THE UNIVERSITY OF CHICAGO MEDICINE

Kovler Diabetes Center

Type 1 Diabetes Research Advances

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JDRF Type 1 Nation Chicago 2017

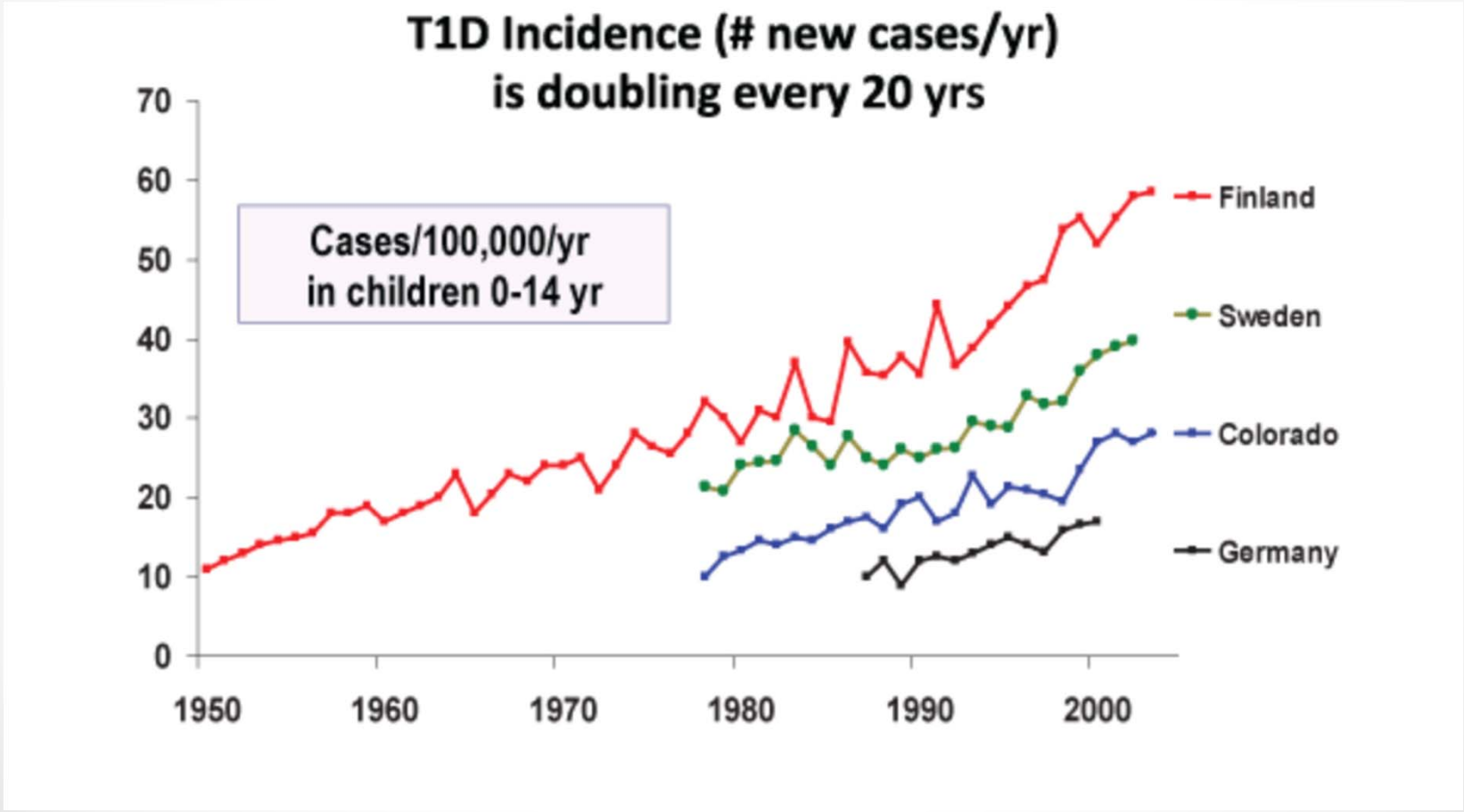
THE UNIVERSITY OF CHICAGO

KOVLER DIABETES CENTER FOR KIDS AT COMER CHILDREN'S HOSPITAL

Overview

- T1D Basics
  - Immune Mechanisms
- Type 1 Diabetes TrialNet
  - Current findings
  - Associated Studies
- Other research

