

Type 1 diabetes recognition and screening

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Disclosures

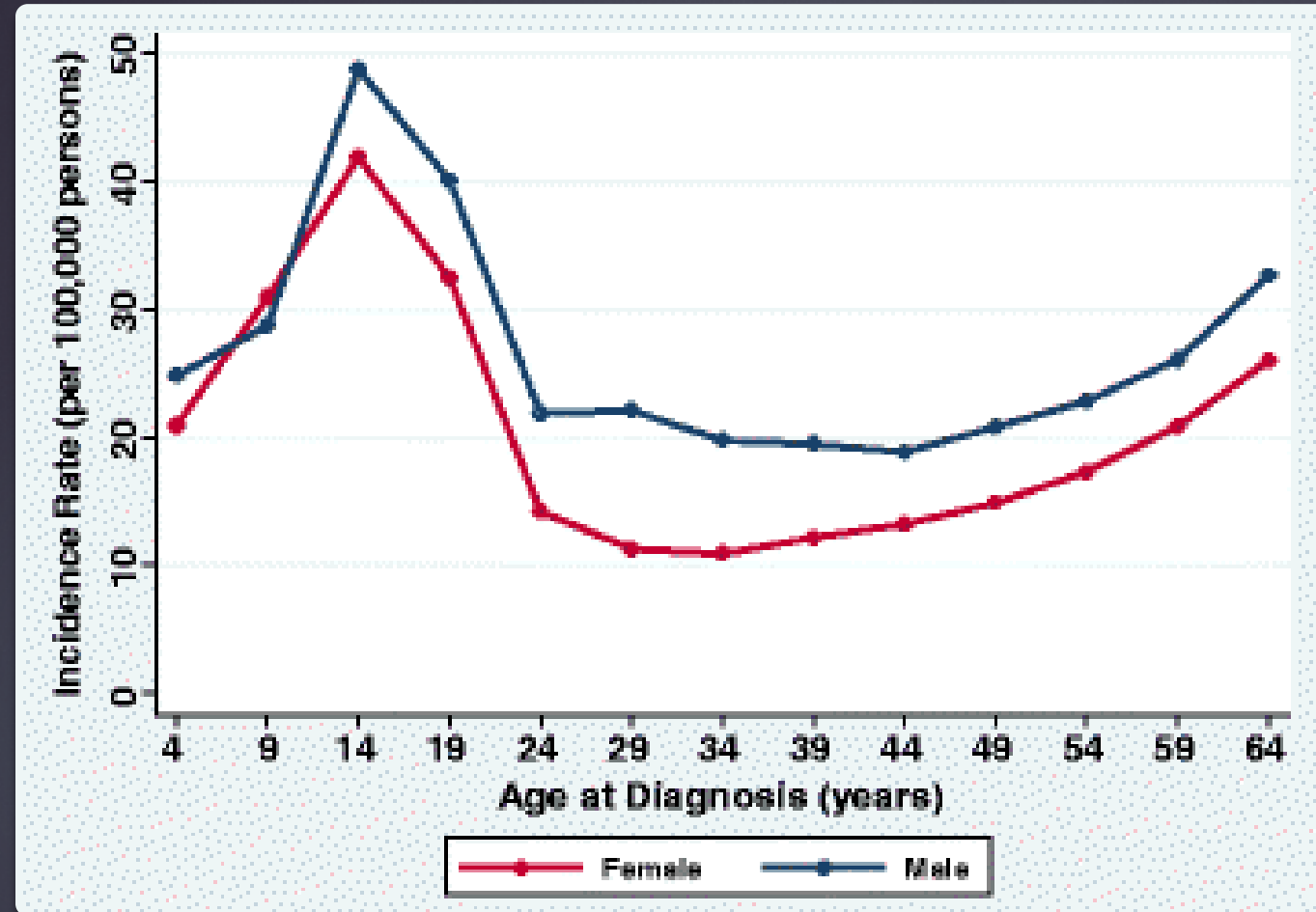
- ▶ Insulet corporation- consultant

Roadmap

- ▶ What is it?
- ▶ Why are we talking about this?
- ▶ Type 1 diabetes in adults
- ▶ Screening for presymptomatic type 1
 - ▶ Stages of diabetes
 - ▶ Who to test
 - ▶ What tests to get
 - ▶ What to do with results
 - ▶ New treatment options

Type 1 Diabetes

- ▶ Condition caused by damage to pancreatic β -cells leading to severe insulin deficiency
- ▶ Accounts for 5-10% of all people with diabetes
- ▶ Can occur at ANY age although highest risk in adolescence/early adulthood
 - ▶ Often more indolent course in adults
- ▶ Incidence and prevalence increasing over the last 50 years



