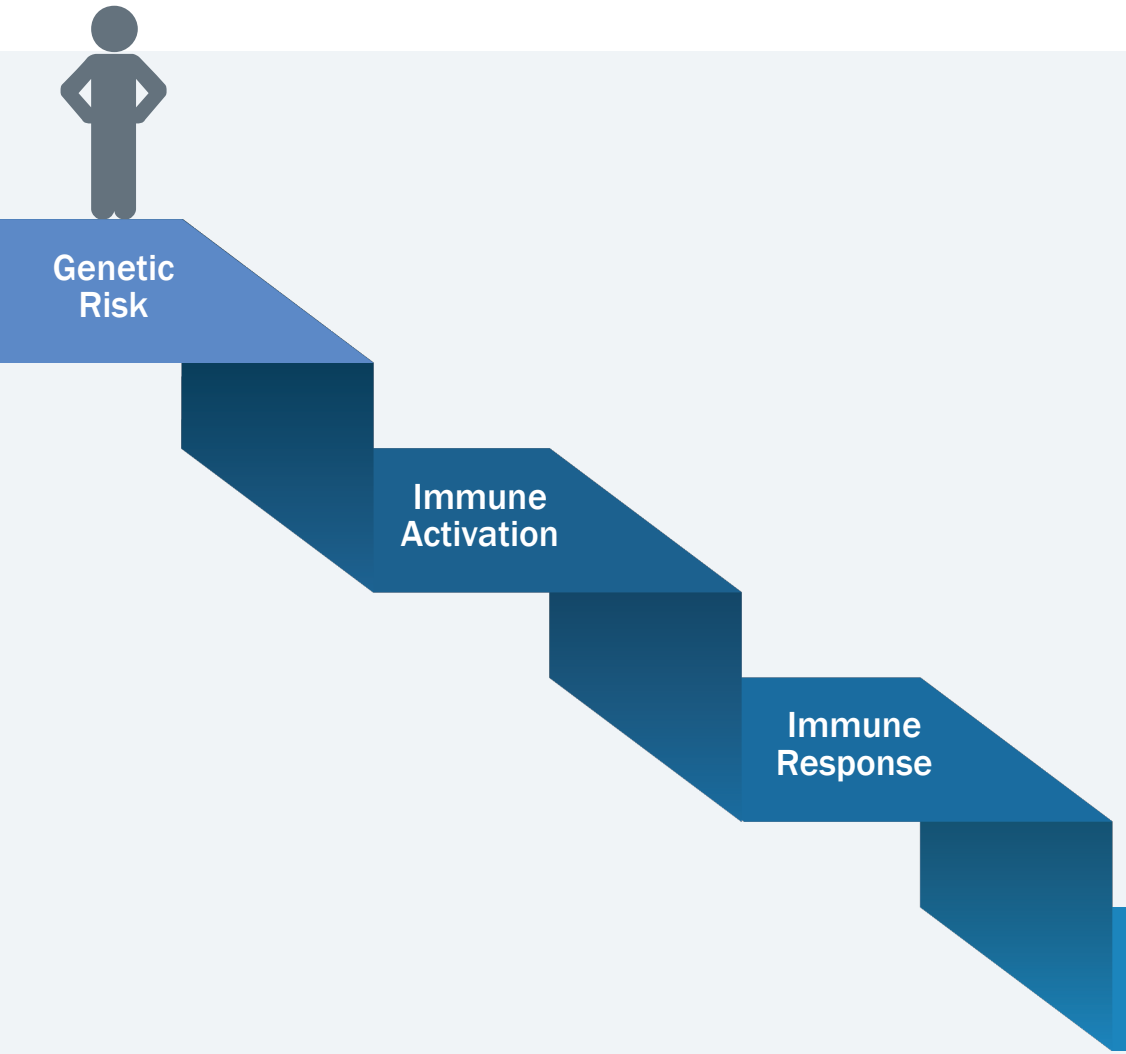
Type 1 Diabetes

- Why does it occur?
- Is prevalence increasing?
- How is it treated?
- Will there be a cure?



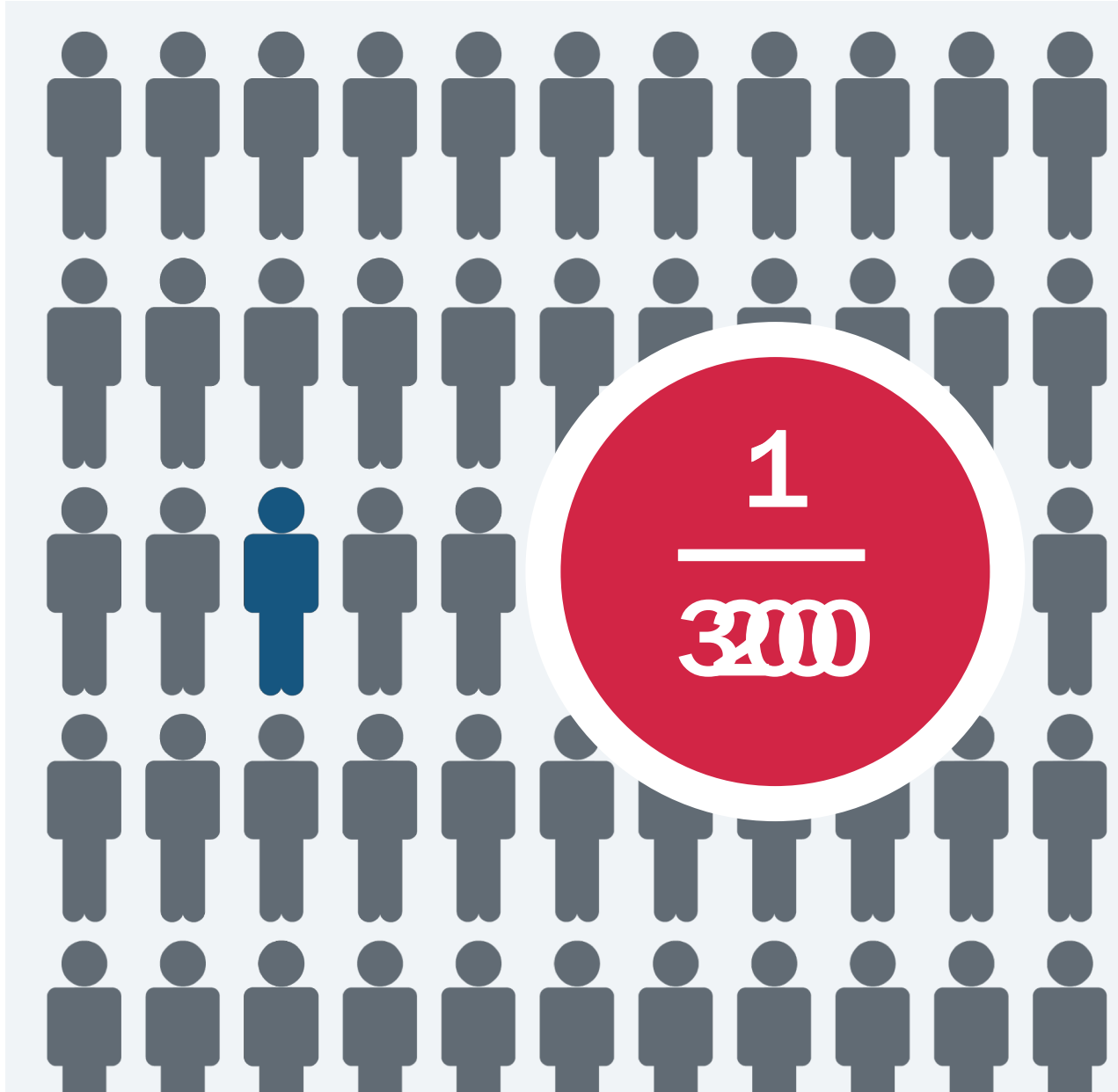
- **Synergy between genetic risk and environmental triggers**