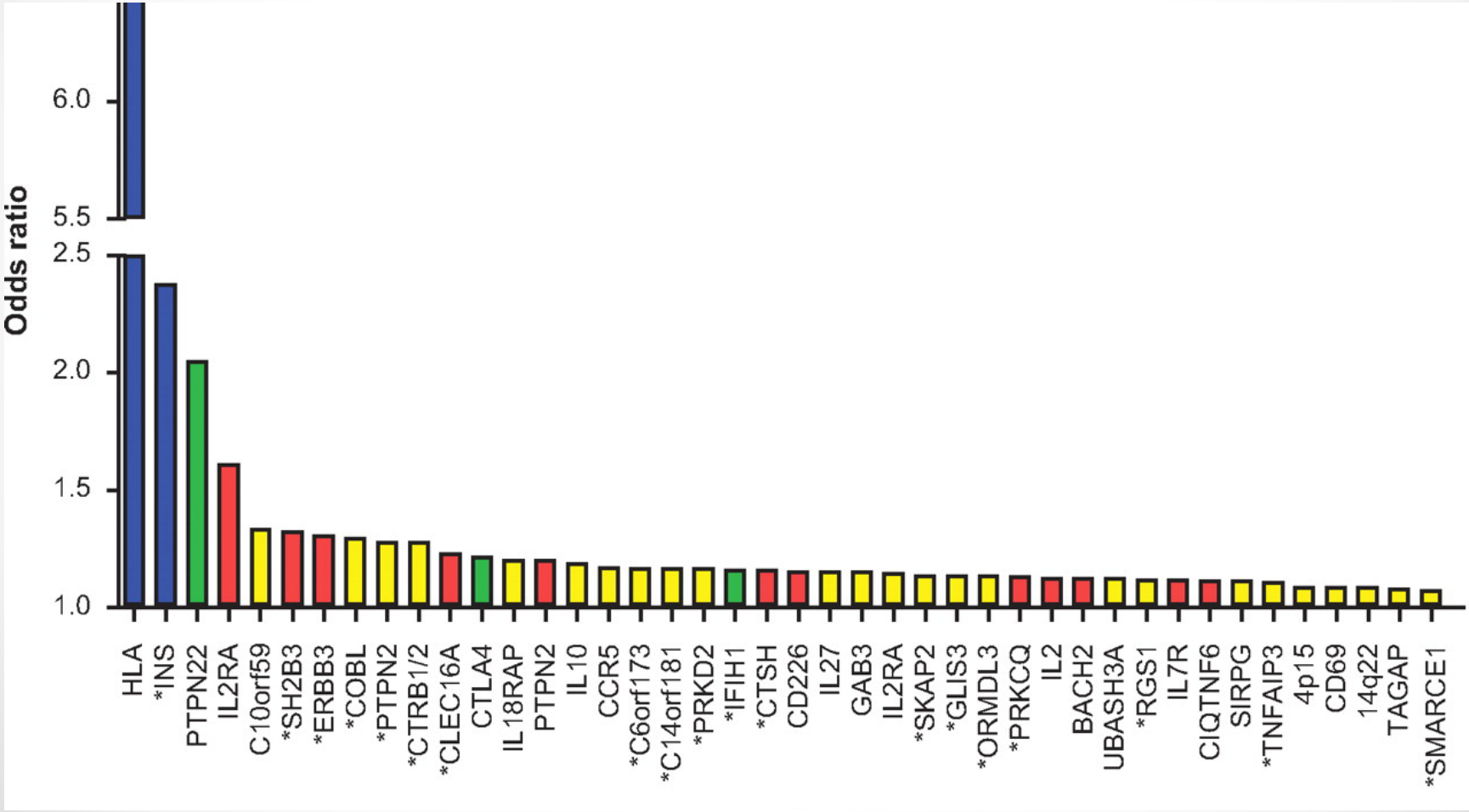
T1D is Increasing



New Ideas about T1D

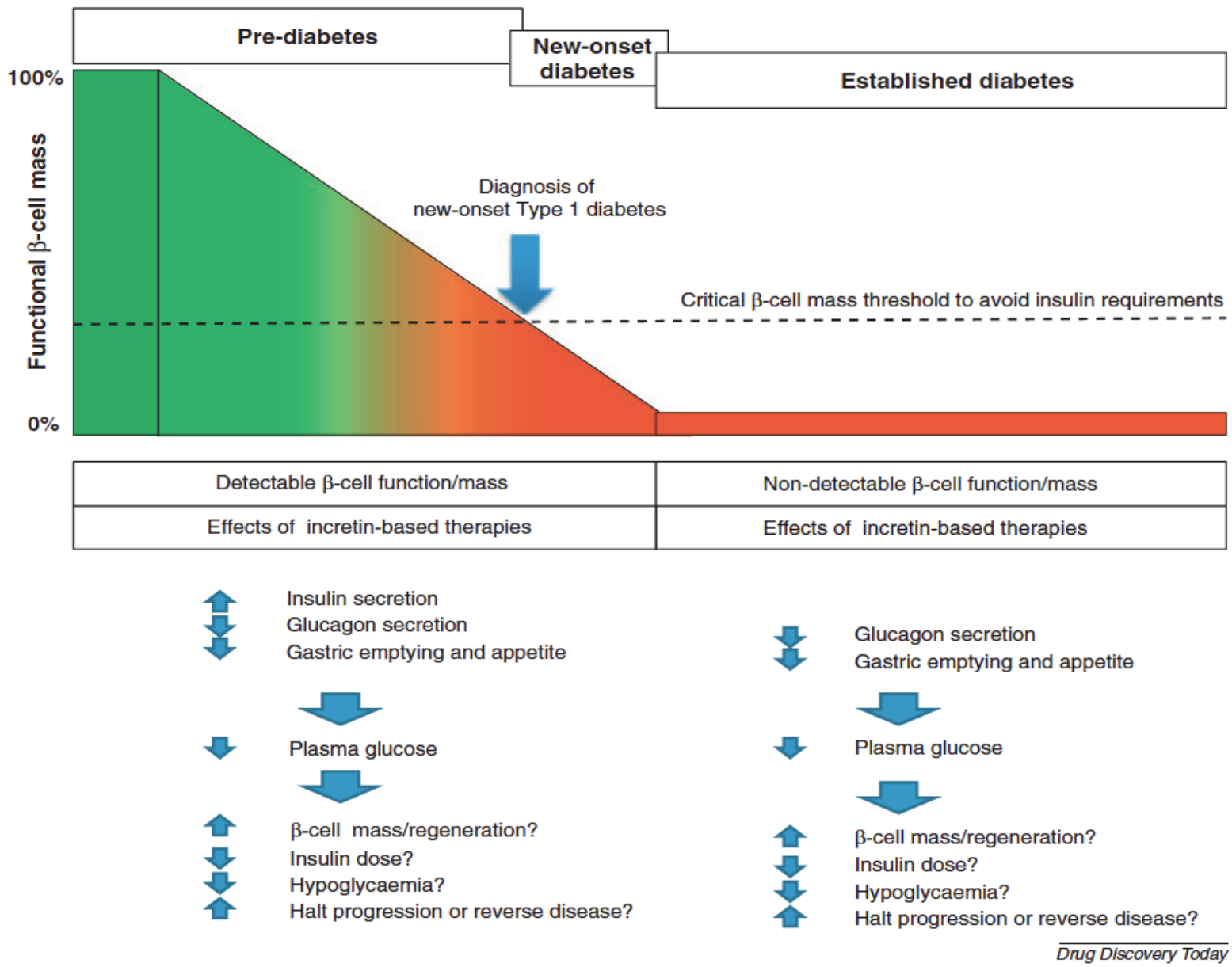
- While peak onset is in youth, T1D can happen at any age
- Anti-beta cell antibodies are variable
- C-peptide may be high early on, then low
- ***Incidence in first degree family members is about 5%***
- Efforts to halt progress of type 1 diabetes have been disappointing
- Is it one disease? Many? Is the beta cell the problem?
- Incidence *is increasing world-wide*, about 8% of all cases in the U.S.

GWAS and Type 1 Diabetes – Lots of Genes



What Have We Learned from Genetic Studies of Type 1 Diabetes?

- Susceptibility highest by a major gene or genes in the HLA region of chromosome 6.
- Effect of HLA region gene(s) modified by at least 40 genes with only a small effect on risk - genetic background.
- Genetics alone is not useful in identifying those at risk of developing type 1 diabetes - presence of autoantibodies to β-cell proteins are more predictive.


Pre-diabetes
New-onset diabetes
Established diabetes
100%
Functional β-cell mass
0%
Diagnosis of new-onset Type 1 diabetes
Critical β-cell mass threshold to avoid insulin requirements
Detectable β-cell function/mass
Non-detectable β-cell function/mass
Effects of incretin-based therapies
Effects of incretin-based therapies
Insulin secretion
Glucagon secretion
Gastric emptying and appetite
Plasma glucose
β-cell mass/regeneration?
Insulin dose?
Hypoglycaemia?
Halt progression or reverse disease?
Glucagon secretion
Gastric emptying and appetite
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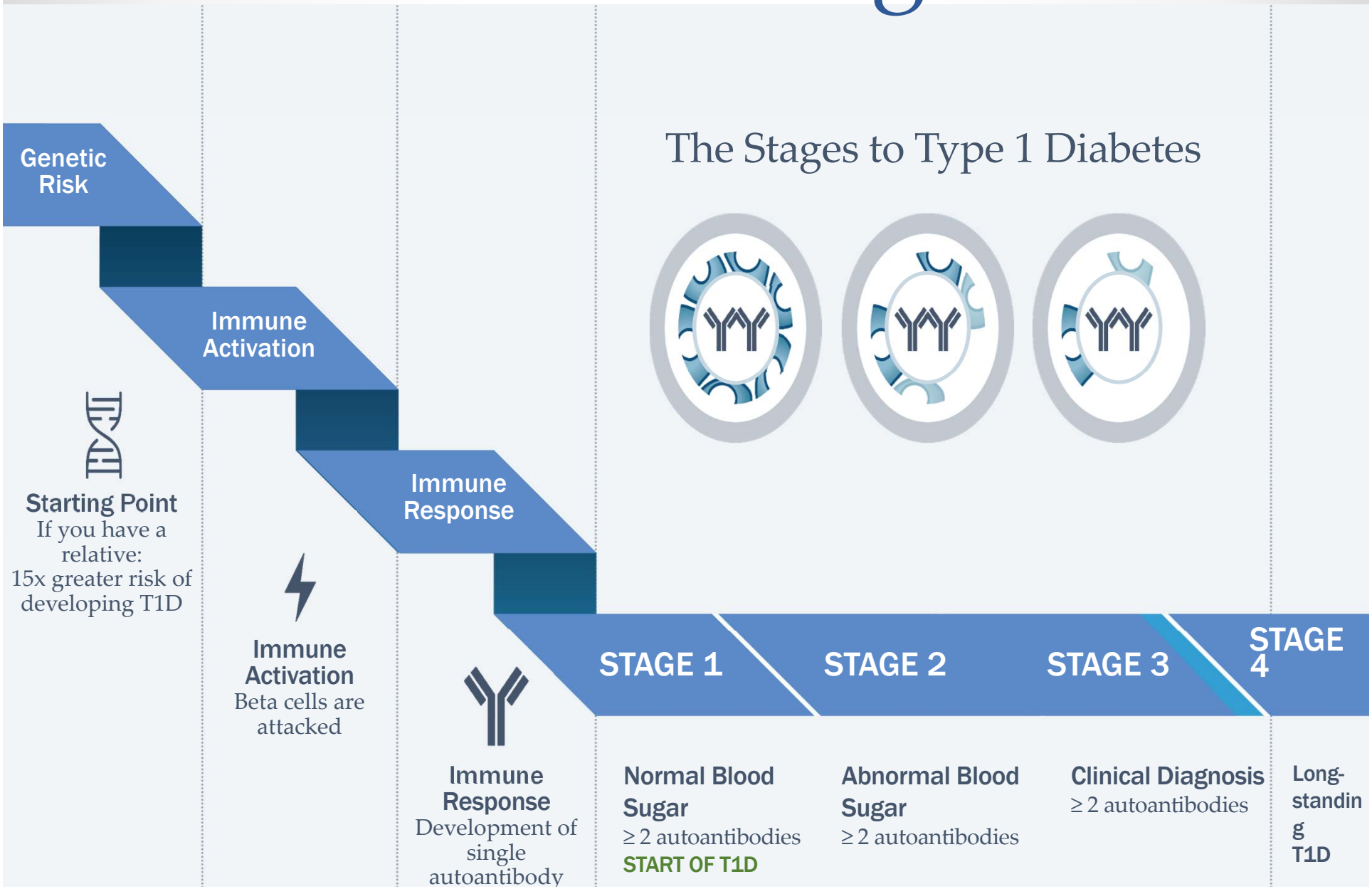
Halt progression or reverse disease?
Drug Discovery Today

T1D Disease Progression



What do we know about treating T1D?

- Importance of blood sugar control to prevent complications and prolong healthy life
- Basal / bolus dosing
- *Insulin pumps*
- *Glucose sensors*
- *Closed loop systems*
- *Beta cell replacement*

- Blood Pressure
- Cholesterol: low LDL, high HDL
- Stop Smoking
- Aerobic Exercise
- Weight loss if high
- Eye care, foot care, dental care
- ***hypoglycemia***

What about preventing T1D?

TrialNet

- An international network of 21 leading academic institutions, physicians, scientists and healthcare teams with over 200 affiliates throughout the United States, Canada, Finland, the United Kingdom, Italy, Germany, Australia, and New Zealand at the forefront of type 1 diabetes research.

- Using knowledge gained through clinical research, the mission is to prevent type 1 diabetes and stop disease progression by preserving insulin production

TrialNet

Funded by the National Institutes of Health

we offer risk screening for relatives of people with type 1 diabetes and

innovative clinical studies to preserve insulin production

TrialNet

- Family members of those with T1D have a 15 times greater risk of developing the disease than the general population (0.03 vs 5%)

- At least 90% of people diagnosed with T1D have diabetes-related autoantibodies. Autoantibody status may change, so we recommend retesting youth annually.