Incidence
rates of T1D
in the US
2000-2015

Case 1

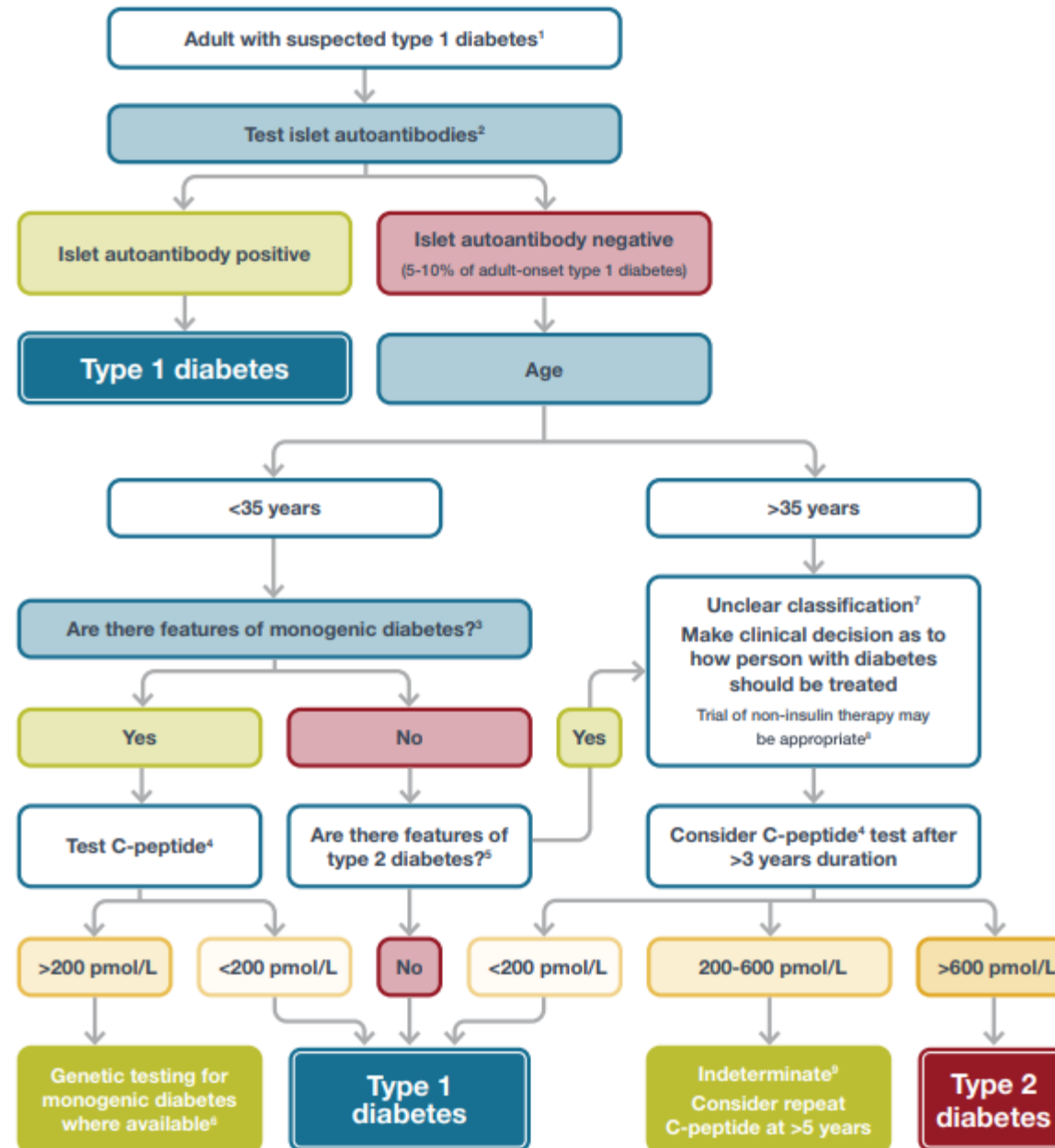
- ▶ 67 yo F with hypothyroidism and HTN presenting for evaluation of Type 2 diabetes
- ▶ Diagnosed one year prior and treated with metformin alone
- ▶ Glucoses around 200 when checked primarily fasting
- ▶ Following good diet and exercising regularly
- ▶ BMI 22, BP 110/70; exam unremarkable
- ▶ Labs:
 - ▶ HGBA1C 9.8 (H) 12/30/2019
 - ▶ HGBA1C 5.7 03/06/2019
 - ▶ HGBA1C 5.3 02/28/2018
 - ▶ C-peptide 1.36; glucose 372
- ▶ Started on basal insulin, metformin continued

