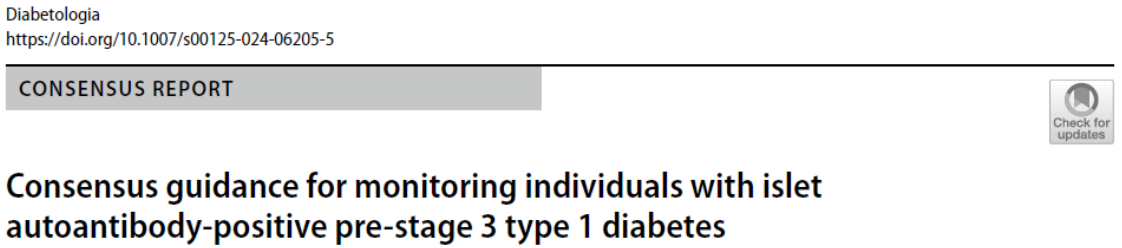
- Can refer per usual referral to Children's National Endocrinology Department
- Any patient <18 years of age with:
  - Positive diabetes autoantibodies
  - A1c 5.7%-6.4% (BMI <85% or with family history of type 1 diabetes)*

*If concerned for type 2 diabetes, referral recommended if A1c 6.0% or above

Follow-up based on antibody results

IF positive antibodies

- 1 antibody positive:
  - Under 3 years of age → follow-up and screening for antibodies and A1c every 6 months for 3 years and then annually for 3 more years if remains 1 antibody positive.
  - 3 years of age or older →follow-up and screen for A1c and antibodies annually for 3 years and stop if remain 1 antibody positive.
  - Can also discuss TrialNet
- ≥2 antibodies positive:
  - Normal A1c
    - <3 years of age →follow-up every 3 months
    - 3-9 years of age →follow-up every 6 months
    - ≥9 years of age →follow-up every 12 months
  - Dysglycemia (A1c 5.7%-6.4%; FBG 100-125)
    - Glucometer education, follow-up every 3 months
    - 8+ years of age → also talk about Tzield (under 8, discuss TrialNet)



IF negative for antibodies: Currently low risk for developing diabetes (but still possible!)

- Family or personal history of autoimmune disease? →consider repeating antibodies in 1 year
- No family or personal history of autoimmune disease? →discuss signs/symptoms of diabetes

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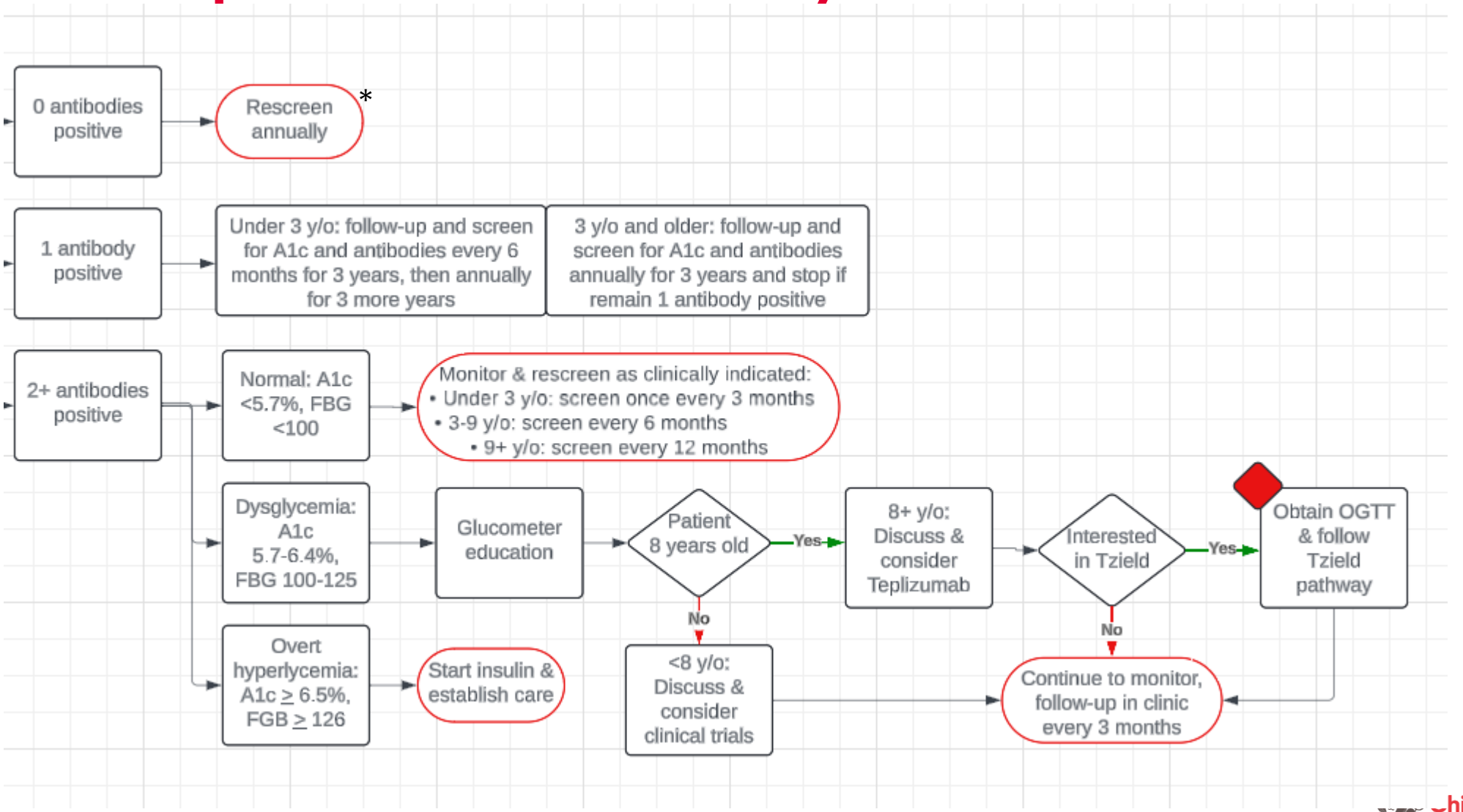
Follow-up based on antibody results