TrialNet

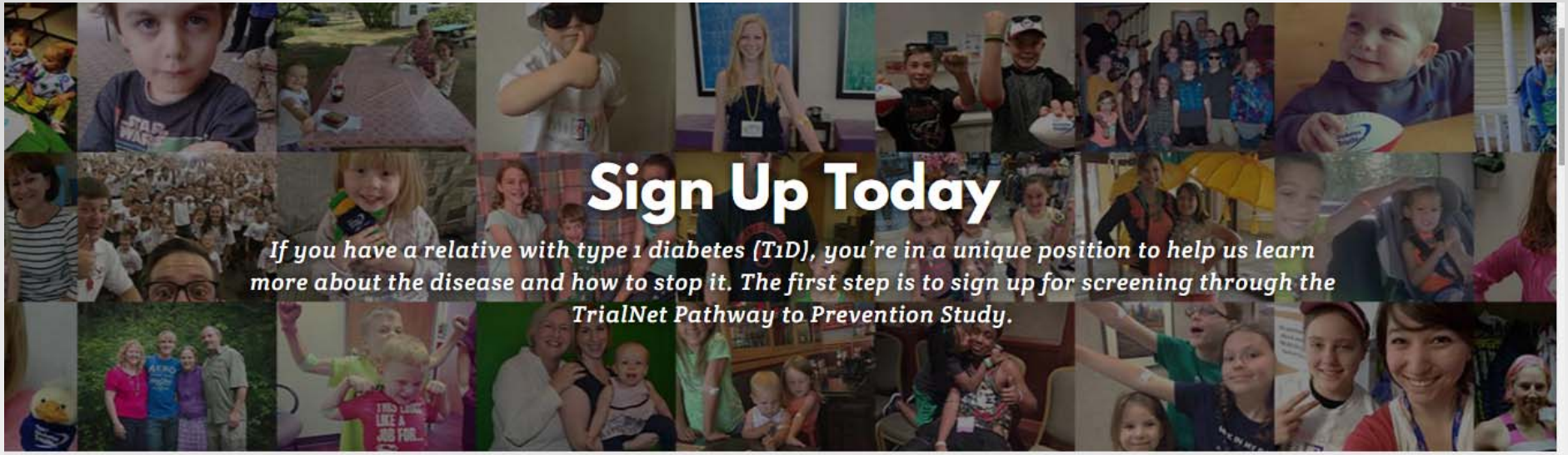
- Any individuals with **2 or more autoantibodies** have a **50-90% risk** of developing diabetes in the next 5 years- **and a near 100% lifetime risk**

- Those with autoantibodies who are not eligible for a clinical trial will be closely monitored. ***Monitored participants who develop Type 1 are typically diagnosed prior to any clinical symptoms of diabetes***

TrialNet: Eligibility

- Anyone between 1 and 45 years of age, with 1st degree relative (a sibling, child, or parent) with T1D

- Anyone between 1 and 20 years of age with a 2nd or 3rd degree relative (***cousin, aunt, uncle, niece, nephew, grandparent, or half-sibling***) with T1D



Take your first step on the Pathway to Prevention!

The Pathway to Prevention Study starts with a simple blood test that can detect your risk of developing T1D years before symptoms appear. Detecting the disease at its earliest stage is super important. If you are in the early stages of T1D, you may be able to join a research study looking for ways to slow down or stop the disease. We invite you to join our TrialNet family and help find a way to prevent T1D.

Sign Up Today!

Pathway to Prevention screening is free to relatives of people with type 1 diabetes. Get started by answering a few simple questions and selecting the screening option that works best for you.

Get Screened!

The first step on the Pathway to Prevention is to sign up for screening. It's easy and convenient. Pick the best option for you:

- Make an appointment at one of 200 TrialNet locations

Your Results

Your screening results will be ready in 4 to 6 weeks. They will be made available only to you. If your test results show you are in the early stages of T1D, the next step will be to go to a TrialNet location for follow-up. You may qualify for participation in a prevention study or

TrialNet: Sign Up

Online

Have questions?

Contact your closest TrialNet Clinical Center with any questions you may have.

Ask us

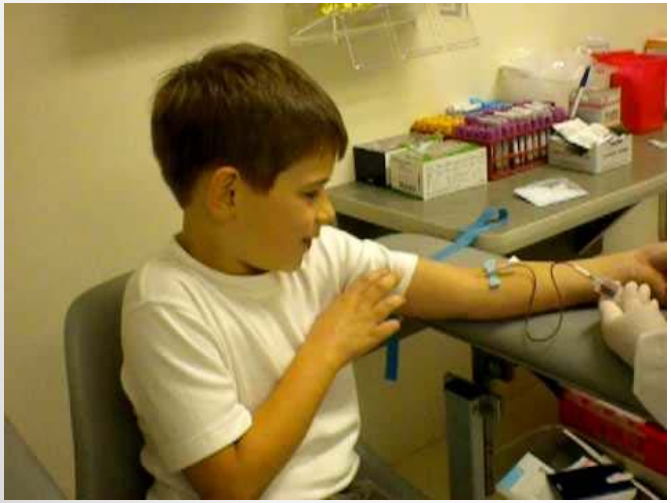
Ready to get started?

Click here to sign up for TrialNet Pathway to Prevention type 1 diabetes risk screening.

Sign up now

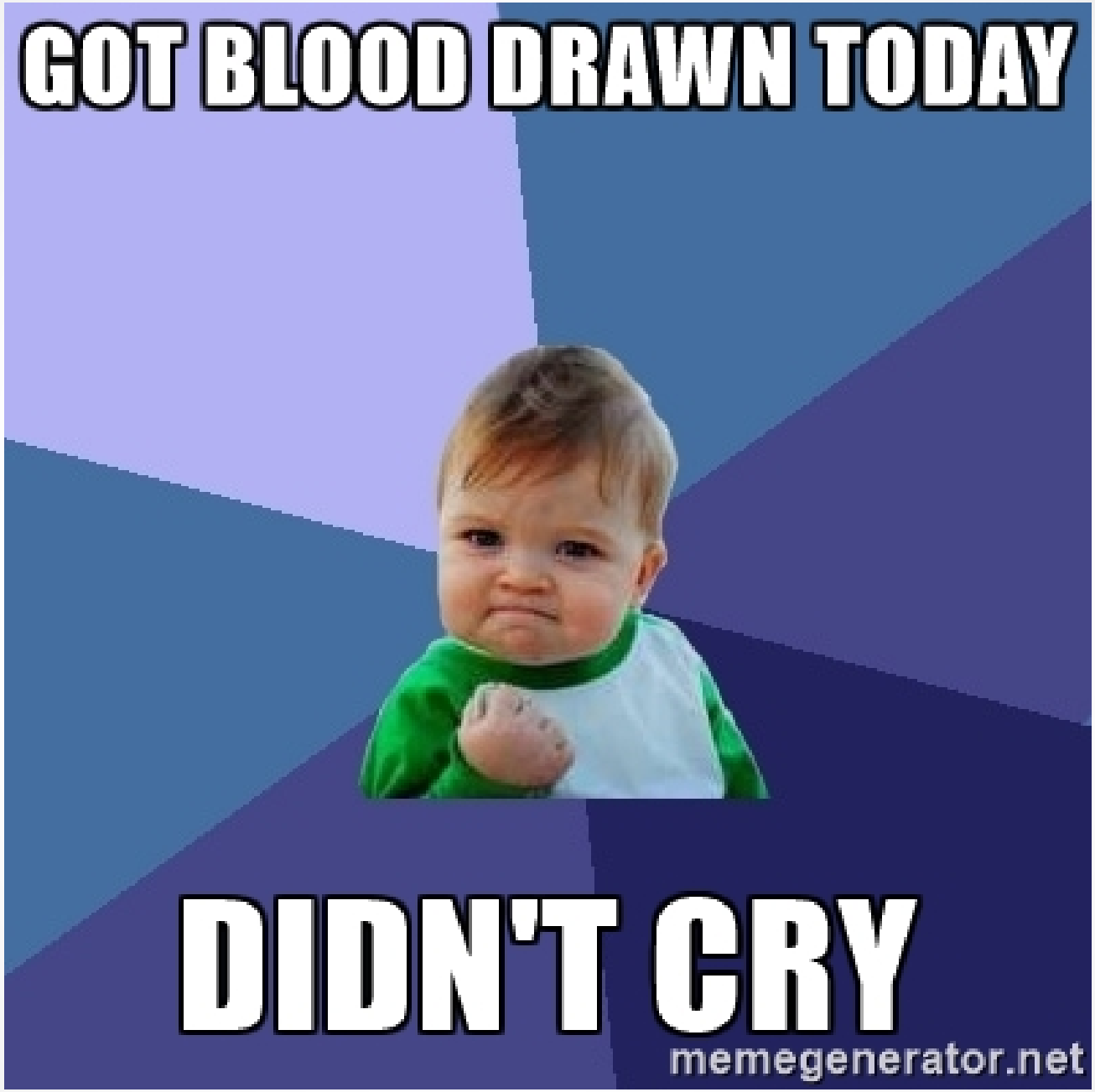
At your local Quest

Quest Diagnostics®



Capillary Kits returning soon

- Screen at your local center


GOT BLOOD DRAWN TODAY
DIDN'T CRY
memegenerator.net

TrialNet: Monitoring

Annual Monitoring
Individuals with one positive autoantibody will have an Oral Glucose Tolerance Test (OGTT) and HbA1c at the first monitoring visit to determine their monitoring plan (annual or semi-annual).