Type 1 Diabetes in Adults

Over 40% of those diagnosed at age > 30 will be misclassified as type 2

- ▶ When to consider type 1:
 - ▶ Younger age (<35)
 - ▶ BMI <25
 - ▶ Weight loss
 - ▶ Ketoacidosis
 - ▶ Glucose >360
 - ▶ Rapid progression to insulin (<3 years)

Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations



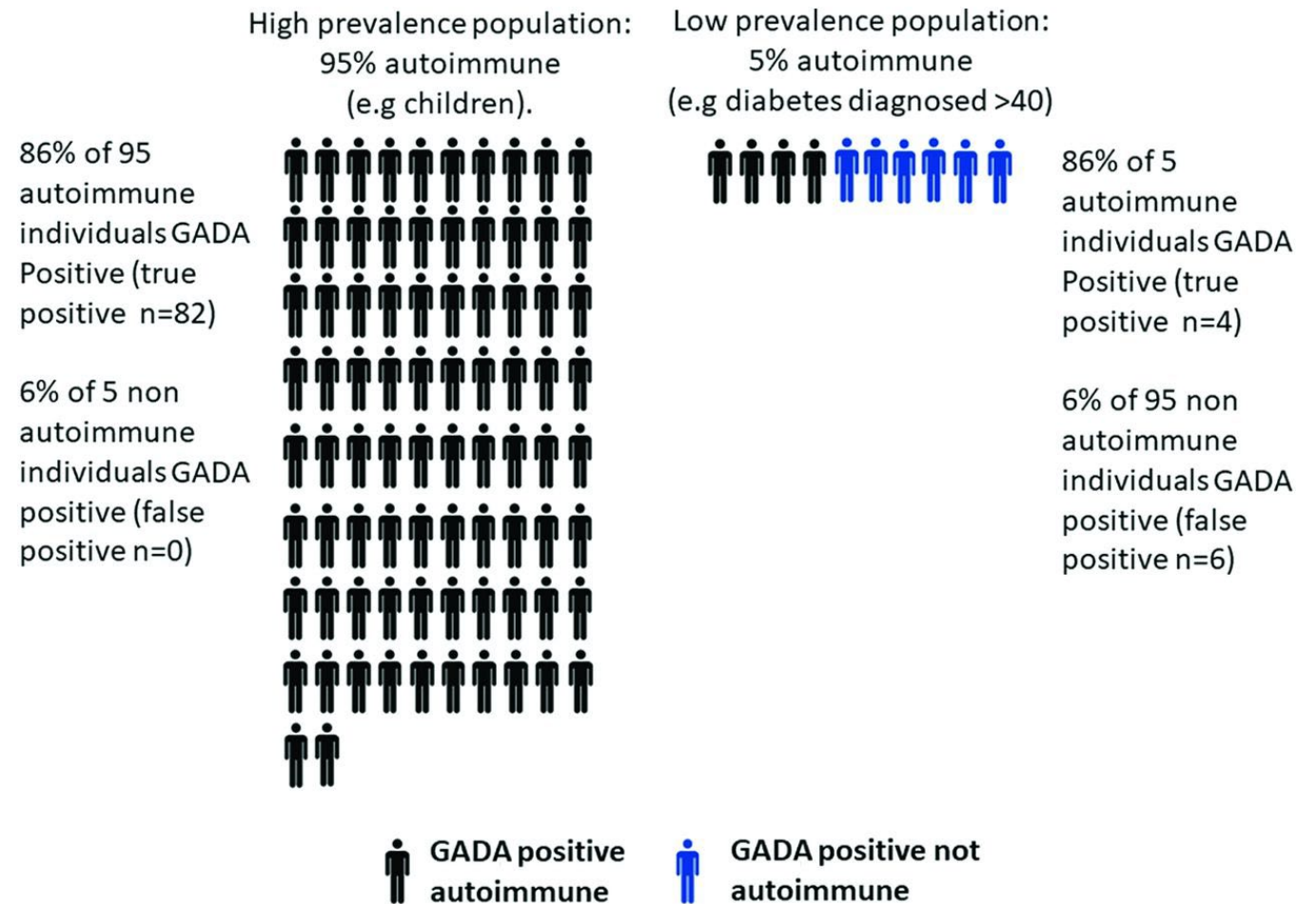
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Islet antibodies

- **START WITH GAD**
- **IF GAD NEGATIVE**
 - Islet tyrosine phosphatase 2 (IA2)
 - Zinc transporter 8 (ZNT8)
- **5-10% HAVE NO ANTIBODIES**

Interpretation of GADA positivity must be done in context of prevalence of autoimmune disease of the study population



What's LADA?

