DISEASE MODIFYING APPROACHES FOR TYPE 1 DIABETES

Jeremy Pettus MD

Steven Edelman MD

TCOYD
TAKING CONTROL OF YOUR DIABETES®

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- Learners must participate in the full activity and complete the evaluation in order to claim continuing education credit/hours.

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- **Presenters:**
- Steven V. Edelman, MD-Speakers Bureau: AstraZeneca, Lilly USA, LLC, MannKind Corporation, Merck, Sanofi-Aventis US, Inc; Consultant: Sensionics, Team Type 1; Advisor: Advisor: AstraZeneca, BrightSight, InPen, Lexicon, Lilly USA, LLC, MannKind Corporation, Merck, Sanofi-Aventis, US, Inc.
- Jeremy H. Pettus, MD Speakers Bureau: Sanofi, MannKind; Consultant: Carmot, Diasome, Sanofi, Novo Nordisk
- **Planners:** Sara Severance-No conflicts of interest
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MY STORY

…To Urgent Care

MY STORY

MY STORY

Blood Sugar = 1235 !!!!

How Are Type 1s Doing?

The Inconvenient Truth

Glycemic management: ~80% of patients A1c > 7%

DKA: 1 out of 20 admitted each year for DKA

CV disease: 2-4 fold risk in well-managed T1D

Insulin resistance: uniform in T1D

Weight: 2/3 of people with T1D are higher weight or clinically obese.

Hypoglycemia: 1 out of 20 admitted each year

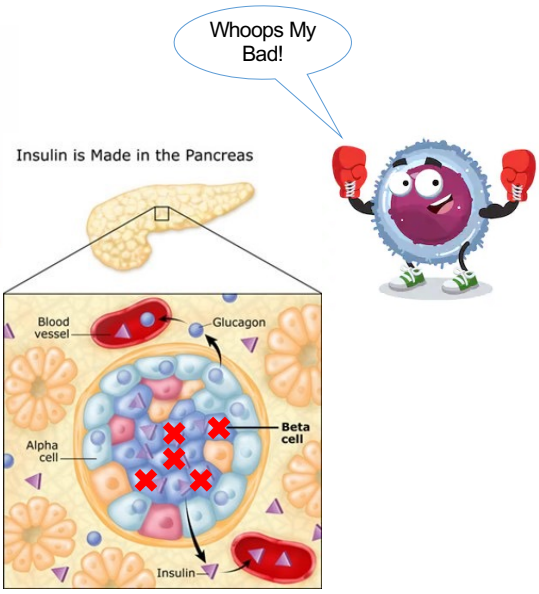
T1D State of Affairs

- We are far from meeting glycemic goals
- DKA and Severe Hypoglycemia are far too common
- Despite advances, these metrics are not improving

friend: how are things?
me: things are good!
narrator: things were not good.

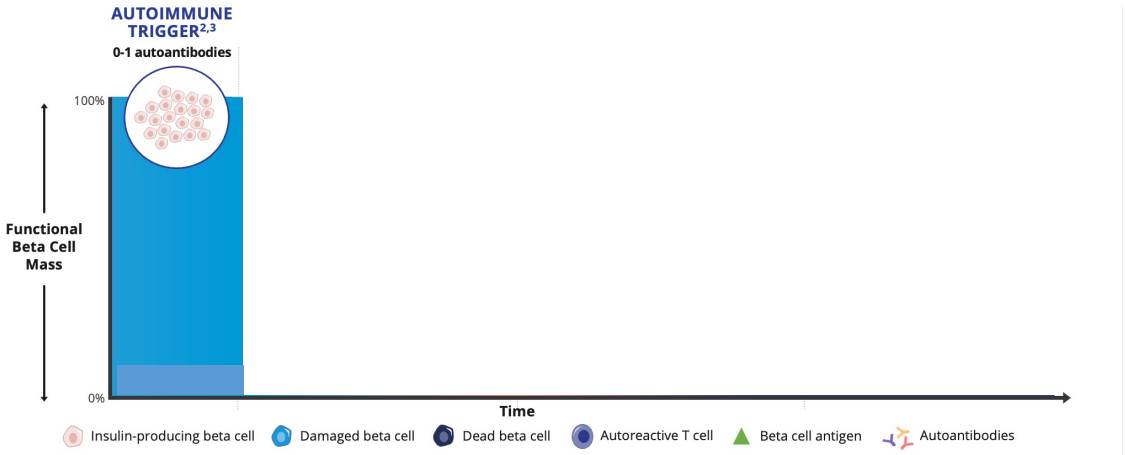
What is Type 1 Diabetes?

What is Type 1 Diabetes?



Natural Progression is <u>months</u> to a <u>few years</u>

The Stages of Type 1 Diabetes



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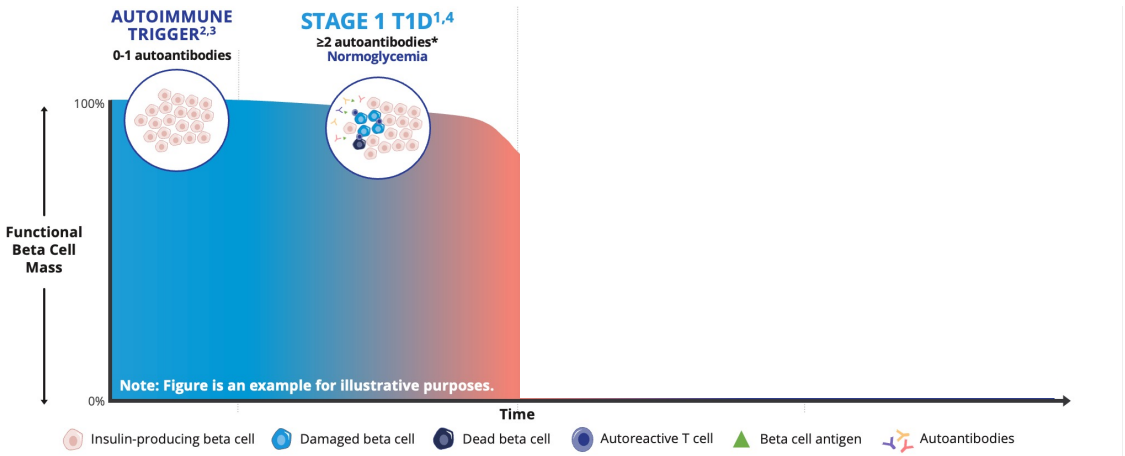