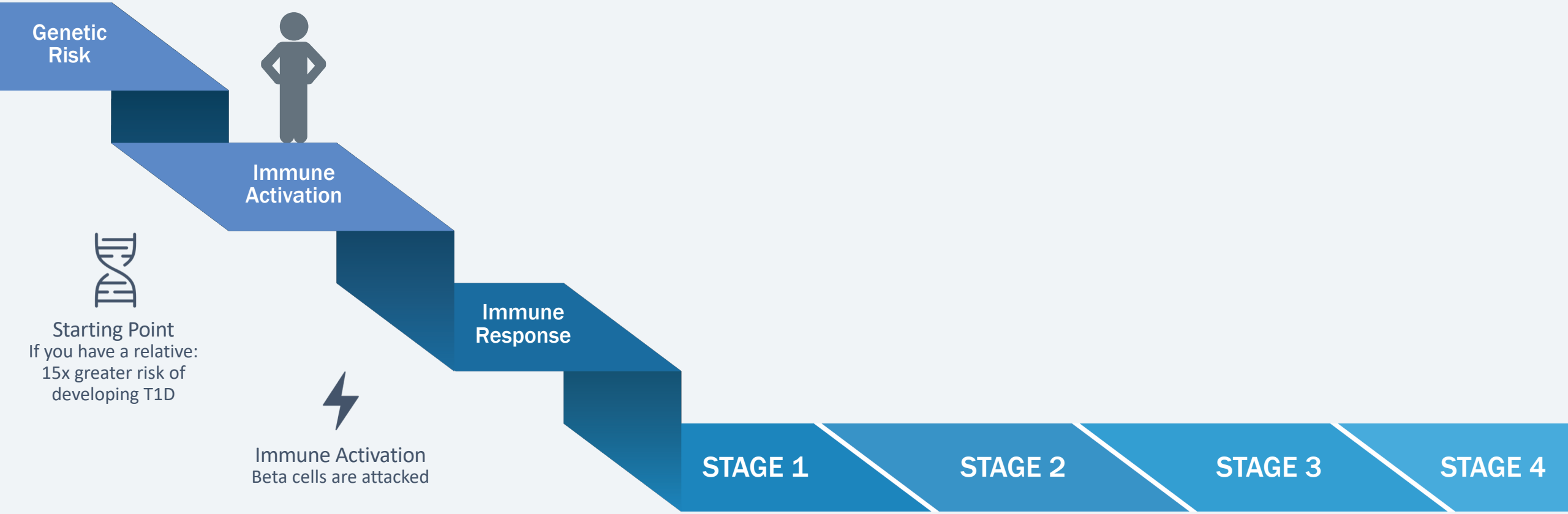
Starting Point

Genetic Risk

The path to T1D starts here

- Everyone who is diagnosed with T1D has the gene(s) 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