- ▶ Latent autoimmune diabetes of the adult
- ▶ New diabetes after age 35 with positive islet autoantibody but slower, more progressive loss of beta cell function
 - ▶ Single positive antibody must be interpreted with caution
- ▶ More heterogeneous group that can have features of both type 1 and type 2 diabetes
- ▶ Typically progress to needing insulin over the course of months to years
- ▶ Debate if this is milder form of type 1 or different entity

Case 1 follow-up

- ▶ Rapid loss of beta cell function
- ▶ Did trial of basal + Januvia but ineffective and started on MDI
- ▶ Now very well controlled on insulin pump with automated insulin delivery

Component	Latest Ref Rng	12/8/2020
C-Peptide	0.78 - 5.19 ng/mL	0.55 (L)
Glutamic Acid Decarb Ab	≤ 0.02 nmol/L	297 (H)
Thyroperoxidase Antibodies	< 6.0 IU/mL	2500.4 (H)

Case 2

- ▶ 34 yo F diagnosed with diabetes during routine wellness visit
- ▶ A1c 11.2% at diagnosis; 5.6% 2 years prior
- ▶ History of GDM in pregnancies
- ▶ Family history of mom with GDM requiring insulin and then never able to stop
- ▶ Started on metformin and SFU by PCP. Self-discontinued SFU due to hypoglycemia
- ▶ BMI 26
- ▶ Labs with positive GAD (51), negative islet cell antibody, C-peptide 2.3

Case 2 cont

- ▶ After initial visit started low dose basal insulin and Januvia
- ▶ A1c decreased to 5.5%
- ▶ Remains on this 2 years later
- ▶ Recent c-peptide 1.14
- ▶ We are slowly adding prandial insulin as needed with larger meals