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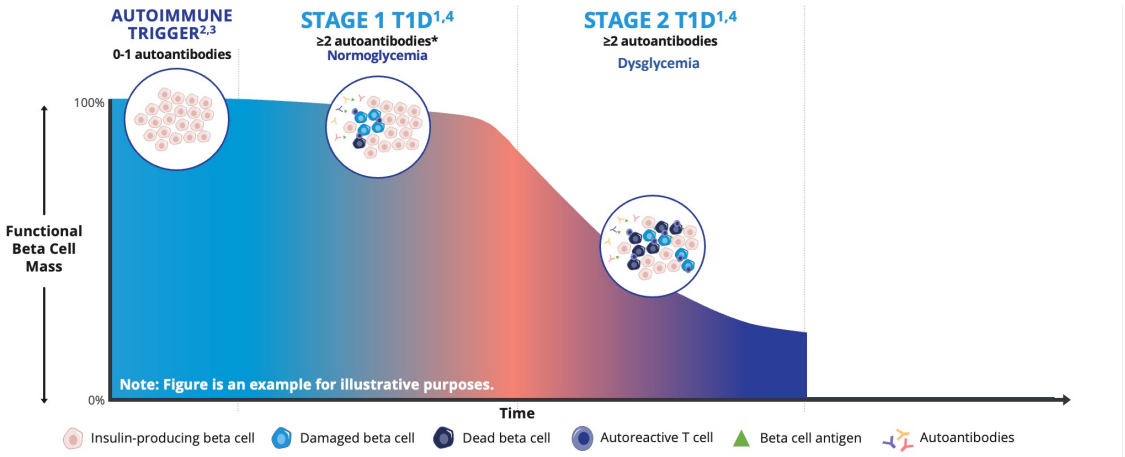

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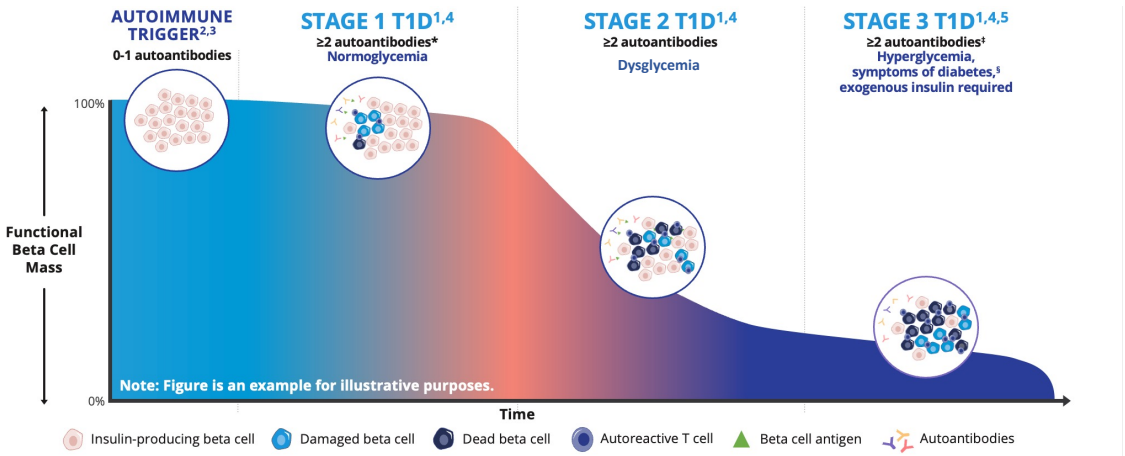
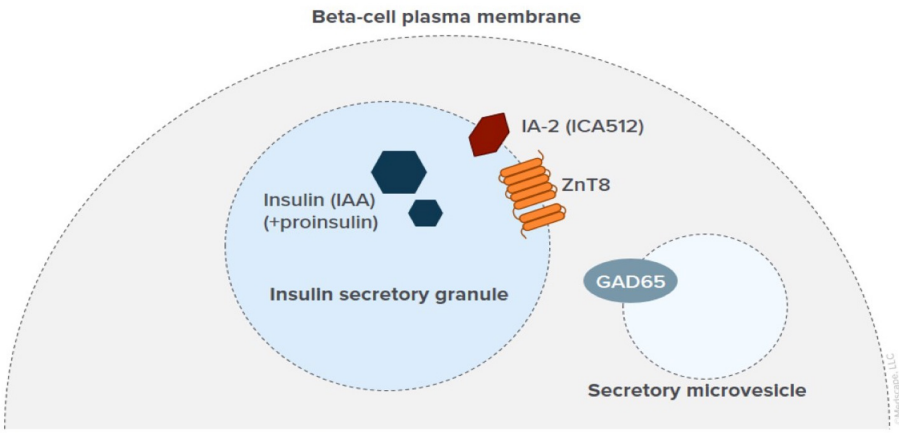


Type 1 Diabetes Autoantibodies

- Insulin (IAA)
- Islet antigen-2 (IA-2)
- Zinc transporter 8 (ZnT8)
- Glutamic acid decarboxylase (GAD65)



Arvan P, et al. Cold Spring Harb Perspect Med. 2012;2:a007658.

Prognosis by Stage

Half of patients will develop Stage 3 T1D in 5 years

3/4 of patients will develop Stage 3 T1D in 5 years

No Diabetes	Stage 1	Stage 2	Stage 3
0-1 islet autoantibodies	≥ 2 islet autoantibodies Normoglycemia[b]	≥ 2 islet autoantibodies Dysglycemia	Insulin-dependent T1D[c]

100% Lifetime Risk

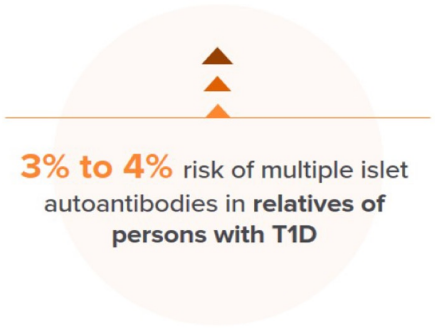
WHO Do We Screen for T1D?