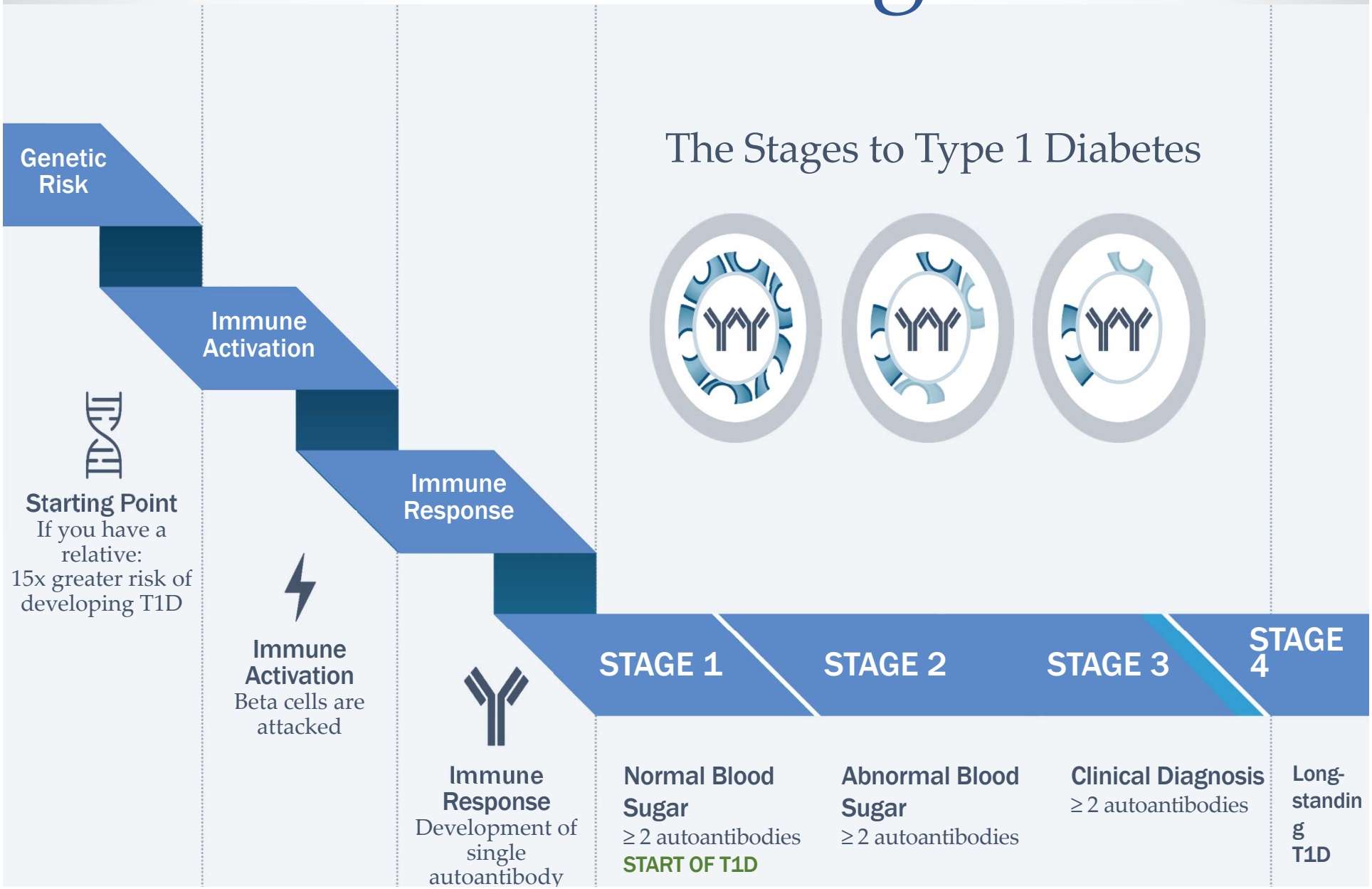
Semi-annual Monitoring
Individuals with a higher 5-year risk of diabetes. Those with two or more autoantibodies during screening, or who were identified as higher risk from a first annual monitoring visit.

TrialNet

Scientific Statement from JDRF, Endocrine Society, ADA
Staging Pre-symptomatic Type 1 Diabetes

- In the January 2016 issue of Diabetes Care, the JDRF, American Diabetes Association (ADA), and Endocrine Society recommend adoption of a new type 1 diabetes staging classification.
- The recommendation is largely based on an immense amount of data collected from TrialNet research spanning two decades and involving more than **150,000 relatives of people with type one diabetes.**
  - Type one diabetes can now be most accurately understood as a disease that progresses in **three distinct stages**.

T1D Disease Progression

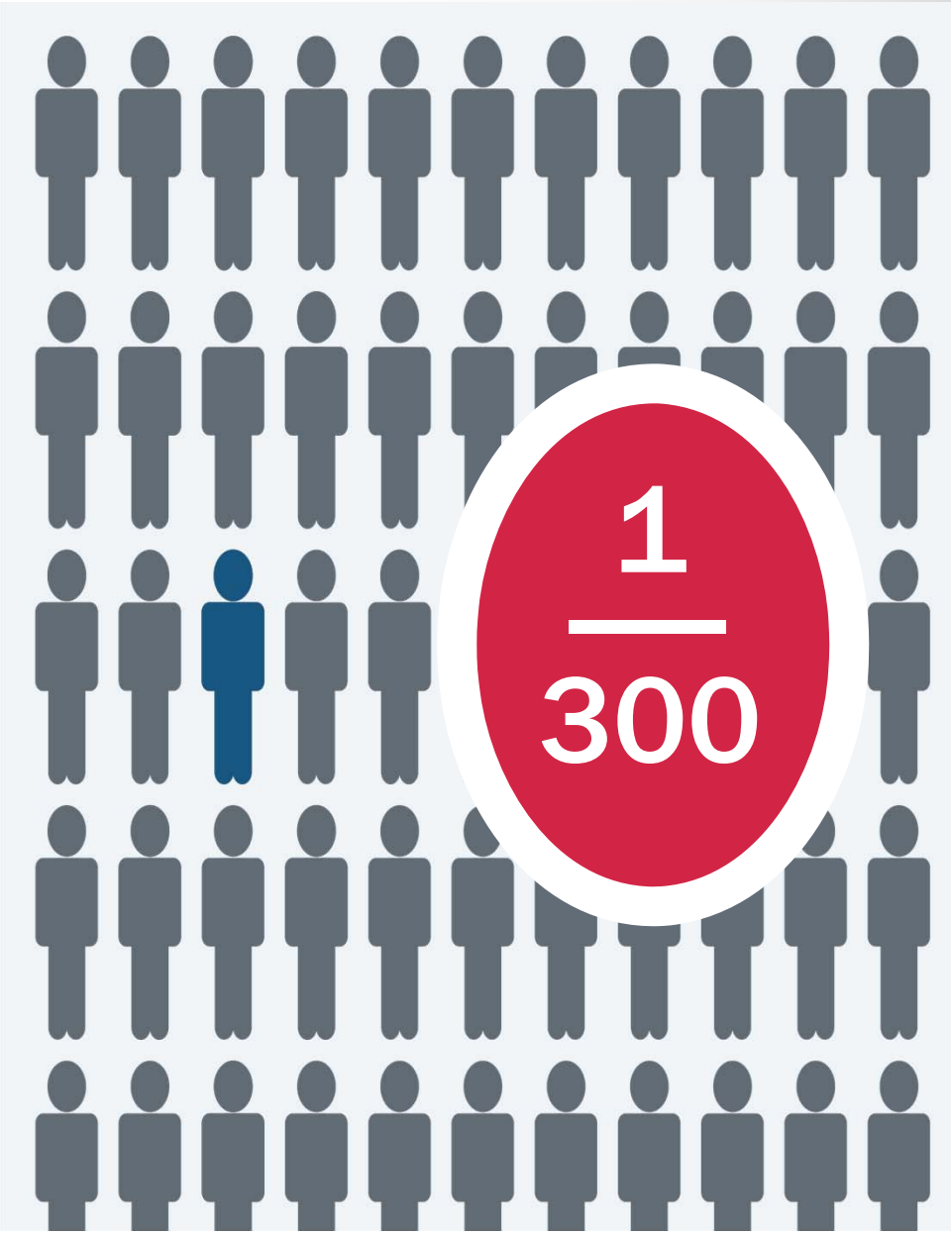


T1D Disease Progression

Starting Point
Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the genes associated with T1D
  - General population risk is 1 in 300
- Family members are at 15x greater risk to develop T1D
  - Relative risk is 1 in 20



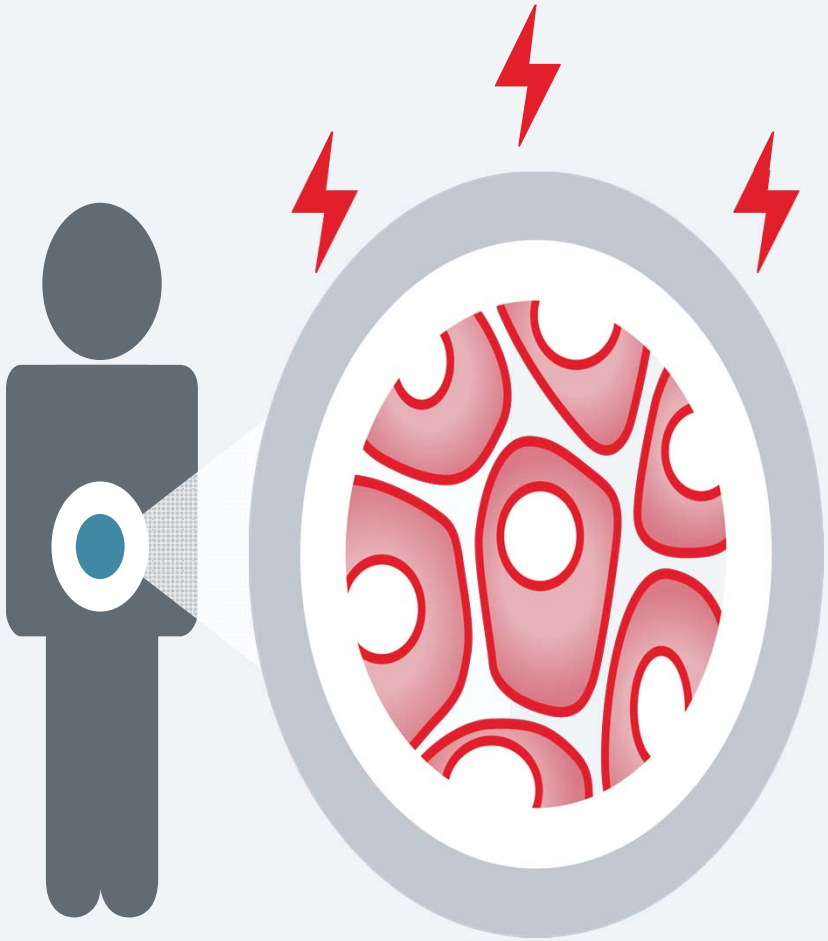
T1D Disease Progression

Immune system is activated

Immune Activation

Immune system attacks beta cells

- Likely a common event
- Research taking place to identify the possible “event” or combination of “events”