Average glucose

152 mg/dL

Standard deviation
39 mg/dL

GMI
7.0 %

Time in Range

2% Very High
18% High
80% In Range
0% Low
0% Very Low

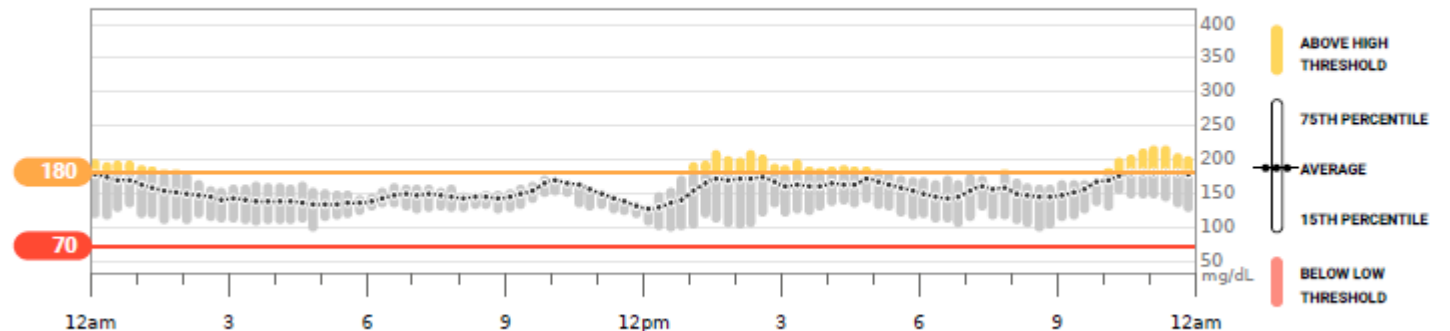
Target Range:
70-180 mg/dL

Sensor usage

Days with CGM data
93 %
13/14

Avg. calibrations per day
0.1

This graph shows your data averaged over 14 days



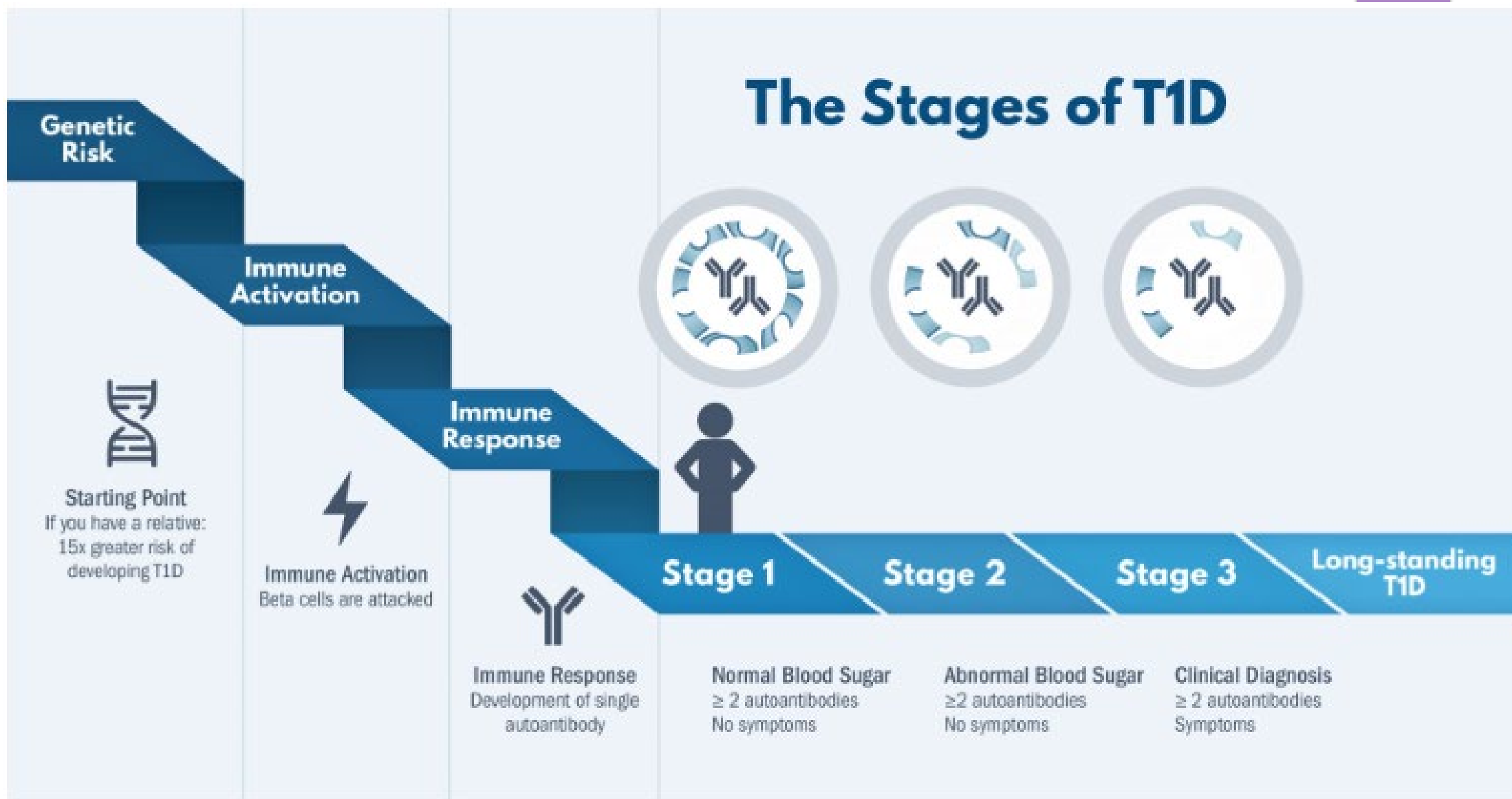
Cancer immunotherapy and type 1 DM

- ▶ Rare, less than 1% of those treatment checkpoint inhibitors
- ▶ Highest risk in those treated with anti-PD-1 (Opdivo) or anti-PD-L1 (Keytruda) antibodies +/- other immunotherapy agents
- ▶ Often do not have typical type 1 antibodies but will have low c-peptide levels requiring insulin
- ▶ Specific risk factors have not been identified so need high index of suspicion in these patients

Screening for type 1 diabetes

Why screen?

- ▶ Less traumatic diagnosis for patients and their families
- ▶ Time for patients and families to learn DM management skills and prepare before disease is present
- ▶ Lower risk of DKA being presenting feature
- ▶ New options for treatment to delay onset of diabetes
- ▶ Identify candidates for clinical trials



Staging of type 1 diabetes

	Stage 1	Stage 2	Stage 3
Autoimmunity	≥ 2 autoantibodies	≥ 2 autoantibodies	≥ 2 autoantibodies
Symptoms Glycemic status	No symptoms Normoglycemia	No symptoms Dysglycemia	Symptoms Hyperglycemia
Glucose metrics	Fasting glucose 70-99 mg/dL A1c <5.7% OGTT <140 mg/dL	Fasting glucose 100-126 mg/dL A1c 5.7-6.4% or 10% increase from prior OGTT 140-199 mg/dL	Fasting glucose ≥ 126 mg/dL A1c ≥ 6.5% OGTT ≥ 200 mg/dL

Who should be screened?