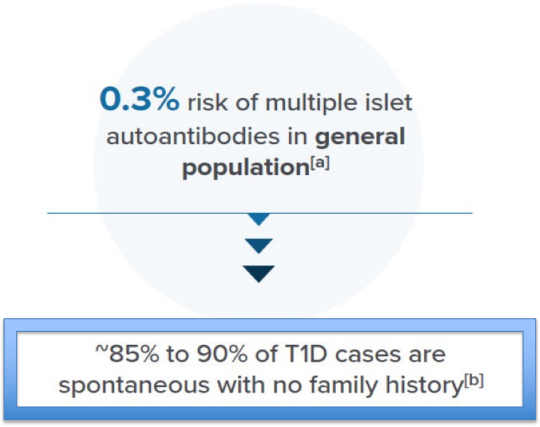
Patient Case: Father of the Bride

You're at a wedding having a good time when word gets out that you know something about type 1 diabetes. The father of the bride comes up and introduces himself. He says he heard about new treatments to delay the onset of type 1 diabetes. He is worried because he has type 1 diabetes and wants to know if he should get his kids and siblings screened, and if so, how to do it.

You put down your rum and diet and say...

Who is at Risk?





a. Ziegler A, et al. JAMA. 2020;323:339-351; b. Insel RA, et al. Diabetes Care. 2015;38:1964-1974.

Patient Case: Father of the Bride

You put down your rum and diet and say...

1. There is about a 95% that your kids will **NOT** get Type 1 Diabetes

Guidelines for Screening

Islet autoantibody screening is currently recommended for research studies and **as an option for first-degree family members**[1]

American Diabetes Association. AMERICAN DIABETES ASSOCIATION JANUARY 2023

General population screening programs using islet autoantibody testing can identify high-risk children[2]

ISPAD International Society for Pediatric and Adolescent Diabetes. INTERNATIONAL SOCIETY FOR PEDIATRIC AND ADOLESCENT DIABETES AUGUST 2022

Patient Case: Father of the Bride

You put down your rum and diet and say…

1. There is about a 95% that your kids will NOT get Type 1 Diabetes
2. The good news is that we can use simple blood tests to screen for risk

….So naturally he asks, how do I do that?

HOW do we Screen for T1D?

How to Screen

3 ways to get tested

T1Detect

Get a test kit shipped to your home through **JDRF's T1Detect** program. Once the test is completed, you can send it back using the prepaid shipping label provided.

ORDER A TEST KIT FROM T1DETECT →

TrialNet

If you are a first-degree family member of someone with T1D, **TrialNet*** can mail you a test kit to be completed at home. Or, you can order a kit to bring to a participating lab, and have the test done there.

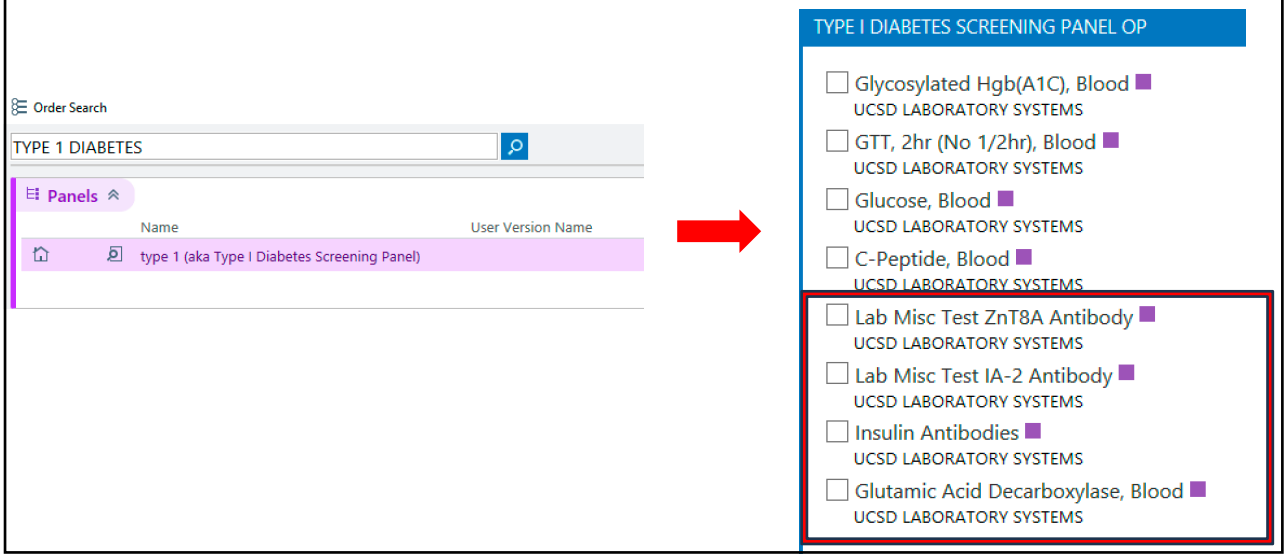
ORDER A TEST KIT FROM TRIALNET →

Doctor's office or lab

Schedule an appointment to take the test at a doctor's office. Your doctor can also give a referral to get tested at a participating lab in your area, like **LabCorp** or **Quest**.

TypeOneTested.com

Ordering Example:



Patient Case: Father of the Bride

You are out at trivia night with your usual Tuesday night crew when you get a frantic call from the father of the bride!

It turns out, the bride and groom had a great honeymoon and when they get home, all the kids get their antibodies tested. The bride and her sisters' results come back negative, but the boy (Drew), gets the following results....

Patient Case: Drew

Zinc Transporter 8 Antibody
ARUP test code 2006196

Zinc Transporter 8 Antibody	86.5 U/mL H	(Ref Interval: 0.0-15.0)

INTERPRETIVE INFORMATION: Zinc Transporter 8 Antibody

A value greater than 15.0 Kronus Units/mL is considered positive for the Zinc Transporter 8 Antibody (ZnT8). Kronus Units are arbitrary. Kronus Units = U/mL. This assay is intended for the semi-quantitative determination of antibodies to ZnT8 in human serum. Results should be interpreted within the context of clinical symptoms.