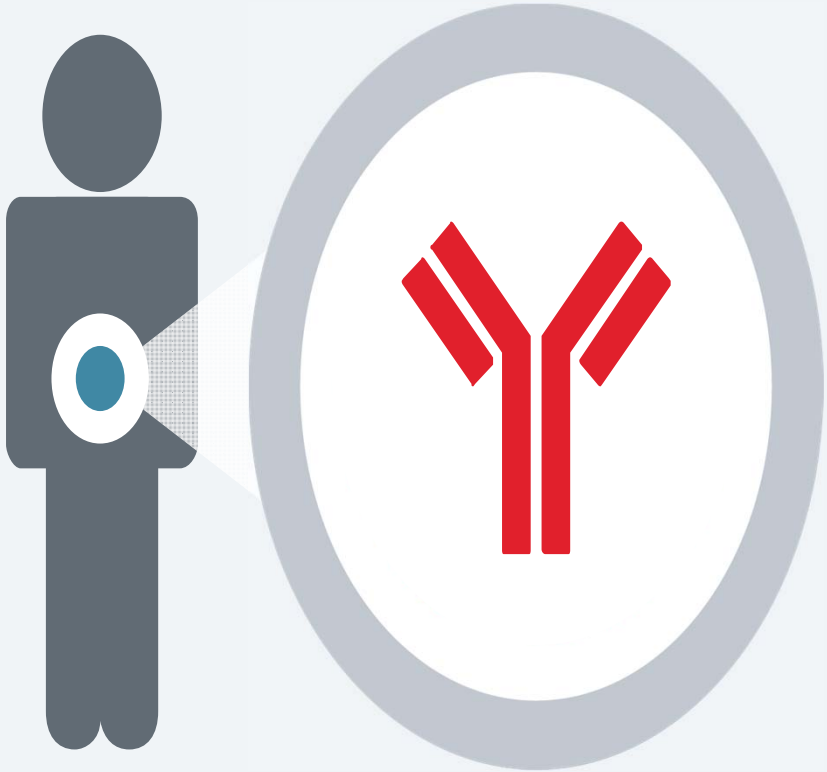


T1D Disease Progression

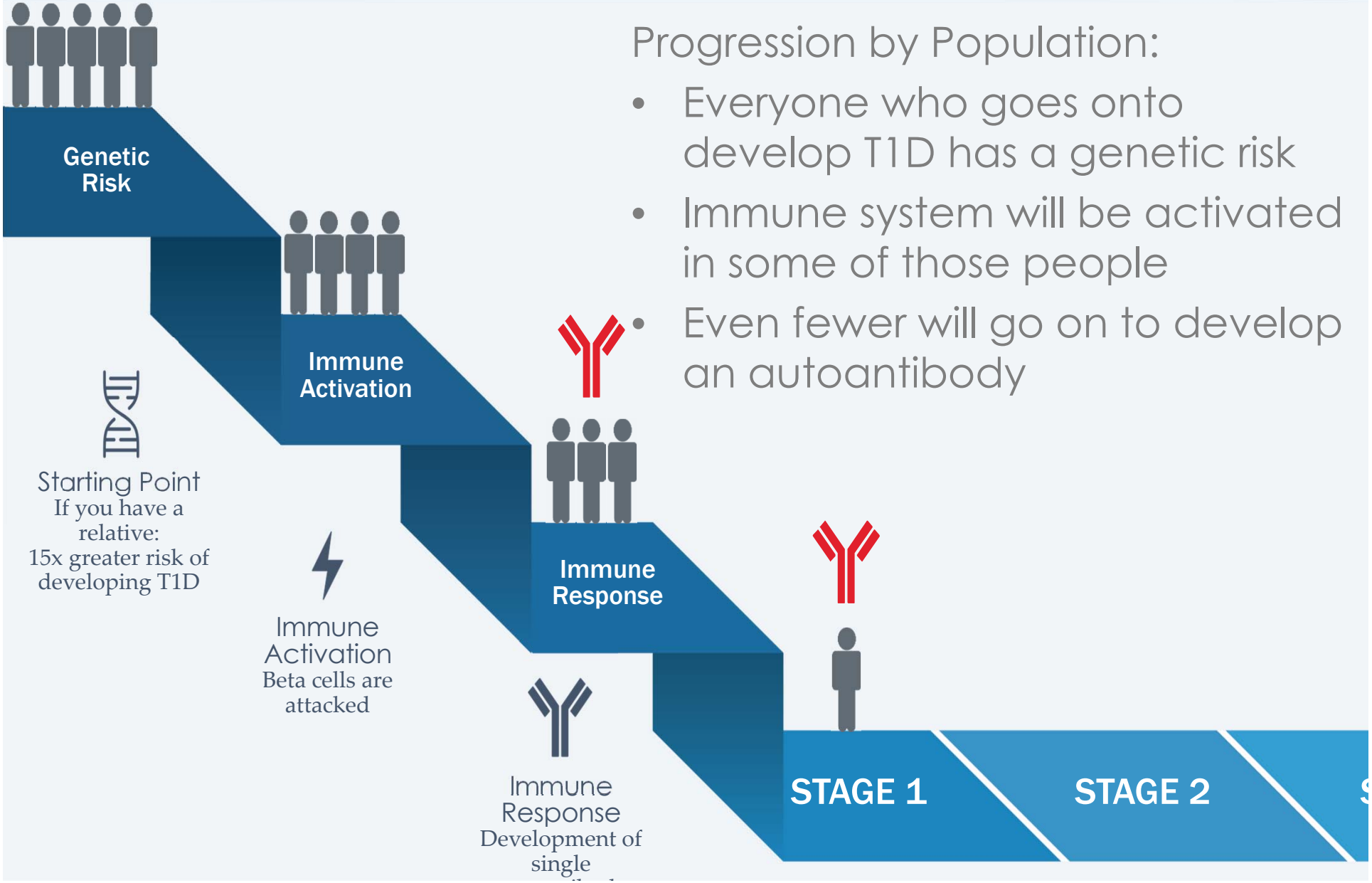
Development of single autoantibody
Immune Response

1 autoantibody

- Immune system responds to beta cells being attacked
- Results in the development of autoantibodies
- Autoantibodies are a “visible” signal that the immune system is activated



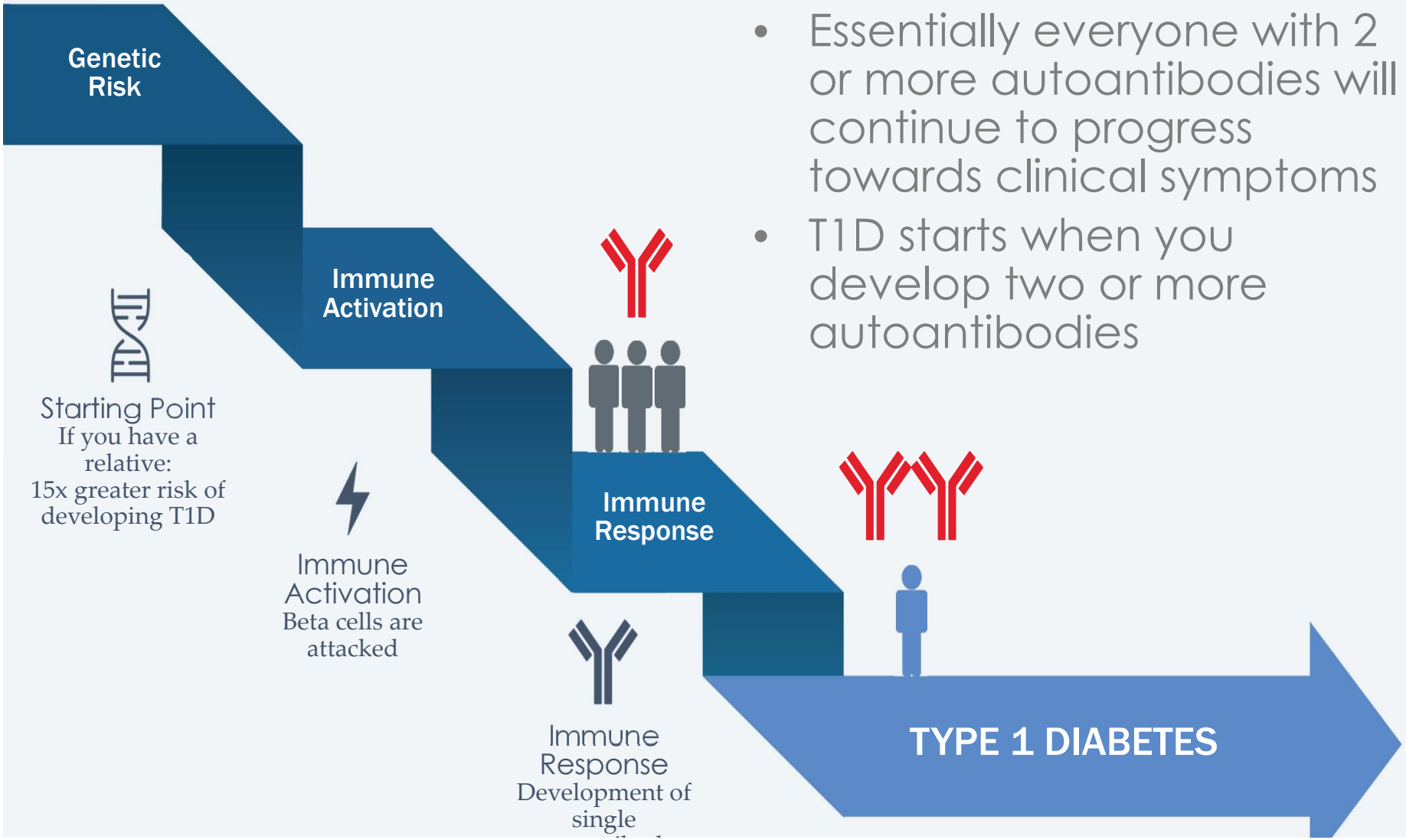
T1D Disease Progression



Progression by Population:

- Everyone who goes onto develop T1D has a genetic risk
- Immune system will be activated in some of those people
- Even fewer will go on to develop an autoantibody

T1D Disease Progression



Progression by Population:

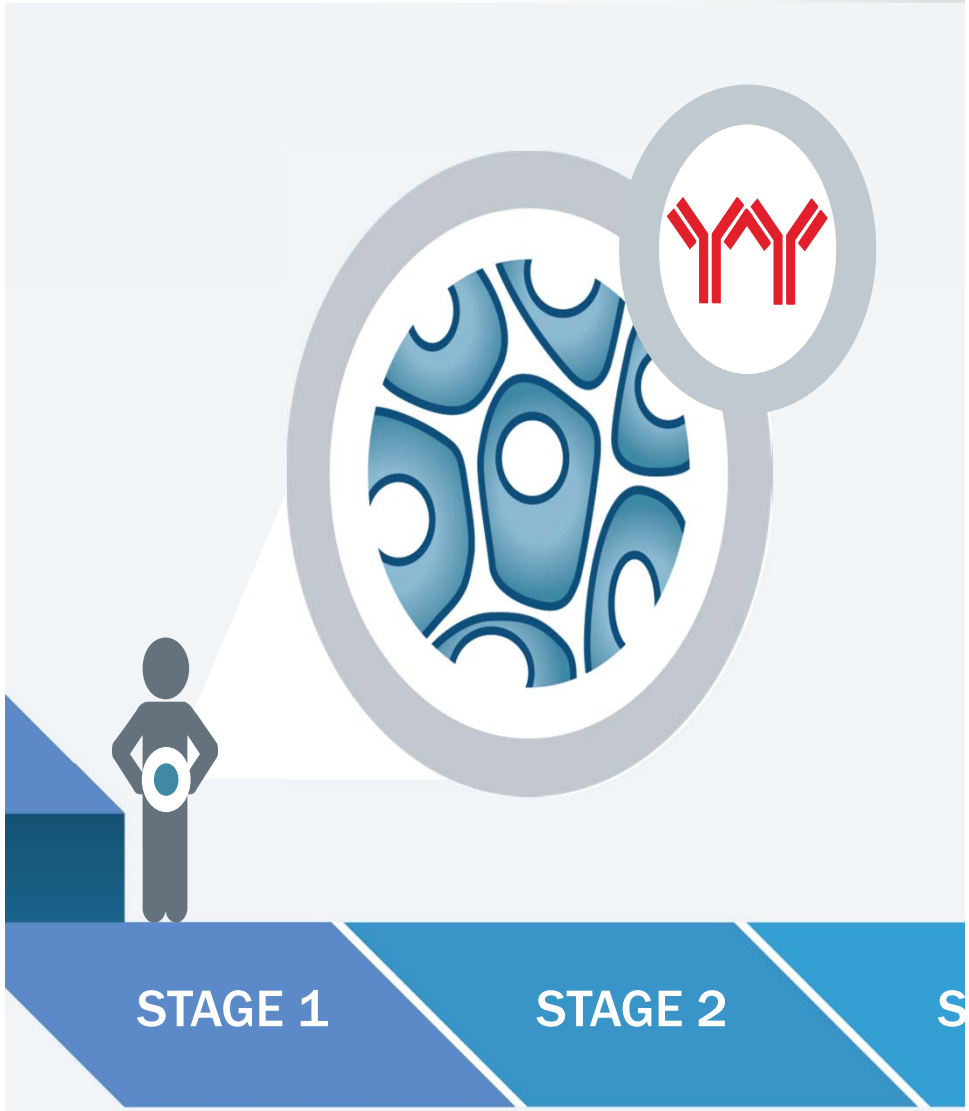
- Essentially everyone with 2 or more autoantibodies will continue to progress towards clinical symptoms
- T1D starts when you develop two or more autoantibodies

T1D Disease Progression

Stage 1 T1D
Normal Blood Sugar

≥ 2 autoantibodies

- START of T1D
- Two or more autoantibodies
- Normal blood sugar
- Lots of beta cells that are able to maintain blood sugar
- No symptoms



T1D Disease Progression

Stage 2 T1D
Abnormal Blood Sugar

≥ 2 autoantibodies

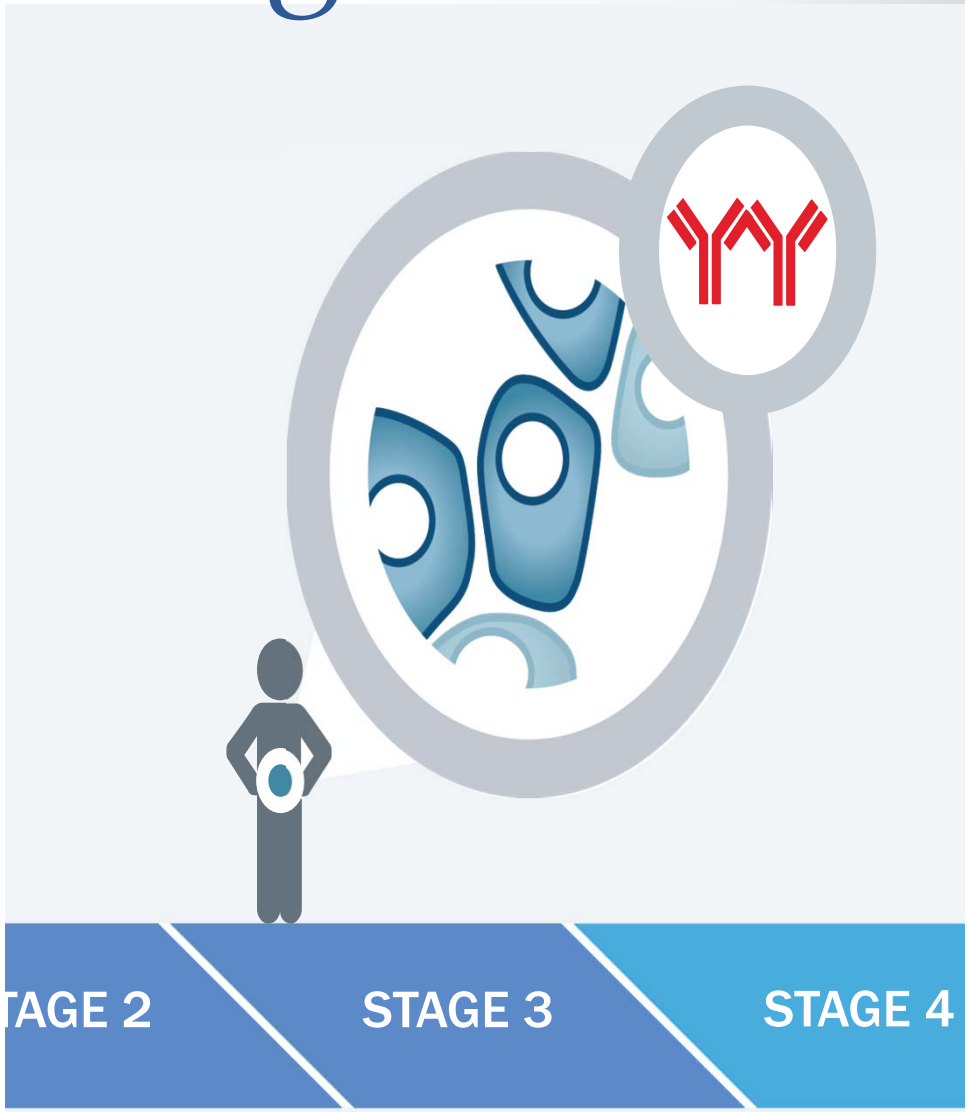
- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
- No symptoms

T1D Disease Progression

Stage 3 T1D
Clinical Diagnosis

≥ 2 autoantibodies

- Marked by clinical diagnosis (Dx)
- Formerly known as “start of T1D”
- Even fewer beta cells
- Symptoms of high blood sugar