- ▶ First degree relative with T1D- 15 x increased risk
- ▶ Personal/family history of autoimmune disease such as thyroiditis, Addison's, celiac disease
- ▶ One day may be population level

2.7 Autoantibody-based screening for presymptomatic type 1 diabetes should be offered to those with a family history of type 1 diabetes or otherwise known elevated genetic risk. **B**

What/how to order

Recommended labs

- ▶ Insulin autoantibody (IAA)
- ▶ GAD
- ▶ Islet antigen 2 (IA-2)
- ▶ Zinc transporter 8 (ZnT8)

Billing codes

- ▶ Z83.3- family history of diabetes
- ▶ R73.9- Hyperglycemia, unspecified
- ▶ Z13.1- screening for diabetes mellitus

Where to order

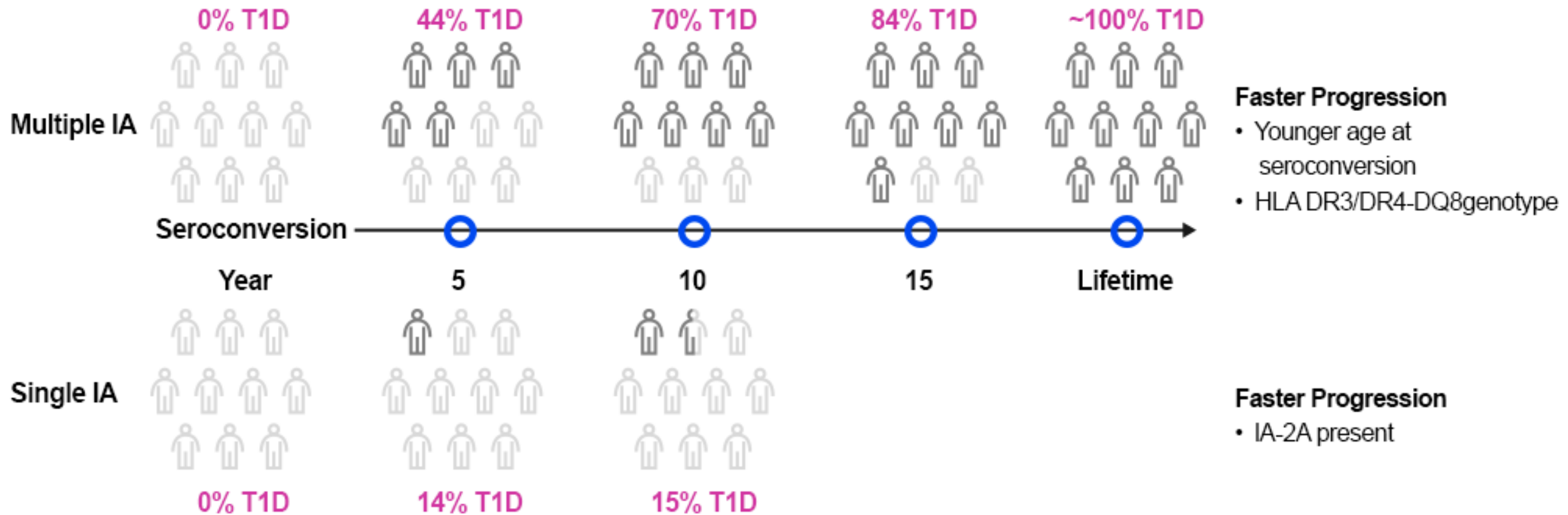
Research programs

- **ASK**
 - Kids and adults age 1 and above
 - No family history required
 - Lab or at home
- **TrialNet**
 - 2-45 yo with parent, sibling or child with T1D or 1+ positive antibodies on another lab
 - 2-20 yo with aunt/uncle, grandparent, cousin, niece/nephew or half-sibling with T1D
 - Lab or at home

Clinical lab panels- required for coverage of Tzield

- Quest
- Labcorp

Risk of T1D Progression to T1D after Seroconversion to Islet Autoantibody Positivity³



FPG = fasting plasma glucose; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; 2-h PG = 2-h plasma glucose.

When to start screening kids

Type 1 Diabetes Intelligence cohort- data from five prospective cohorts (Finland, Germany, Sweden, USA)

About 25,000 children at high risk enrolled before 2 years old and followed until age 15 or presence of T1 antibodies

Found that optimal screening ages were 2 and 6 years old

Sensitivity 82% and PPV of 79%

Antibodies usually present by age 6 even if no hyperglycemia until later in childhood

Initial screening results

If negative

- ▶ Consider repeat screen for kids age 9-11¹
- ▶ If family history, consider repeat screen 1 year for kids and adults
- ▶ For adults, no further testing may be necessary if no family history

1. Lancet Child Adolesc Health. 2023 Apr;7(4):261-268

2. Diabetes Technol Ther. 2023;25(11):790-799

Initial screening results

If positive

- ▶ Repeat ABs to confirm 6-12 months
 - ▶ One third of positive single Ab screen will be negative on confirmatory testing
 - ▶ Rare to have negative confirmatory testing with multiple + Ab on initial screen
- ▶ If confirmed, obtain glucose testing
- ▶ Provide education and consider expert referral

1. Lancet Child Adolesc Health. 2023 Apr;7(4):261-268
2. Diabetes Technol Ther. 2023;25(11):790-799

One positive antibody, confirmed

Children

- ▶ Rescreen every 6-12 months for 3 years and if no progression stop
- ▶ Can consider family history
- ▶ Twins higher risk even with 1 antibody