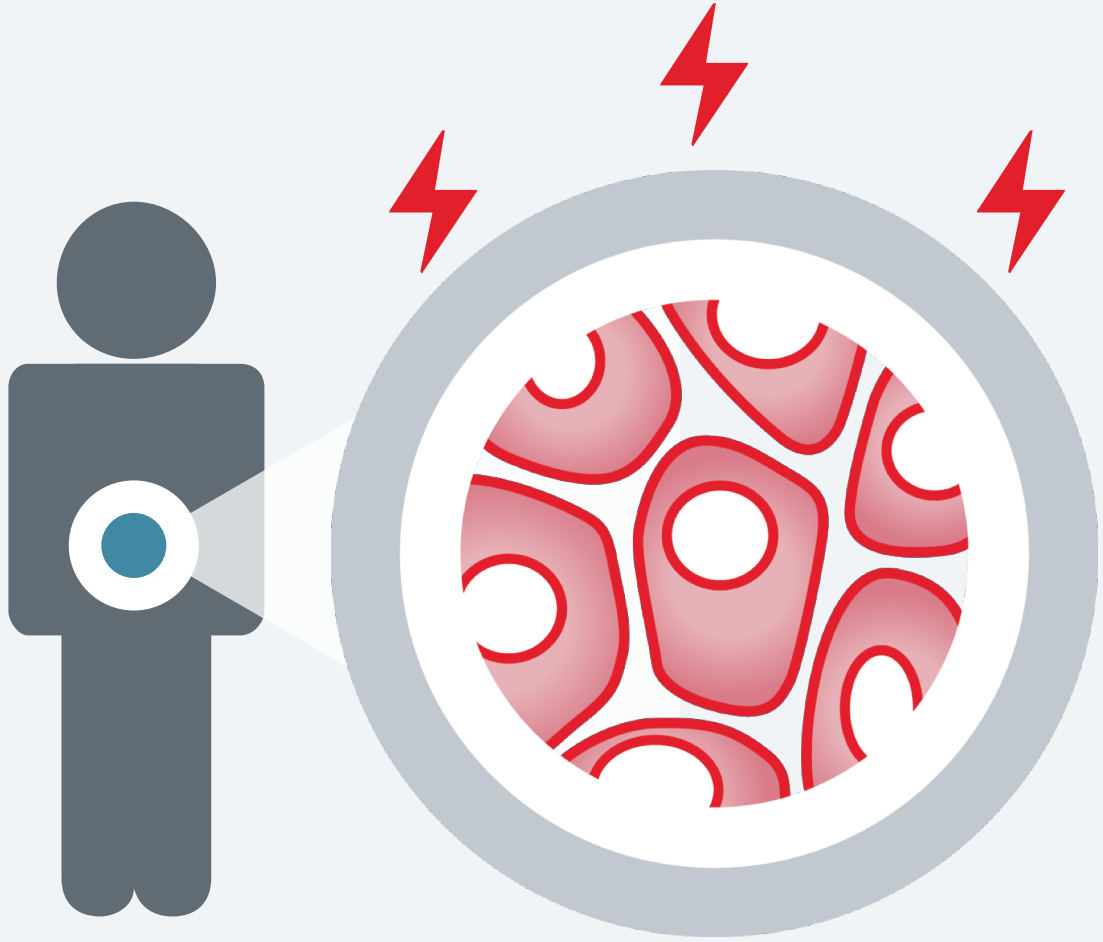

Genetic Risk
Immune Activation
Immune Response
STAGE 1
STAGE 2
STAGE 3
STAGE 4
Starting Point
If you have a relative:
15x greater risk of
developing T1D
Immune Activation
Beta cells are attacked

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”