Islet Antigen-2 (IA-2) Autoantibody, Serum
ARUP test code 3001499

IA-2, Autoantibody	<5.4 U/mL	(Ref Interval: 0.0-7.4)

INTERPRETIVE INFORMATION: Islet Antigen-2 (IA-2) Autoantibody, Serum

A value greater than or equal to 7.5 Units/mL is considered positive for IA-2 autoantibodies.

This assay is intended for the quantitative determination of autoantibodies to Islet Antigen-2 (IA-2) in human serum. Results should be interpreted within the context of clinical symptoms.

GAD65 Ab Assay, Serum

Collected:	11/01/22 1518
Result status:	Final
Resulting lab:	ARUP
Reference range:	0.0 - 5.0 [IU]/mL
Value:	37.9 ^

Patient Case: Bride and Sister

Autoantibody screen

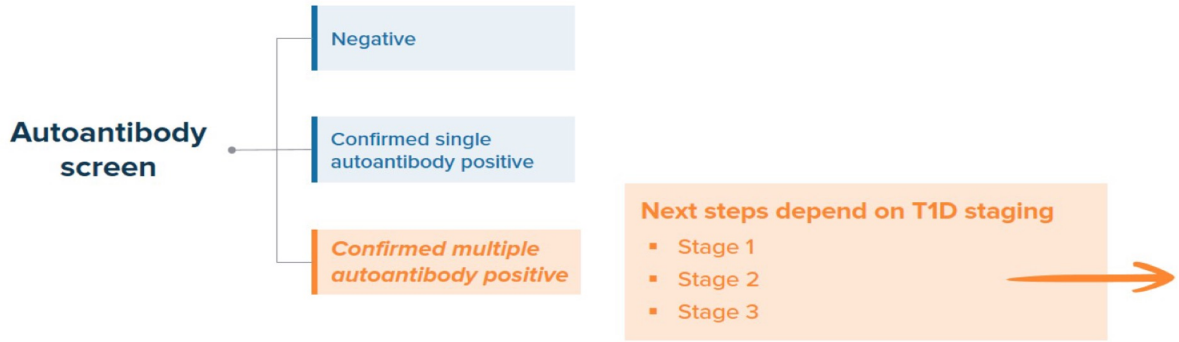
- ***Negative***
- Confirmed single autoantibody positive
- Confirmed multiple autoantibody positive

Next Steps:

- Rescreen if diabetes-like symptoms
- Consider rescreening:
  - At age 5 years if aged < 5 years at first screen
  - At age 11 years if aged 5-10 years at first screen

Note: Evidence-based guidelines for the follow-up and monitoring of patients after T1D autoantibody screening are not yet available (currently in development). The suggestions outlined above are based on expert opinion, and a lack of consensus exists among experts.
BG, blood glucose; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test.
Adapted with permission from Dr Frank Martin.

Patient Case: Drew



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Adapted with permission from Dr Frank Martin.

Patient Case: Drew

-Get him in to see a type 1 diabetes specialist

-Confirm antibody results

-perform metabolic testing (HbA1c, OGTT, CGM if available)

Stage 1 T1D
- HbA1c < 5.7%

Stage 2 T1D
- Fasting glucose 100-125 mg/dL
- 2-hour 140-199 after OGTT
- HbA1c 5.7% to < 6.5%

Stage 3 T1D
- HbA1c ≥ 6.5%
- Repeat OGTT in diabetic range
- Diabetes symptoms

What Can We Do For Antibody Positive Individuals?

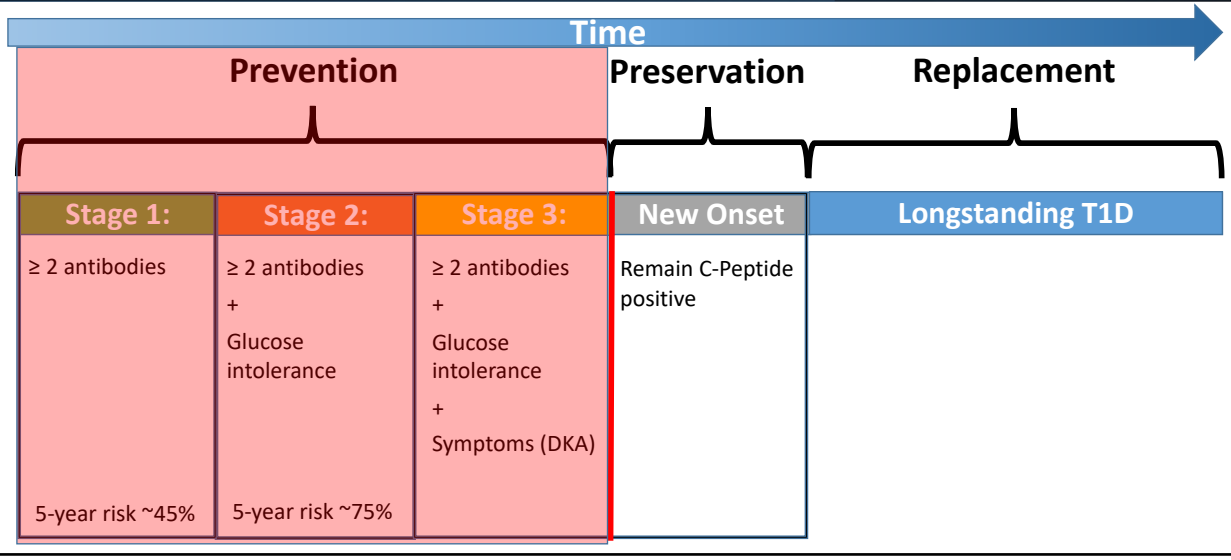
Natural History of Type 1 Diabetes

Time

Clinical T1D Diagnosis

Stage 1:	Stage 2:	Stage 3:	New Onset	Longstanding T1D
≥ 2 antibodies 5-year risk ~45%	≥ 2 antibodies + Glucose intolerance 5-year risk ~75%	≥ 2 antibodies + Glucose intolerance + Symptoms (DKA)	Remain C-Peptide positive	