Adults

- ▶ If family history, rescreen in 3-5 years
- ▶ If no family history, unclear data to guide need for rescreening
- ▶ If return to seronegativity, no need to continue screening

2+ positive antibodies, confirmed

- ▶ Glucose monitoring recommended
- ▶ OGTT is gold standard and used to stage disease
- ▶ Then glucose should be monitored via HbA1c, serum glucose +/- CGM for 10-14 days at 3-6 month intervals
- ▶ Interval can be determined pending patient age, stage of DM with younger patients and stage 2 patients receiving more frequent monitoring

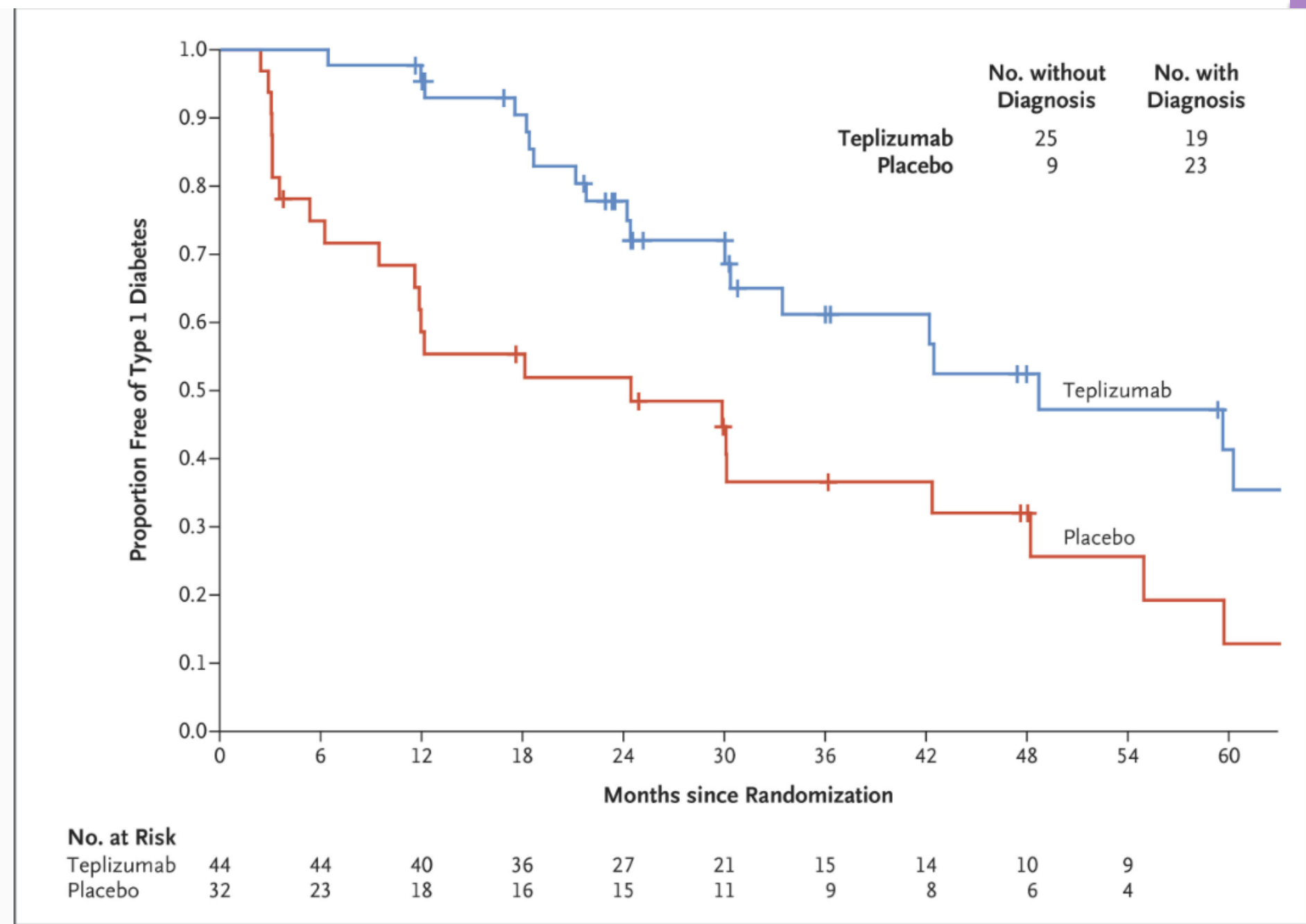
Education based on status

- ▶ Risk of progression should be discussed pending number of positive antibodies and glucose testing
- ▶ Patients with stage 2 should be given consideration of treatments to help delay progression
- ▶ All patients and families should receive education about signs of hyperglycemia/DKA as well as glucose testing and possible future need for treatment