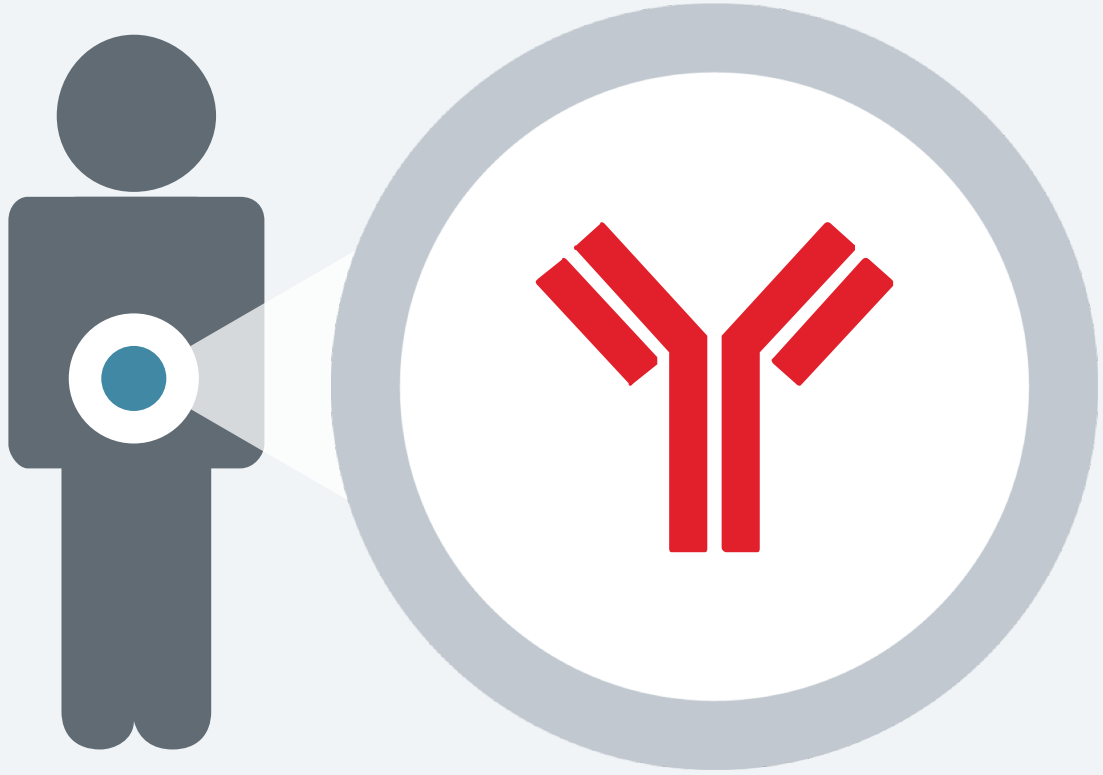


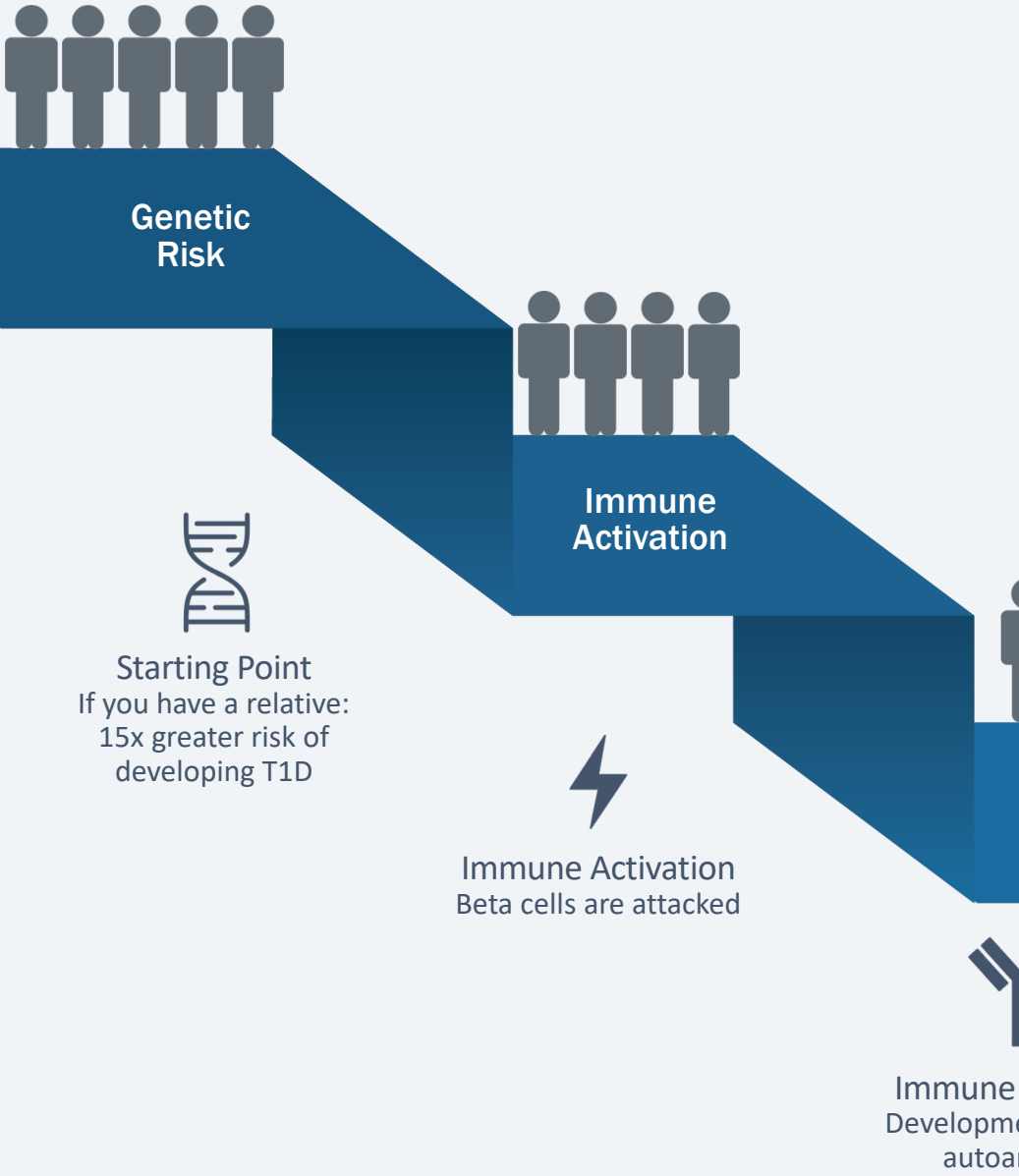
Development of single autoantibody

Immune Response

1 autoantibody

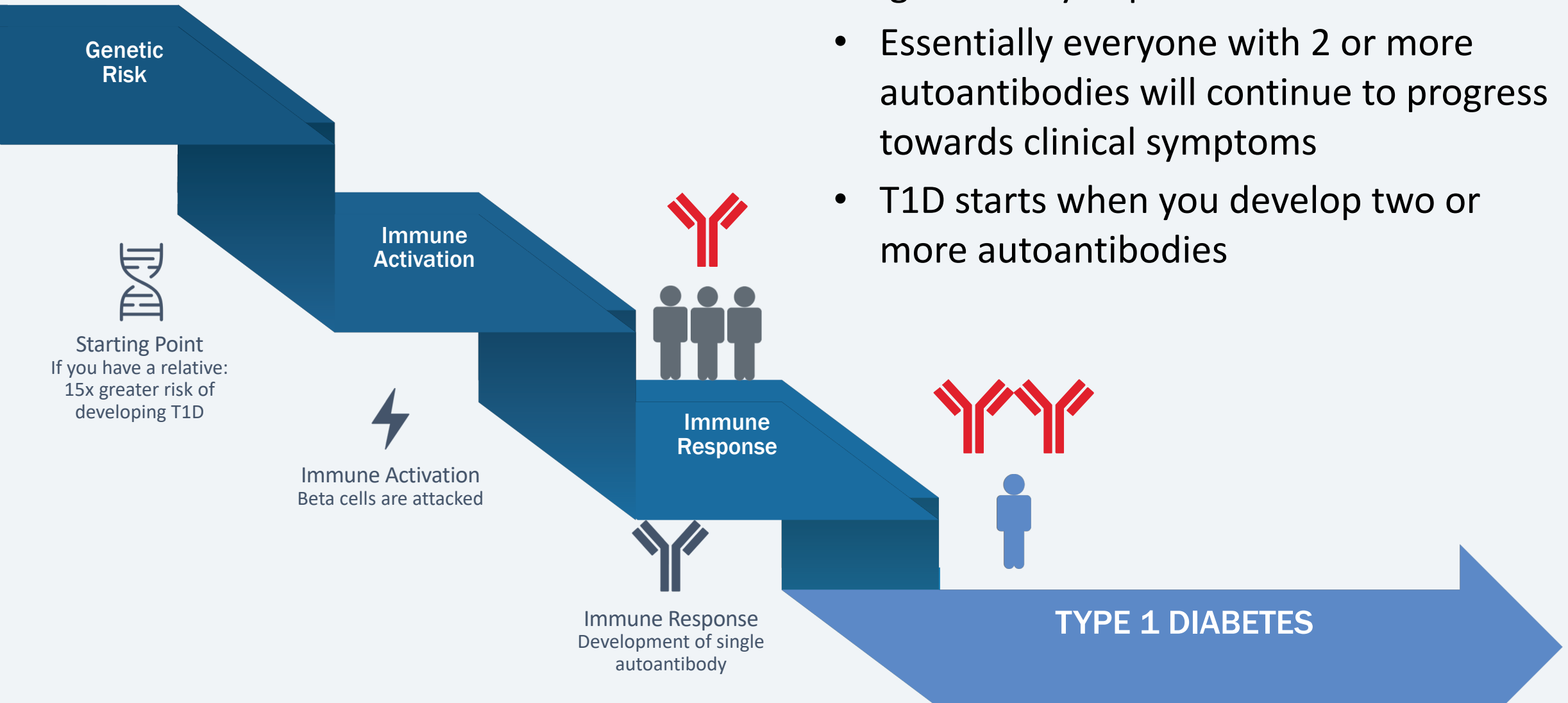
- Immune system responds to beta cells being attacked
- Results in the development of autoantibodies
- Autoantibodies are a “visible” signal that the immune system is activated
  - They do not cause the destruction of beta cells





Progression by Population:

- Everyone who goes on to 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



Progression by Population:

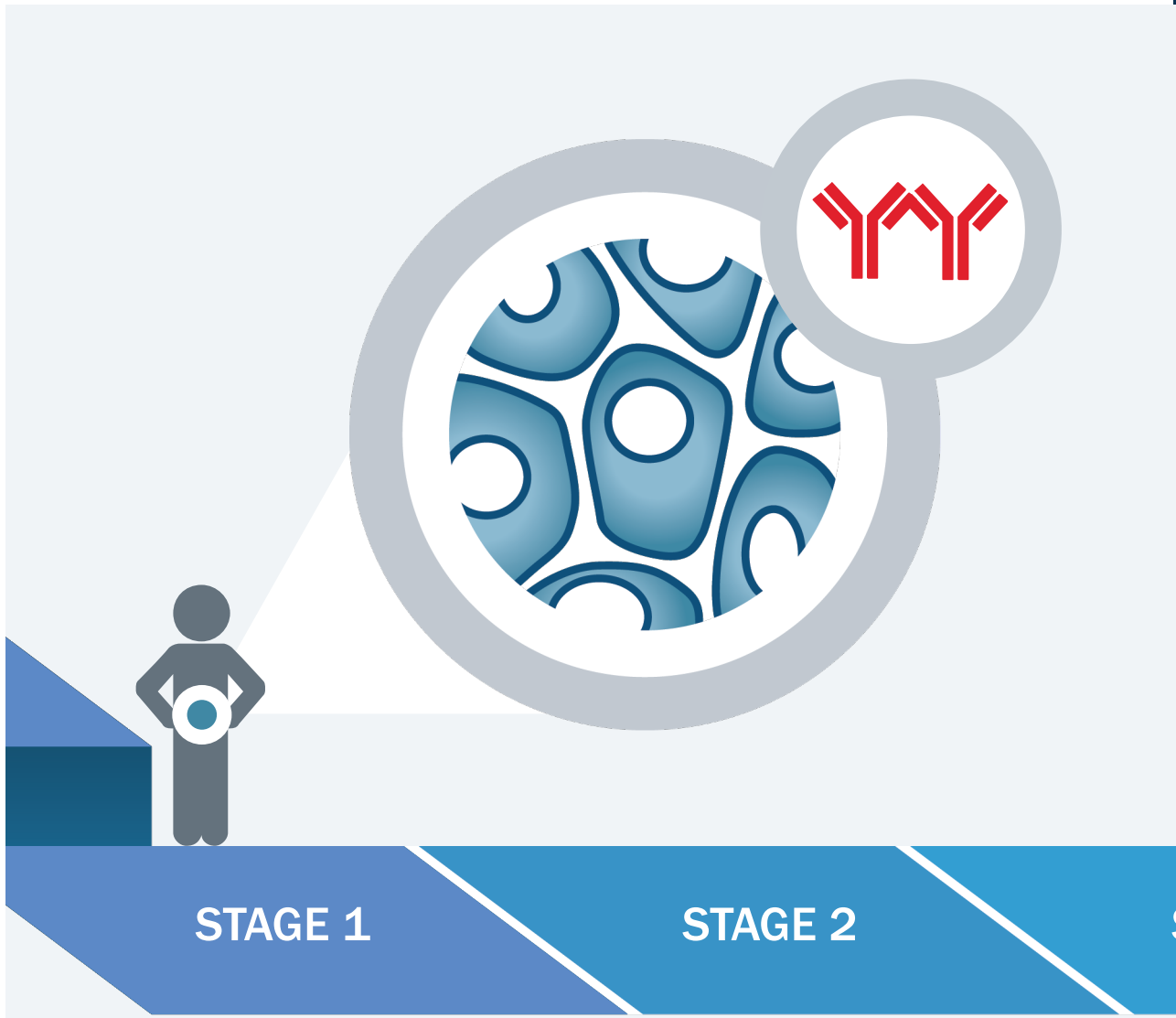
- Essentially everyone with 2 or more autoantibodies will continue to progress towards clinical symptoms
- T1D starts when you develop two or more autoantibodies