Natural History of Type 1 Diabetes



Patient Case: Drew

-Drew comes into clinic to see you with his mom, dad, 2 sisters, and his ex-girlfriend

-He is a healthy 26 yo male with 2 + autoantibodies

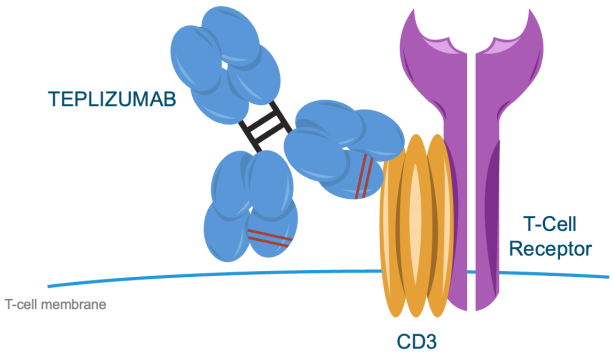
-He has an A1c of 5.9% without diabetes symptoms

What do you tell Drew and Crew?

Teplizumab

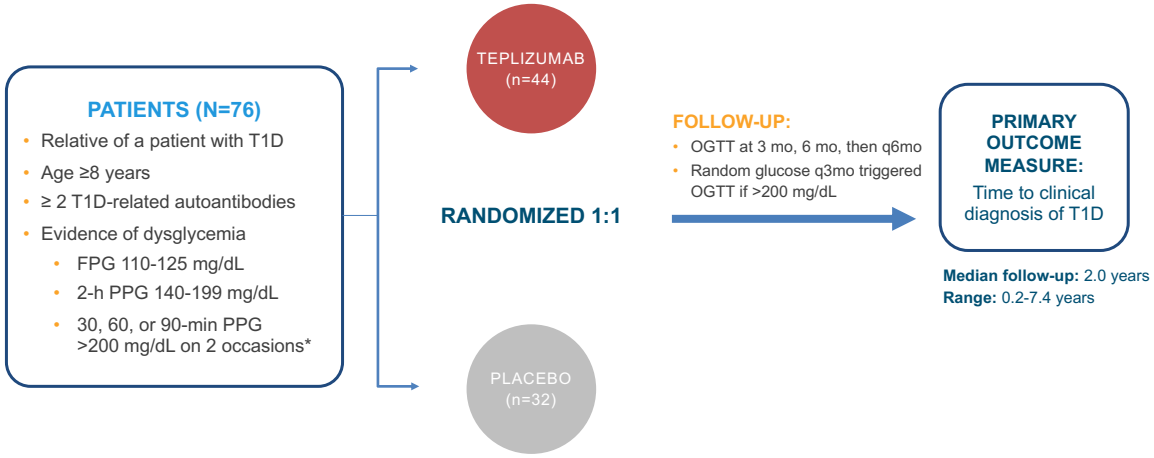
Teplizumab (Tzeild) Mechanism

- The T-cell receptor does not signal on its own, but rather through association with CD3 coreceptors[1]
- CD3 is the intracellular signaling component of the T-cell receptor complex[1]
- Teplizumab binds to CD3, causing internalization of the receptor complex and changes in gene expression[2]



1. Murphy K, Weaver C. *Janeway's Immunobiology*. 9th ed. Garland Science; 2017:257-293. 2. Kuhn C, Weiner HL. *Immunotherapy*. 2016;8(8):889-906.

TN-10 Study Evaluated the Delay or Prevention of T1D



*Amended to include participants aged ≥18 years with a single abnormal OGTT.

Herold KC, et al. *N Engl J Med*. 2019;381(7):603-613.

TN-10: Baseline Characteristics

Characteristic	Teplizumab (n=44)	Placebo (n=32)
Age, years		
Median (IQR)	14 (12-22)	13 (11-16)
Range	8.5-49.5	8.6-45.0
<18	66%	81%
Sex, % male	57%	53%
Relationship to person with T1D		
Sibling	64%	50%
Child	14%	19%
Parent	14%	9%
Multiple	5%	9%
Other	5%	13%

Characteristic	Teplizumab (n=44)	Placebo (n=32)
Autoantibody-positive		
GAD65	91%	88%
Microinsulin	45%	34%
IA-2	61%	75%
ICA	66%	88%
ZnT8	73%	75%
Glycated Hb, %		
Median	5.2%	5.3%
IQR	4.9-5.4	5.1-5.4

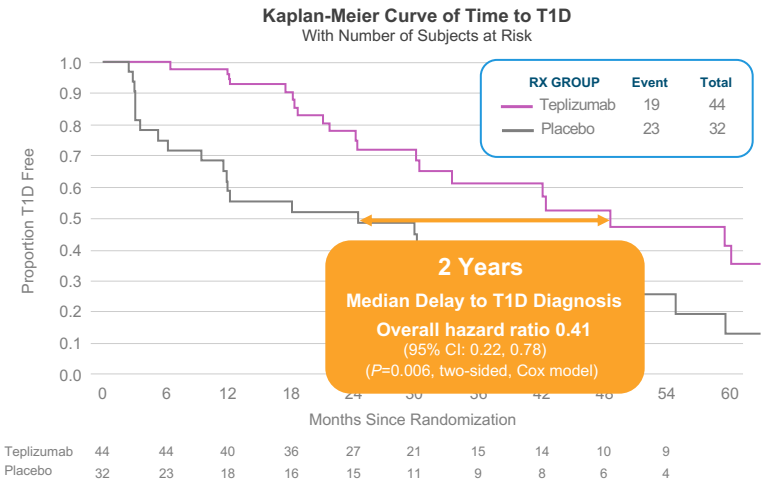
Herold KC, et al. *N Engl J Med*. 2019;381(7):603-613.

TN-10: Results

Primary analysis with median 2 years of follow-up

Median time to diagnosis of stage 3 T1D

Teplizumab: 48.4 months
Placebo: 24.4 months



Herold KC, et al. *N Engl J Med*. 2019;381(7):603-613.