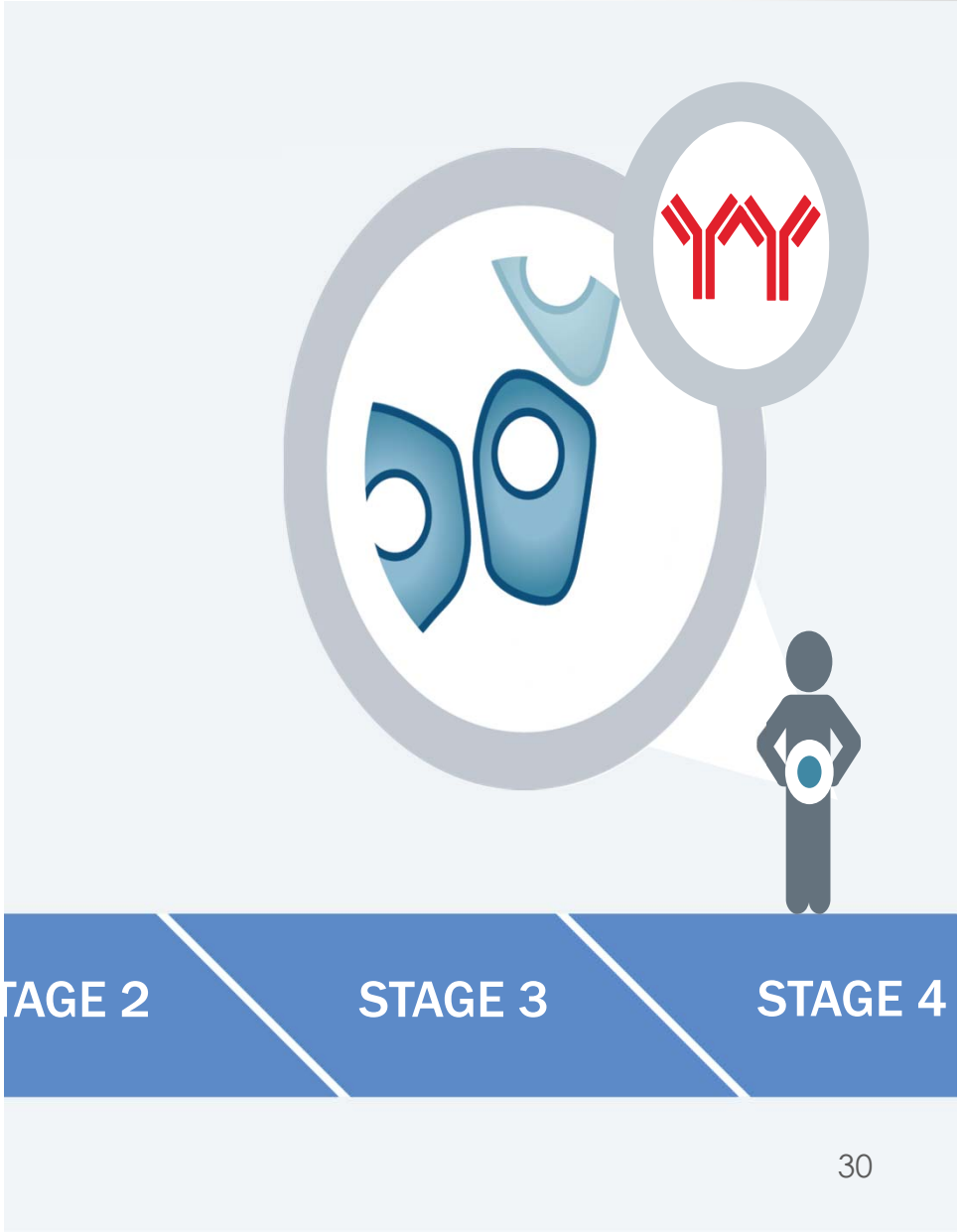


T1D Disease Progression

Stage 4 T1D
Long-Standing T1D

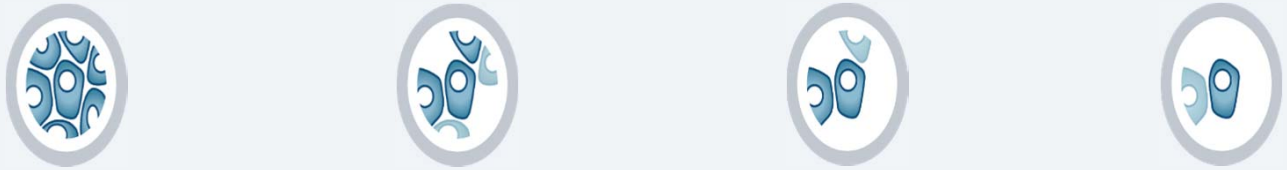
Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet is working to replace or replenish beta cells



T1D Disease Progression

The impact of AGE on disease progression & beta cell decline



	STAGE 1 (Start of T1D) ≥ 2 autoantibodies	STAGE 2 ≥ 2 autoantibodies	STAGE 3 (Clinical Dx) ≥ 2 autoantibodies	STAGE 4 Long-standing T1D
Age <5				
Age 5-9				
Age 10-14				
Age 15-19				
Age ≥ 20				

T1D Progression: Importance of Staging

1. **Accelerate the clinical development of therapies by providing a common framework for**
   - Regulators, funders, academia and industry

2. **Identification of T1D in it's earliest stages can lead to a decreased risk of diagnosis in DKA**

3. **Staging diabetes allows us to treat T1D early to delay progression and ultimately prevent stage 3 (symptomatic T1D)**
   - Treating high blood pressure, allows us to treat the disease early and ultimately prevent a heart attack or stroke

SUMMARY POINTS

T1D Disease Progression

1. Type 1 diabetes starts with two or more autoantibodies
2. There are three defined stages:
   - Stage 1: Presence of 2 or more autoantibodies with normal blood sugar
   - Stage 2: Presence of 2 or more autoantibodies with abnormal blood sugar
   - Stage 3: Clinical diagnosis (Dx) of type 1 diabetes
3. Age matters!
   1. Time from 2 or more autoantibodies to Dx is faster the younger you are
   2. Beta-cell decline is also faster the younger you are and continues through stage 4

T1D Progression Intervention

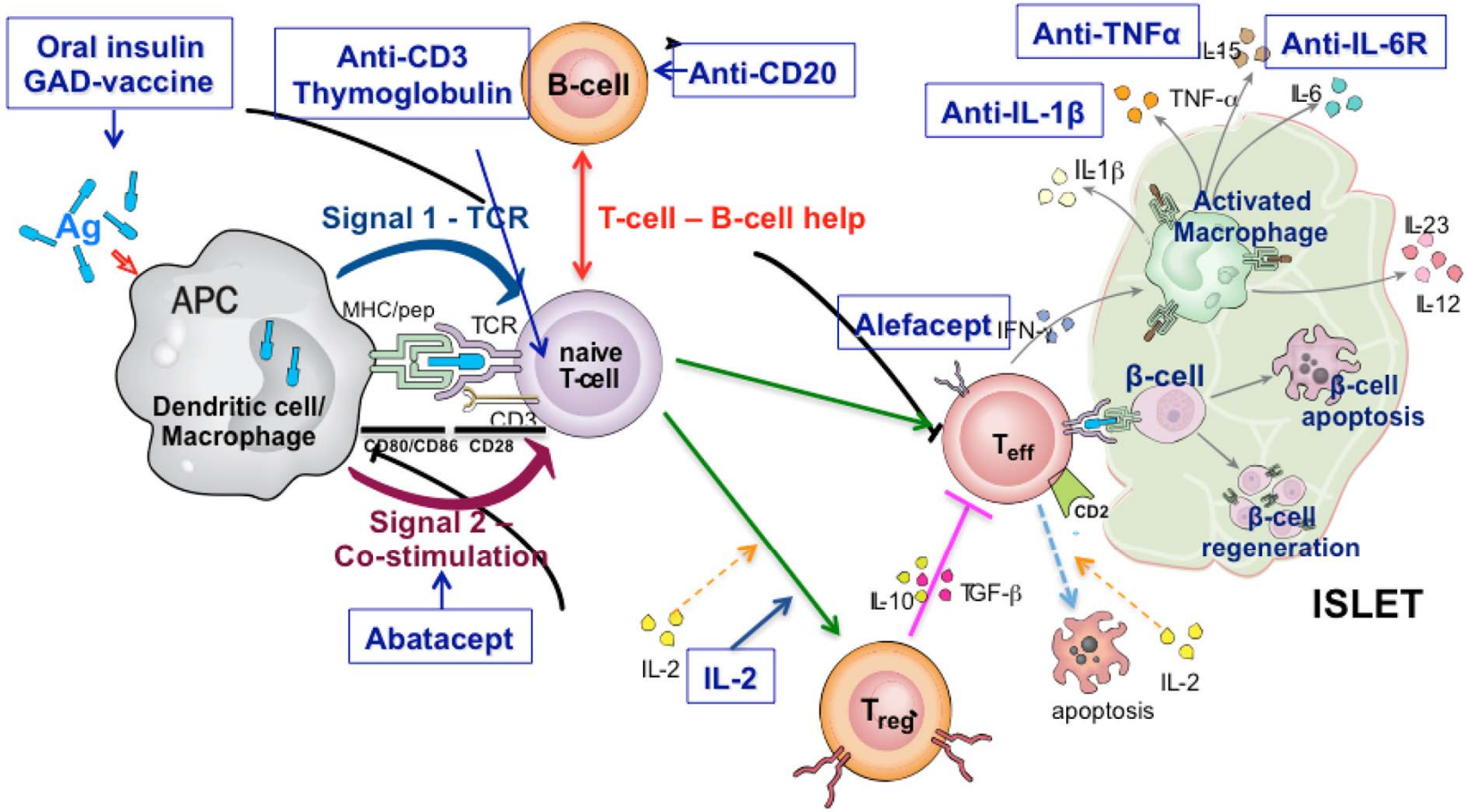
THE UNIVERSITY OF CHICAGO
KOVLER DIABETES CENTER FOR KIDS
AT COMER CHILDREN'S HOSPITAL