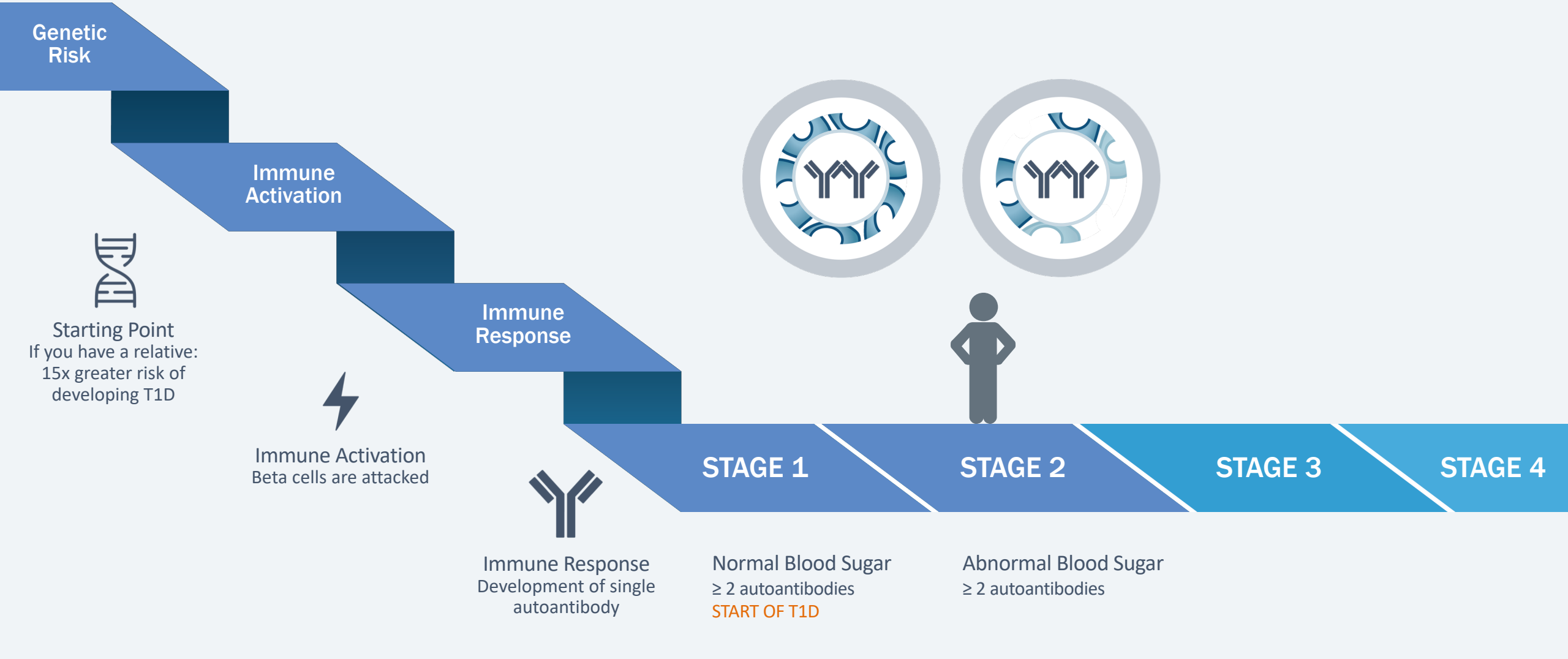
Stage 1 T1D

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




Genetic Risk
Immune Activation
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Starting Point
If you have a relative:
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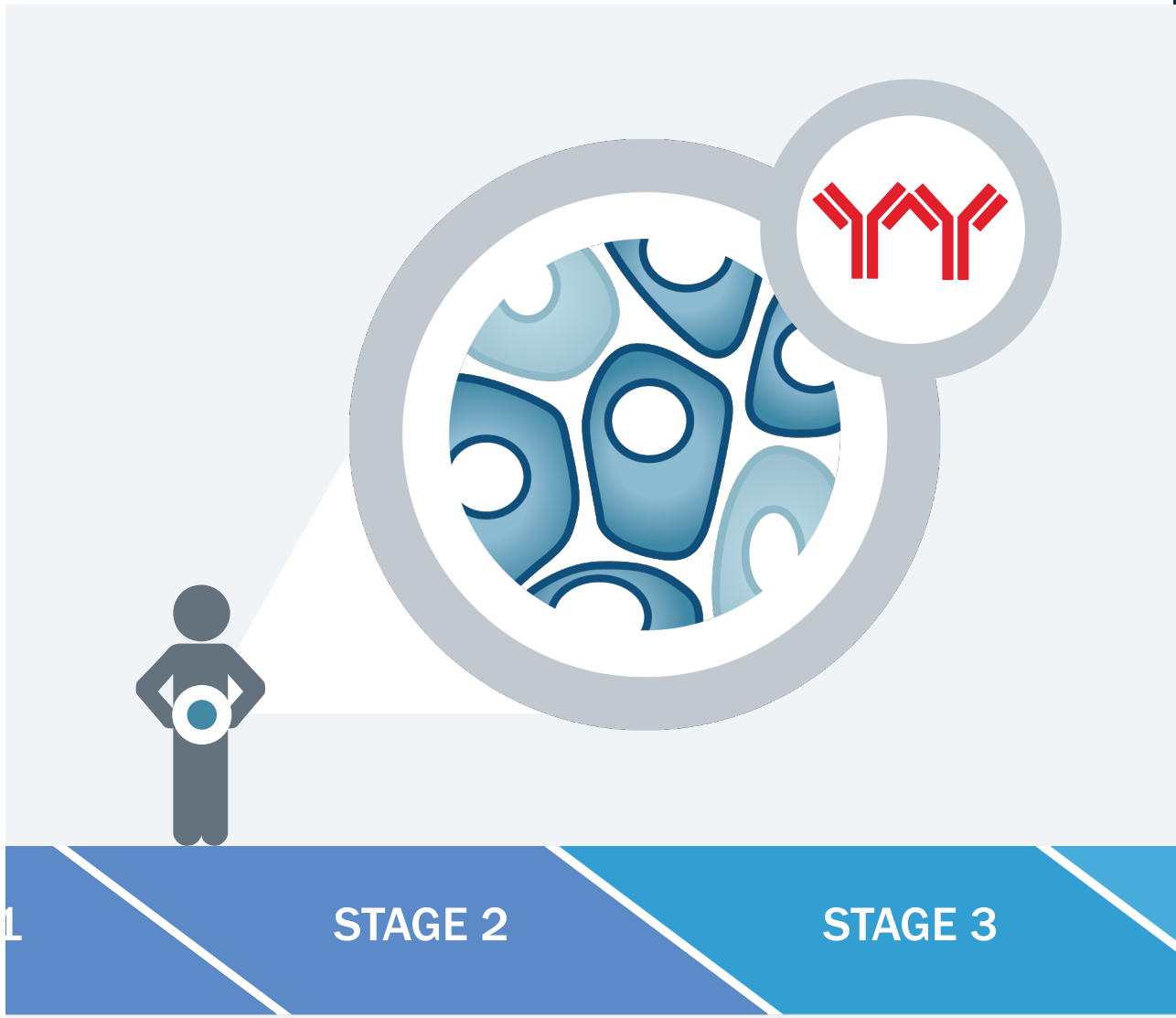
Immune Activation
Beta cells are attacked
Immune Response
Development of single autoantibody
STAGE 1
STAGE 2
STAGE 3
STAGE 4
Normal Blood Sugar
≥ 2 autoantibodies
START OF T1D
Abnormal Blood Sugar
≥ 2 autoantibodies

Stage 2 T1D

Abnormal Blood Sugar

≥ 2 autoantibodies

- Two or more autoantibodies
- Fewer beta cells, but not enough to keep blood sugar normal
  - Impaired gluose tolerance or “dysglycemia”
- No symptoms