TN-10: Results

- At the end of the study ~60% of teplizumab-treated patients were free of T1D, compared to ~30% of subjects who received placebo
- The rate of T1D development was decreased by ~60%

	Teplizumab (N=44)	Placebo (N=32)	
DEVELOPED T1D DURING STUDY	19/44 = 43%	23/32 = 72%	
FREEDOM FROM T1D AT STUDY END	25/44 = 57%	9/32 = 28%	*P* = 0.012
ANNUALIZED RATE OF T1D	14.9%	35.9%	58% DECREASE

1. Herold KC, et al. *N Engl J Med*. 2019;381(7):603-613. 2. Provention Bio, Inc. 2020. Data on file.

TN-10: Adverse Events

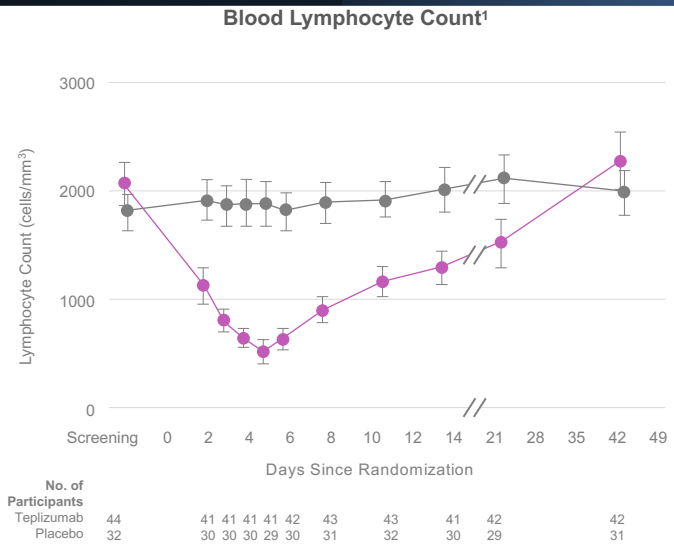
Adverse Effect Category *(possibly, probably, definitely related to study drug)*	Teplizumab		Placebo	
EVENTS OCCURRING IN ≥5% OF SUBJECTS	Number of Events	Number of Subjects (%)	Number of Events	Number of Subjects (%)
Blood/Bone Marrow*	45	33 (75.0)	2	2 (6.2)
Dermatology/Skin*	17	16 (36.4)	1	1 (3.1)
Pain	11	5 (11.4)	5	3 (9.4)
Infection	8	5 (11.4)	5	3 (9.4)
Gastrointestinal	5	4 (9.1)	3	3 (9.4)
Metabolic/Laboratory	7	4 (9.1)	2	2 (6.2)
Pulmonary/Upper Respiratory	6	4 (9.1)	0	0 (0)
Endocrine	0	0 (0)	2	2 (6.2)
TOTAL EVENTS AND SUBJECTS	112	44 (100)	23	32 (100)

Consistent with early studies: transient drop in WBC due to margination, mild rash which resolves without intervention

No opportunistic infection or Epstein-Barr virus reactivation

Mild and transient pulmonary and upper respiratory AEs

TN-10: Lymphocyte Counts



-T cells returned to circulation on Day 6

-Lymphocyte count returned to normal after teplizumab treatment

Early Studies: Safety Data

Most Common AEs >10% in Protégé, Protégé Extension, and Encore

System Organ Class	Placebo (n=160)	Full 14-Day Course (n=308)
At least 1 AE	160 (100.0)	308 (100.0)
Blood and lymphatic system disorders	64 (40.0)	233 (69.1)
Lymphopenia	23 (14.4)	195 (57.9)
Leukopenia	31 (19.4)	122 (36.2)
Neutropenia	24 (15.0)	69 (20.5)
Gastrointestinal disorders	44 (27.5)	115 (34.1)
Nausea	19 (11.9)	46 (13.6)
Vomiting	9 (5.6)	33 (9.8)
General disorders and administration site conditions	54 (33.8)	132 (39.2)
Pyrexia	28 (17.5)	78 (23.1)
Infections and infestations	79 (49.4)	163 (48.4)
Upper respiratory tract infection	21 (13.1)	53 (15.7)
Nasopharyngitis	19 (11.9)	43 (12.8)
Investigations	146 (91.3)	327 (97.0)
Blood bicarbonate decreased	64 (40.0)	166 (49.3)
White blood cell count decreased	31 (19.4)	130 (38.6)
Aspartate aminotransferase increased	44 (27.5)	103 (30.6)
Hemoglobin decreased	49 (30.6)	105 (31.2)
Alanine aminotransferase increased	23 (14.4)	91 (27.0)
Lymphocyte count decreased	15 (9.4)	104 (30.9)
Neutrophil count decreased	25 (15.6)	81 (24.0)

Transient and mechanism-based cytopenias

No opportunistic infections or EBV reactivation

Rash and pruritus were higher in the teplizumab group

System Organ Class	Placebo (n=160)	Full 14-Day Course (n=308)
Investigations		
Blood sodium decreased	33 (20.6)	70 (20.8)
Blood alkaline phosphatase increased	30 (18.8)	54 (16.0)
Platelet count decreased	15 (9.4)	51 (15.1)
Blood calcium decreased	20 (12.5)	49 (14.5)
Blood potassium increased	17 (10.6)	40 (11.9)
Metabolism and nutrition disorders	93 (58.1)	190 (56.4)
Hyponatremia	47 (29.4)	89 (26.4)
Hypocalcemia	34 (21.3)	62 (18.4)
Hyperkalemia	16 (10.0)	43 (12.8)
Musculoskeletal and connective tissue disorders	13 (8.1)	43 (12.8)
Nervous system disorders	38 (23.8)	93 (27.6)
Headache	29 (18.1)	77 (22.8)
Renal and urinary disorders	15 (9.4)	51 (15.1)
Proteinuria	15 (9.4)	39 (11.6)
Respiratory, thoracic, and mediastinal disorders	29 (18.1)	51 (15.1)
Skin and subcutaneous tissue disorders	37 (23.1)	176 (52.2)
Rash	12 (7.5)	89 (26.4)
Pruritus	8 (5.0)	40 (11.9)

Patient Case: Return of the Drew

-You explain Teplizumab to Drew and after considering for 2 days, he calls to initiate therapy.