Teplizumab for Stage 2 Type 1 Diabetes

FDA Approval for Teplizumab

Teplizumab is an anti-CD3 monoclonal antibody affecting the autoimmune mediated destruction of beta cells through effects on subpopulations of T cells, including:

-Decrease of the effector function of T cells
-Increase in number and function of regulator T cells
-"Exhaustion" in a subset of effector CD8+ T cells

Tzield (teplizumab-mzwv) is the first and only FDA-approved treatment to delay the onset of Type 1 diabetes (Stage 3) for people 8 years and older with Stage 2 Type 1 diabetes

Teplizumab Trial

Participants:

- N=76 (N=44 received Teplizumab; N=32 received Placebo)
- Ages 8-45; relatives of those with T1D
- Stage 2 Diabetes (defined by OGTT result)

Study Design:

- Randomly assigned 1:1 to treatment or placebo
- 14 day course of teplizumab or saline
- Monitored every 3 months after getting drug
  - Median follow-up time 745 days (>2 years)

Teplizumab Trial

Results:

- 43% of those receiving Teplizumab went on to develop T1D vs 72% of those treated with placebo
  - Median time to diagnosis in Teplizumab group = 48.4 months
  - Median time to diagnosis in Placebo group = 24.4 months

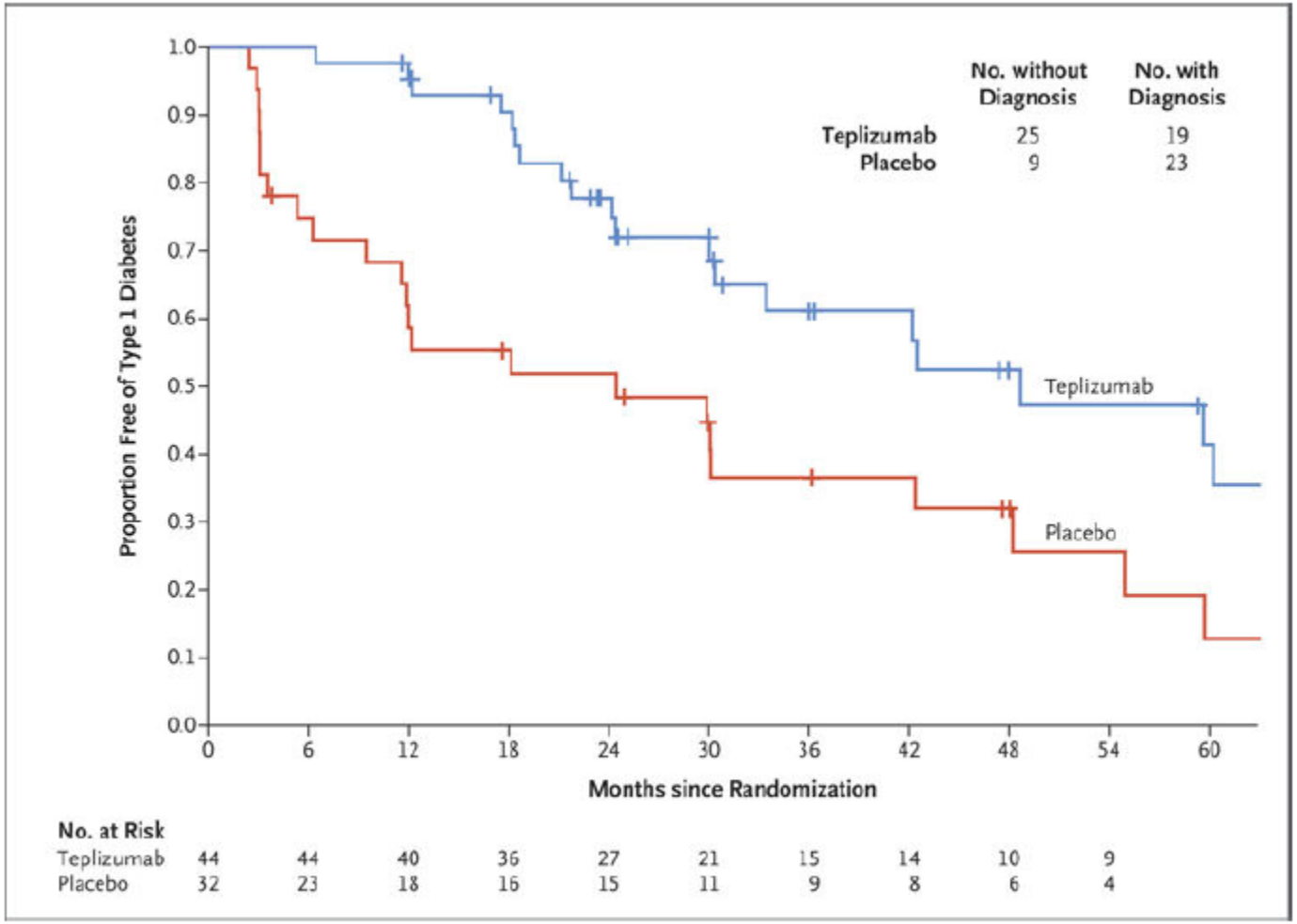


Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes.

Side Effects seen in Teplizumab study (TN-10)

Adverse Reaction	Tzield (N=44)	Placebo (N=32)
Lymphopenia	**73%**	**6%**
Rash	**36%**	**0%**
Leukopenia	21%	0%
Headache	11%	6%
Neutropenia	5% (N=2)	3%
Increased ALT	5%	3%
Nausea	5%	3%
Diarrhea	5%	0%
Nasopharyngitis	5%	0%

Cytokine Release Syndrome