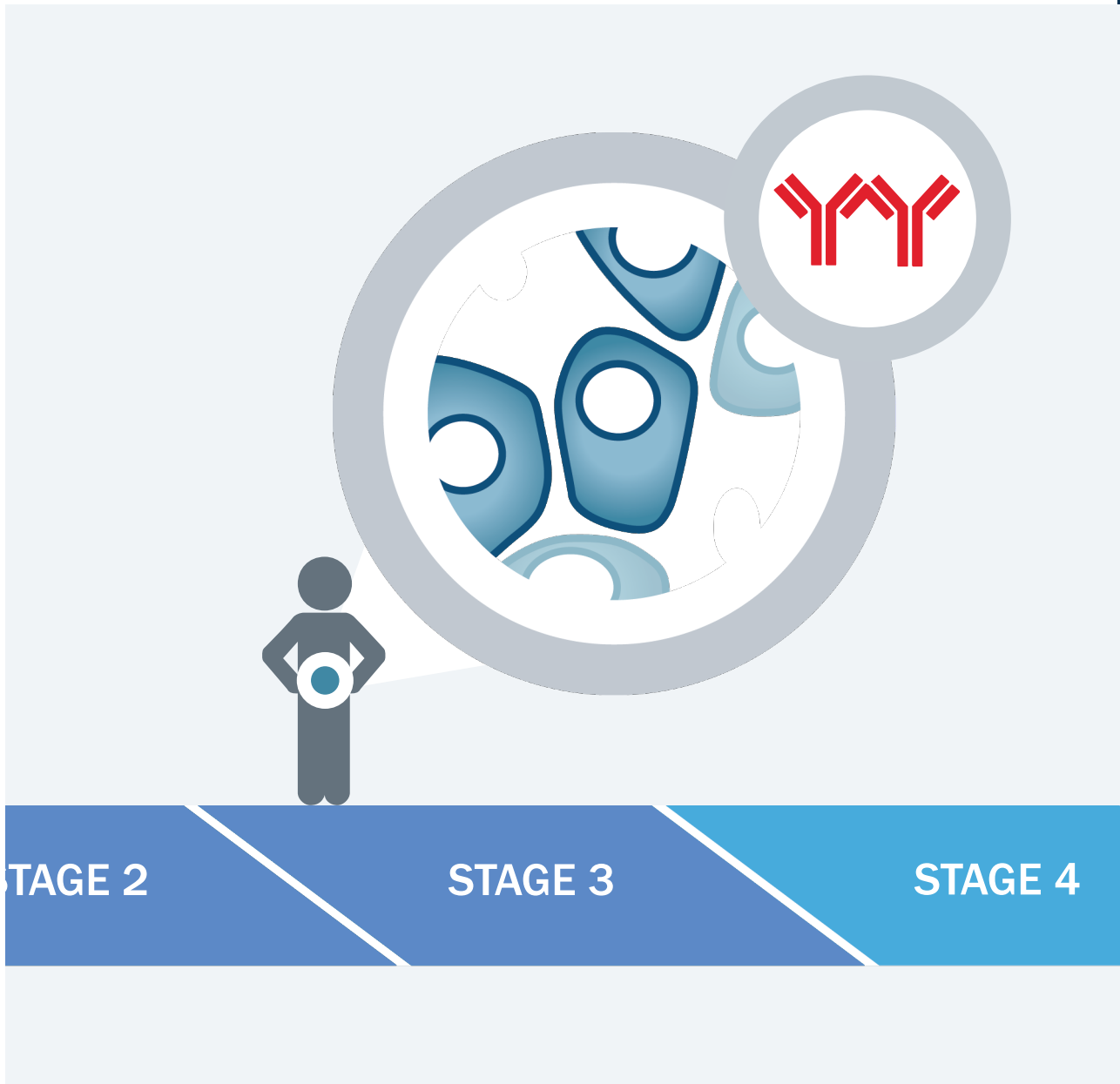


Stage 3 T1D

Clinical Diagnosis

≥ 2 autoantibodies

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



Stage 4 T1D

Long-Standing T1D

Post diagnosis

- Continued loss of beta cells over time
- Research outside of TrialNet
  - Engineer's approaches
    - Closed loop systems
  - Beta cell replacement
    - Whole pancreas transplant
    - Islets
    - Stem cell derived beta cells

TAGE 2 STAGE 3 STAGE 4

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				

P2P
Pathway to Prevention

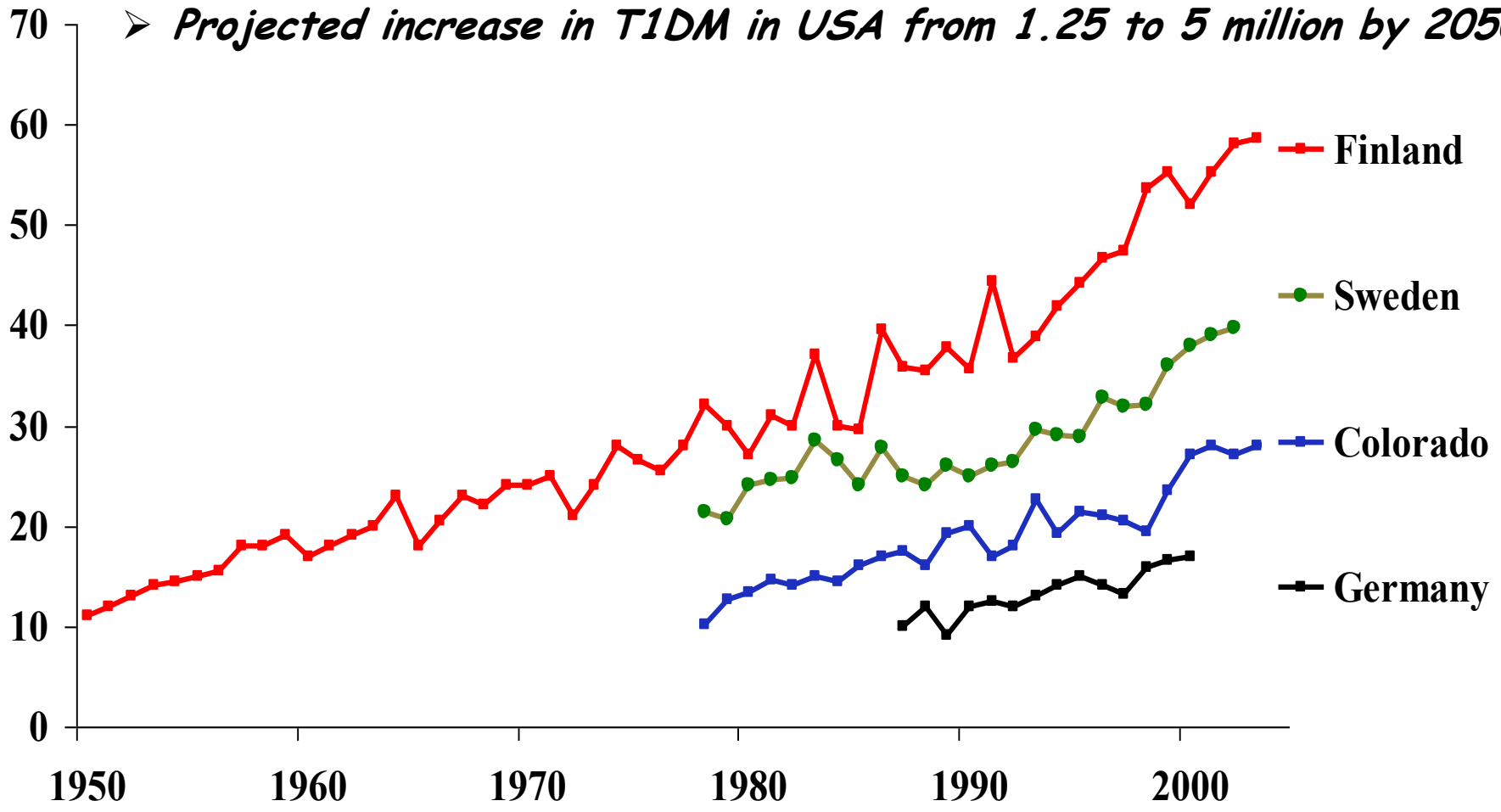
Eligibility Requirements

- In immediate family:
  - Anyone between age 1 and 45 with a sibling, child or parent with type 1
- In extended family:
  - Anyone between age 1 and 20 with a sibling, child, parent, cousin, uncle, aunt, niece, nephew, grandparent or half-sibling with T1D
- Those under 18 who do not have autoantibodies can be retested every year