Advocate Children's Hospital

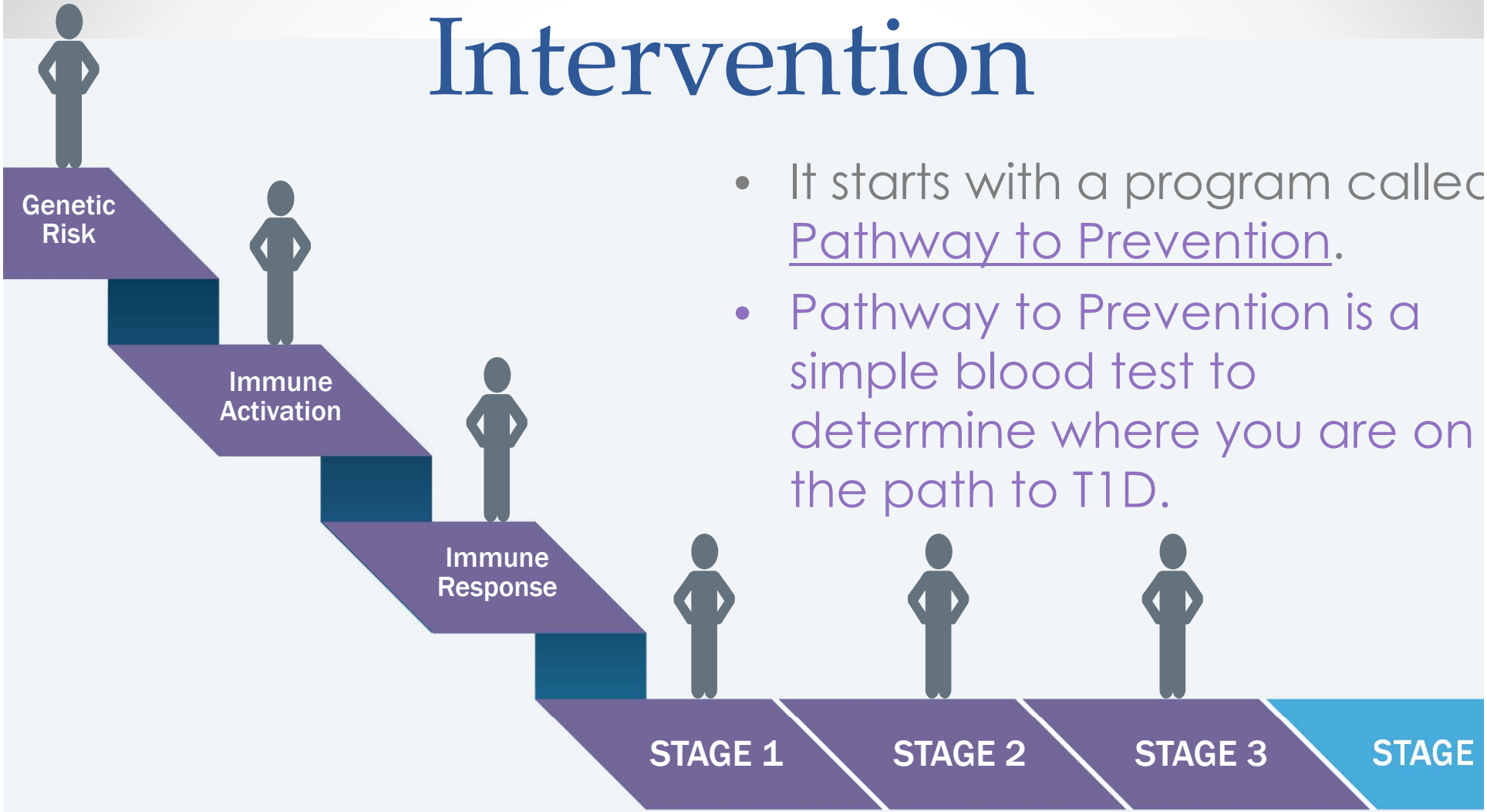
Ann & Robert H. Lurie Children's Hospital of Chicago™

Riley Hospital for Children
Indiana University Health

Interventions Target Different Mechanisms



TrialNet Disease Intervention



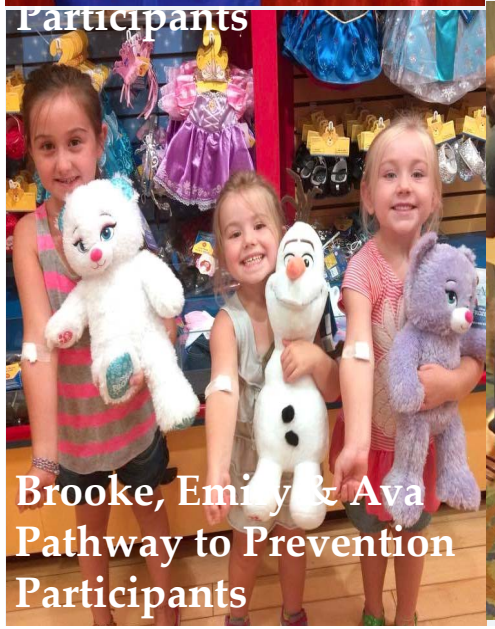
- It starts with a program called Pathway to Prevention.
- Pathway to Prevention is a simple blood test to determine where you are on the path to T1D.

TrialNet Intervention

P2P
Pathway to Prevention

Determine where you are on the path

- No cost
- 1st 2nd 3rd degree relatives
- Screens for autoantibodies
- Based on results
  - Look to enroll in clinical trial to preserve beta cell function
  - Or monitor for disease progression



TrialNet: Intervention at Every Stage

P2P **Pathway to Prevention**	TN20 **Immune Effects of Oral Insulin**	TN18 **Abatacept**	TN10 **Teplizumab** (Anti-CD3)	TN19 **ATG/GCSF**
RISK SCREENING	**STAGE 1**	**STAGE 1**	**STAGE 2**	**STAGE 3**
This study screens relatives of people with T1D to study risk and learn about how the disease occurs. • Screens for five autoantibodies • 1st and 2nd degree relatives • First step to identify eligibility for clinical trial participation	Mechanistic study to learn how different doses and intervals of oral insulin affect immune response. • 1st stage toward T1D • 2 or more autoantibodies	This study test whether abatacept helps stop or slow beta-cell decline in people who are at high risk of developing T1D. • 1st stage toward T1D • 2 or more autoantibodies • Approved and efficacious for treatment of RA/JIA	This study tests whether teplizumab helps stop or slow down beta-cell decline in people who are at high risk of developing T1D. • 2nd stage toward T1D • 2 or more autoantibodies with abnormal glucose tolerance	This study tests whether ATG used alone or together with GCSF will help people continue to produce their own insulin. • 3rd stage diagnosis of T1D • Combination therapy using two medications

TrialNet Intervention

Your Participation is Impactful

How to participate

- Visit www.diabetestrialnet.org
- Or contact the Diabetes TrialNet Recruitment Hub: hub@benaroyaresearch.org

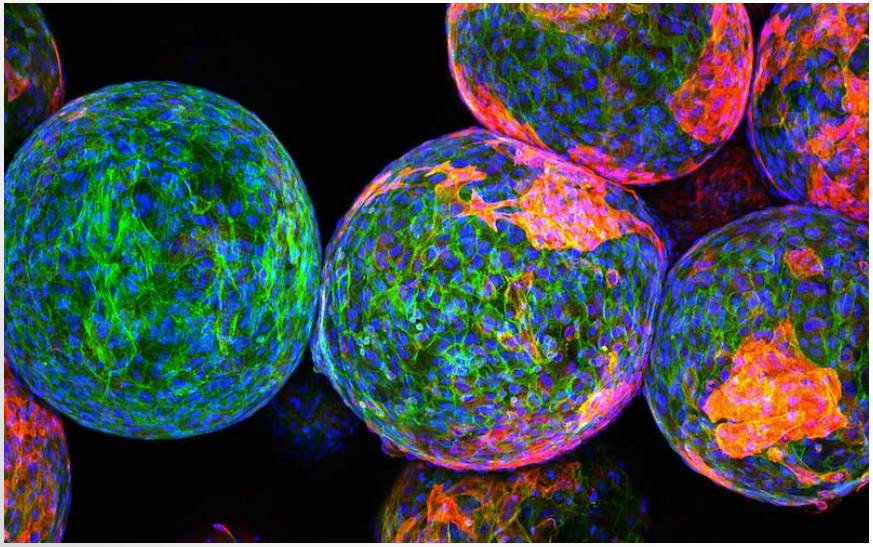
Neil
Proud Pathway to Prevention Participant

TrialNet T-shirt wearing Pathway to Prevention Participant

Jadah, Abatacept Participant
&
Beth, TrialNet Coordinator

Multiple Approaches to T1D:

- Decrease stress to the beta cell
- Early intensive insulin therapy



- Combinations with immune suppression
- Role of gut flora
- GLP-1 agonists
- SGLT-2 inhibitors

TrialNet Conclusions

- Type 1 diabetes is highly linked to HLA genes that control autoimmunity
- The immune system attack does not fully explain type 1 diabetes
- Targeting the immune system alone has not been successful in slowing or preventing t1D
- Future studies are aimed to better understand that role of the islet and the beta cell in the start an progress of T1D
- New studies to begin at the end of 2017

Other Research

- T1GER-Simponi (Janssen)
- WISDM (T1D Registry)
- Cell Level Research(ADA)
  - Autologous Stem Cell transplantation
  - Pig Islet Xenotransplantation

T1GER, Simponi

- Goal to arrest Beta cell loss in patients with new onset T1D
- Eligibility: Age 6-21, enrollment within 100 days of diagnosis of T1D
- Double blinded, placebo controlled with 2:1 placement (For every two individuals getting Simponi (Golimumab), one received placebo)

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

T1GER
Clinical Research Study for Type 1 Diabetes

WISDM

- Determine if CGM use can reduce hypoglycemia and improve quality of life in older adults with T1D.

- Inclusion criteria
  - Current age >60.0 years
  - Clinical diagnosis of T1D at >6months and <10yrs of age
  - HbA1c <10%
  - Insulin regimen requiring multiple injections per day
  - No use of CGM in the last 3 months

T1D Exchange

JCHR
JAEB CENTER FOR HEALTH RESEARCH

Cell Level Research

- Autologous transplantation of induced pluripotent stem cells
  - Work being done to turn inducible cells into insulin producing beta cells
  - Need to find a way to bypass the immune system
- Pig islet cells as substitutes for human pancreatic islet cells
  - Research has been conducted in Monkeys with diabetes receiving pig islet transplants
  - Requires immunosuppressant drug therapy
  - Survival rates of more than one year without needing insulin injections

NICHD

Thank you.

NIAID

ADA