Delaying Progression

Teplizumab (Tziel)

- ▶ Anti-CD3 monoclonal antibody that binds CD3 antigens on T cells
- ▶ 76 people with a relative with type 1 DM and stage 2 type 1 diabetes (dysglycemia with 2 positive antibodies) randomized to treatment or placebo
- ▶ 14 day IV infusion treatment course
- ▶ Median time to type 3 diabetes was 48 months in treatment group, 24 months in placebo group
- ▶ Most common side effect was lymphopenia followed by rash



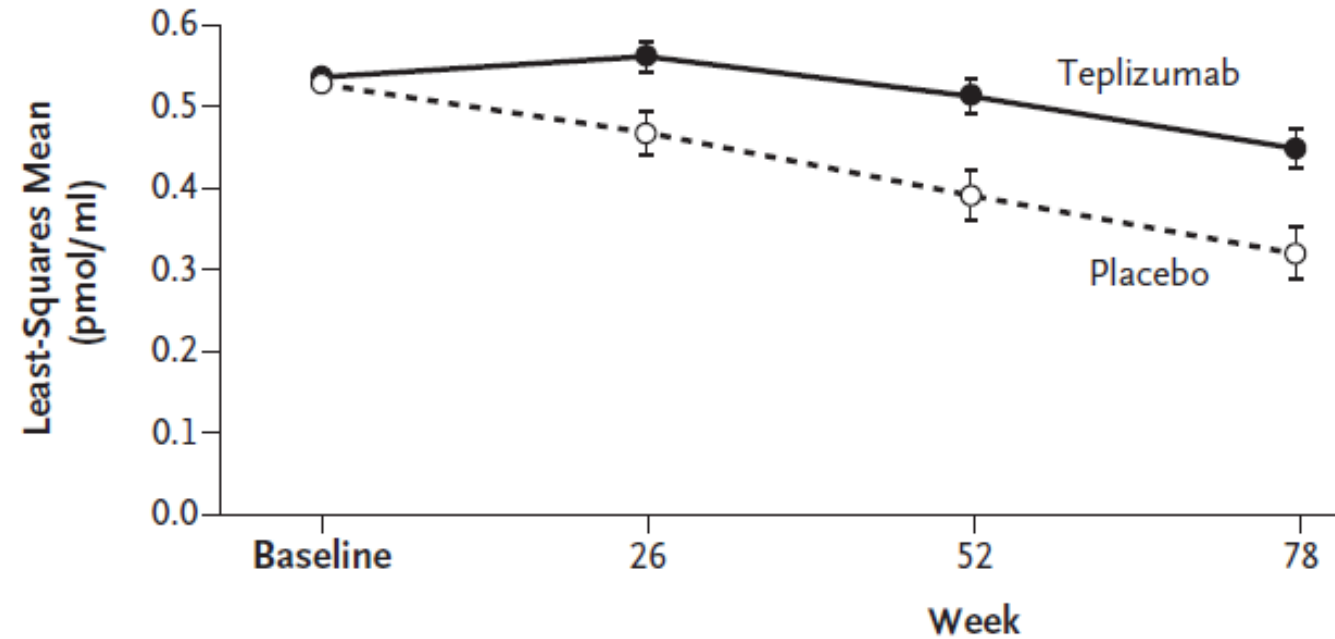
Teplizumab (Tziel)

- ▶ Approved for age 8-65 to prevent progression from stage 2 to stage 3 diabetes
- ▶ Require 2 antibodies and dysglycemia
 - ▶ Insurance requires commercial lab (Quest, Labcorp)
 - ▶ Some insurances required OGTT
- ▶ 2.7 year difference in time to onset of stage 3

Teplizumab in Newly Diagnosed Type 1 Diabetes

- ▶ Phase 3 trial to investigate if those with new diagnosed DM would have delay in disease progression
- ▶ Children and adolescents randomized to two, 12 day courses of treatment or placebo
- ▶ Primary end point was change from baseline in beta cell function at week 78
- ▶ Secondary end points included insulin doses, A1c, time in range, hypoglycemia

A C-peptide Level



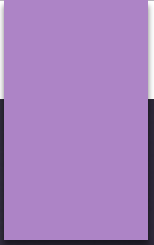
No. at Risk

Teplizumab	217	198	191	188
Placebo	111	101	98	88

- Preserved beta cell function but no significant difference in secondary endpoints

Ongoing questions, future directions

- ▶ Need for further access to screening
- ▶ Possibility of universal antibody screening programs
- ▶ Other immunotherapy options being evaluated
- ▶ Expanded label for Tziel?
 - ▶ Newly diagnosed type 1, stage 3
 - ▶ Repeat courses



Thank you!