-How do you do this????

Things to Consider for Teplizumab: Indication

- TZIELD is indicated to delay the onset of Stage 3 type 1 diabetes in adults and pediatric patients 8 years of age and older with Stage 2 type 1 diabetes
  - Confirm Stage 2 T1D by documenting:
    - ☑ At least 2 positive pancreatic islet cell autoantibodies
    - ☑ Dysglycemia without overt hyperglycemia using an OGTT or, if an OGTT is not available, an alternative method for diagnosing dysglycemia without overt hyperglycemia

Things to Consider for Teplizumab : Lab monitoring

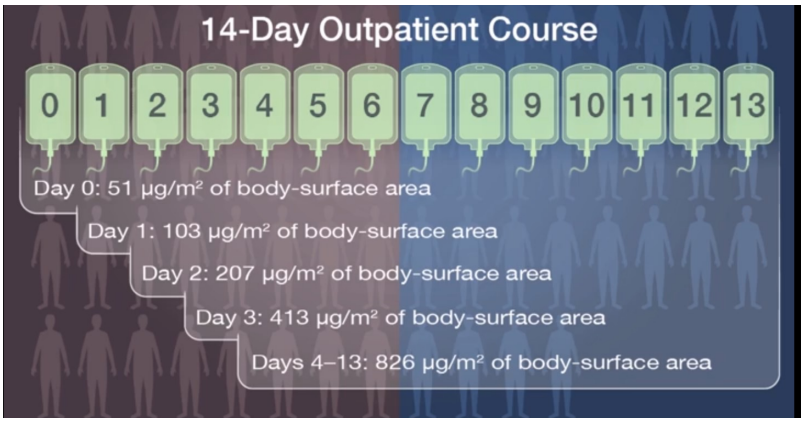
CBC: Baseline, day 5-6, and at week 2 (minimum)

Discontinue Teplizumab (Tzeild) for prolonged lymphopenia (< 500 cells/mcl for longer than 1 week)

CMP: Baseline, day 5-10, week 2

Main issue to evaluate for is LFT abnormalities

Things to Consider for Teplizumab : Infusion



Can be in infusion center or at home (PICC line)

Patient Case: Drew Conclude

-Drew does very well with the infusion with very minimal side effects

-He asks what's next?

Screening Lowers Risk of DKA

Rates of DKA in T1D Screening Studies

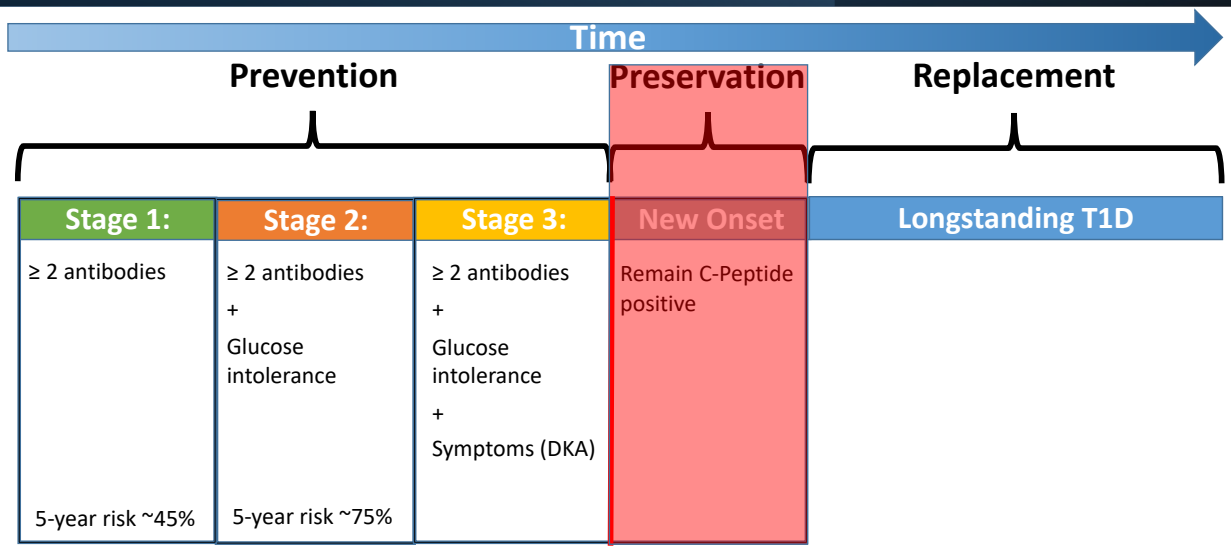
Study	Setting	DKA Rate		Expected DKA Rate Without Screening	
ASK[a]	GENERAL POPULATION (Colorado, USA)	2/13	15%	6/13	46%
Fr1da[b]	GENERAL POPULATION (Bavaria, Germany)	2/62	3%	32%[d]	
DAISY[c]	RELATIVES/GENETIC RISK (Colorado, USA)	1/30	3%	44/101	44%*
TEDDY[d]	GENETIC RISK, AGE < 5 YEARS (USA, Sweden, Finland, Germany)	9/79	11%	17%-36%	

Patient Case: Alice

Alice is a 19yo girl who was just diagnosed with T1D 3 months ago. She comes into see you for the first time. She is now on basal insulin only now at 10 units per day and occasionally using 1-2 units of RAI with meals. She is on a CGM with an avg. BG of 122 mg/dl and TIR of 95%.

She is adjusting well, but says her mom asked to ask you about research studies for T1D...

Natural History of Type 1 Diabetes

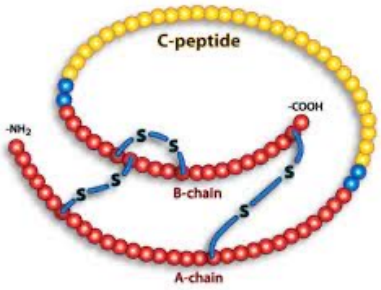


New Onset T1D: Its not too late!