When large numbers of white blood cells are activated and release inflammatory cytokines

- Results in rash, headache, nausea, vomiting, chills, fever

Usually seen in the initial days of infusion (days 1-5)

Manifestations in the study include:

- Fever
- Rash (pruritic urticarial rash on hands and/or trunk and feet)
- Nausea
- Fatigue
- Headache
- Myalgia
- Arthralgia
- Increased ALT, AST
- Increased total bilirubin

Teplizumab in Clinical Use - Experiences

Infusion:

- Daily for 14 days

Infusion location:

- Specialty Infusion Center at Children's National
- Saturday/Sunday CCBD at Children's National

Typical infusion day (~3 hours):

- Arrival, Vitals, set up for treatment
- Pre-treatment with Benadryl, Tylenol, Zofran (Days 1-14)
- Labs (day 1-5, day 14; additional days if needed)
- Infusion – 30 minutes
- Post-infusion monitoring – 1 hour

Summary

- Type 1 Diabetes results in a lifelong need for insulin and individuals often present in DKA
  - We have ways (antibody screening, treatment) to delay the need for insulin and decrease the risk of DKA at diagnosis
- Type 1 Diabetes is often diagnosed in those without a family history of type 1 diabetes
- General population diabetes autoantibody screening would be best done at ~2 years of age and ~6 years of age (and ~10 years of age)
- Monitoring and follow-up for those with diabetes antibodies is needed, and collaborative care with a Pediatric Endocrinologist is ideal
- Teplizumab can delay the onset of clinical (Stage 3) Type 1 Diabetes by a median of 2 years

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Thank You!

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