- 10-20% of Beta Cells are present at diagnosis
- Maintaining *any* beta cell function has been linked to:
  - Better Glycemic Control
  - Less Hypoglycemia
  - Lower Rates of Microvascular Complications

New Onset T1D: Study Concepts

- The closer you intervene to diagnosis, the better
- Need to have some degree of C-peptide to maintain
- Studies are generally 1-2 years in duration with C-peptide measurements throughout



Therapies Being Investigated for New Onset

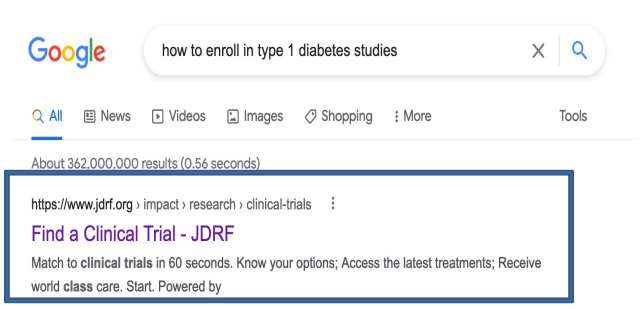
- Teplizumab
- Verapamil
- ATG
- GLP-1 RA
- Others

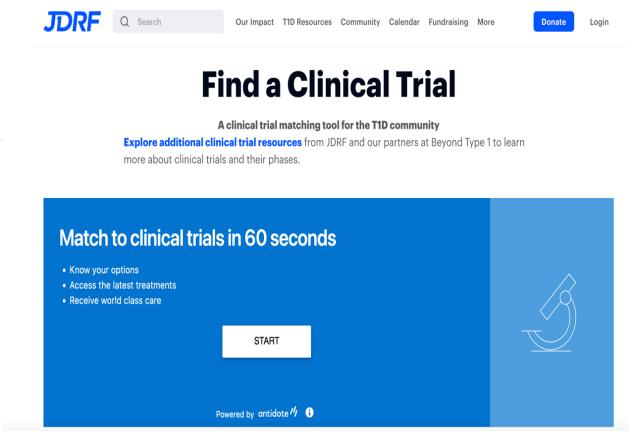
Patient Case: Alice

You tell Alice a couple things:

1. She is going to have a LONG and HEALTHY life
2. Tell her that her blood sugars are AMAZING. They likely will slowly get worse and this could happen over months to years
3. Explain the honeymoon phase with an emphasis on an opportunity to intervene
4. Hook her up with clinical trials…

Clinical Trial Finder





Patient Case: Steve and Jeremy

Replacement

TIME

Prevention			Preservation	Replacement
Stage 1:	**Stage 2:**	**Stage 3:**	**New Onset**	**Longstanding T1D**
≥ 2 antibodies 5-year risk ~45%	≥ 2 antibodies + Glucose intolerance 5-year risk ~75%	≥ 2 antibodies + Glucose intolerance + Symptoms (DKA)	Remain C-Peptide positive	

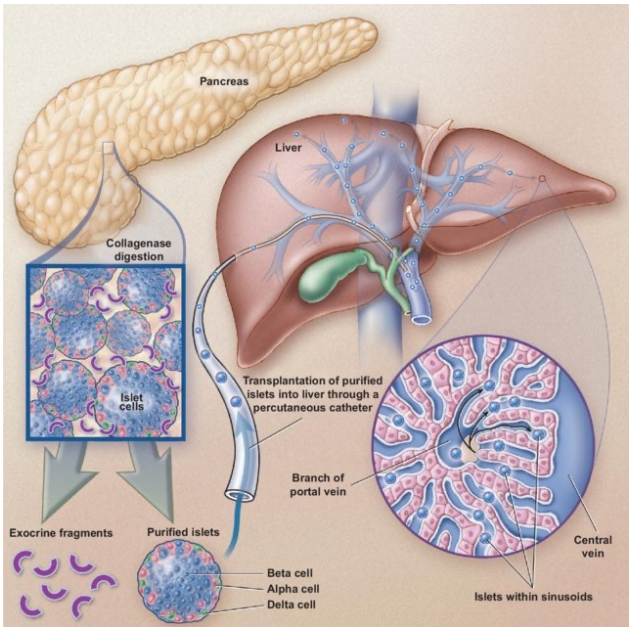
Ways To Give Back Beta Cells

- Whole Pancreas Transplant
- Islet Cell Infusion
- Islet Cell "Implant"

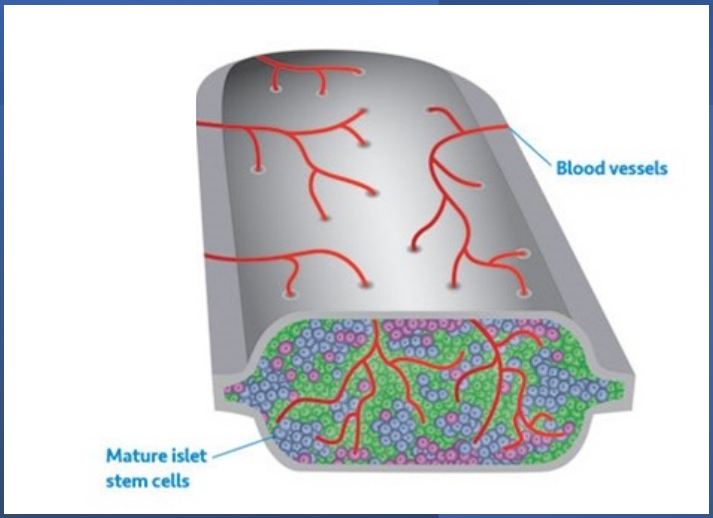
Islet Cell Infusion

Sources of Cells:

-Human Donors
-Stem Cells



Islet Cell "Implant"



In Summary:

- We Can and Should Screen for Individuals at Risk for T1D
  - This can be done with simple antibody tests
- We now have the first, FDA, approved therapy to delay the progression of T1D
- New therapies will likely be approved for patients with existing diabetes soon
- So…

Thank You!
Steve & Jeremy

TCOYD
TAKING CONTROL OF YOUR DIABETES®