Tracy Rodriguez
TrialNet Coordinator, UCSF

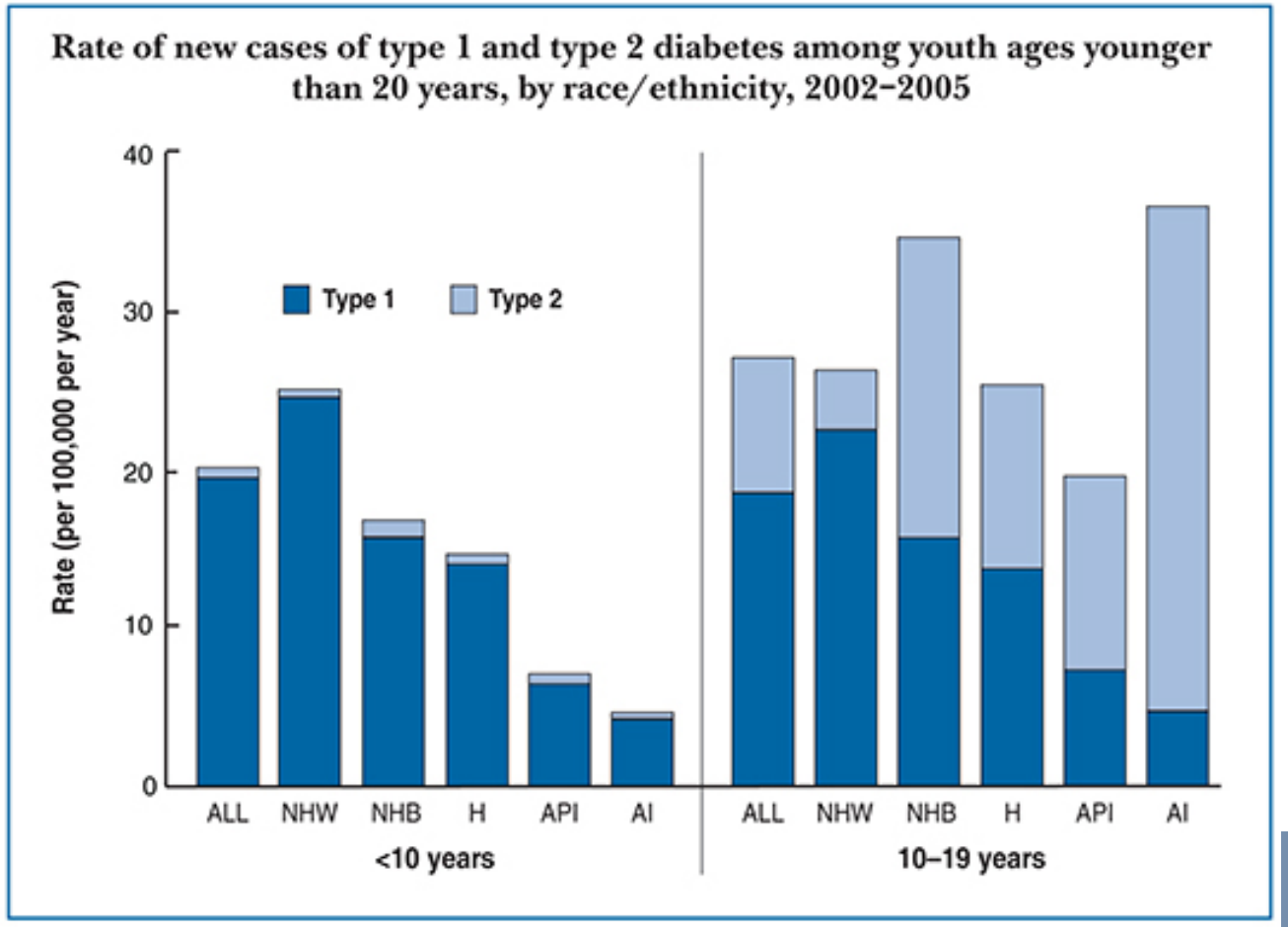
Increasing Incidence of T1DM

- *Projected increase in T1DM in USA from 1.25 to 5 million by 2050*



Rewers M. Ann NYAS 2008

Diabetes in Youth



Diabetes Center
University of California San Francisco

UCSF Benioff Children's Hospital
San Francisco

TIDM

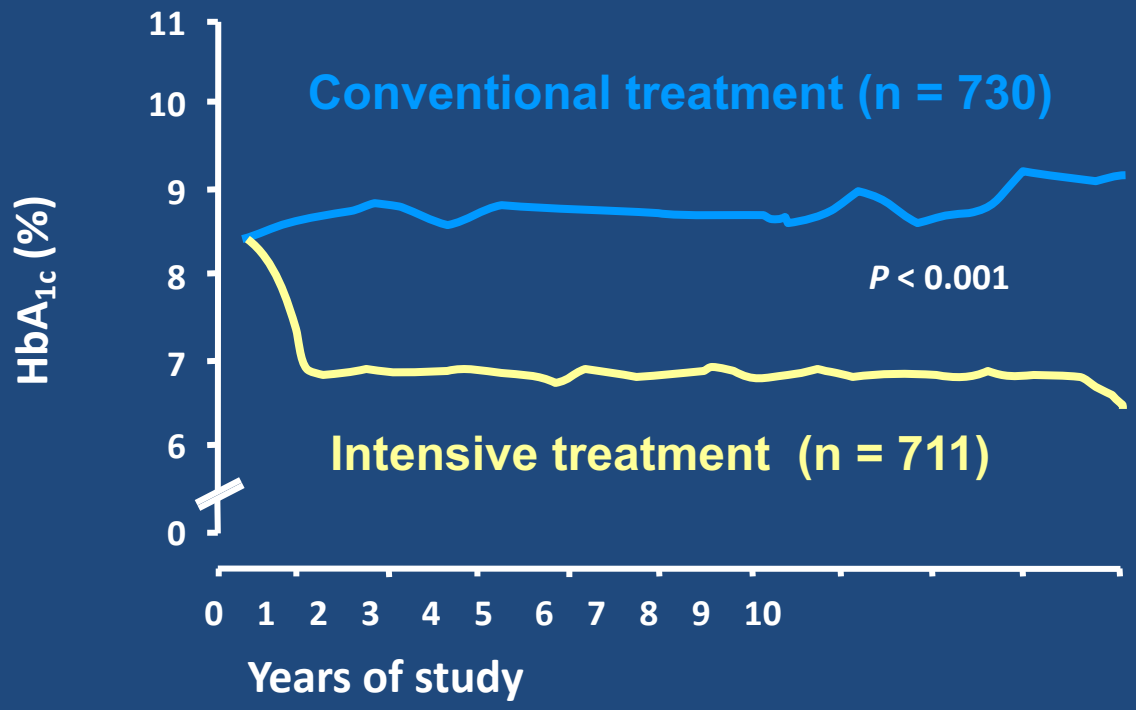
- Most common presentation in children and adolescents
- Approximately 50% new-onset < age 20
- Peak incidence
  - Puberty for boys and girls
- More common in Northern European heritage
- Autoimmune
- 1 of 350 children
- 3-5% risk in siblings
- 30% for identical twins
- Risk of DKA
- Dependence on insulin for survival
- Related autoimmune disorders
  - Thyroid- up to 15%
  - Celiac -5%

T2DM

- > 30% of children > 10 presenting with T2DM
- Insulin Resistance
- Obesity
- NAFLD
- PCOS
- Increasing prevalence
- [+] family history
- Ketosis can be present (KPT2)
- Life style mod, Metformin, insulin
- Elements of Metabolic Syndrome
  - HTN
  - Acanthosis Nigracans
  - Dyslipidemia
  - Microalbuminuria

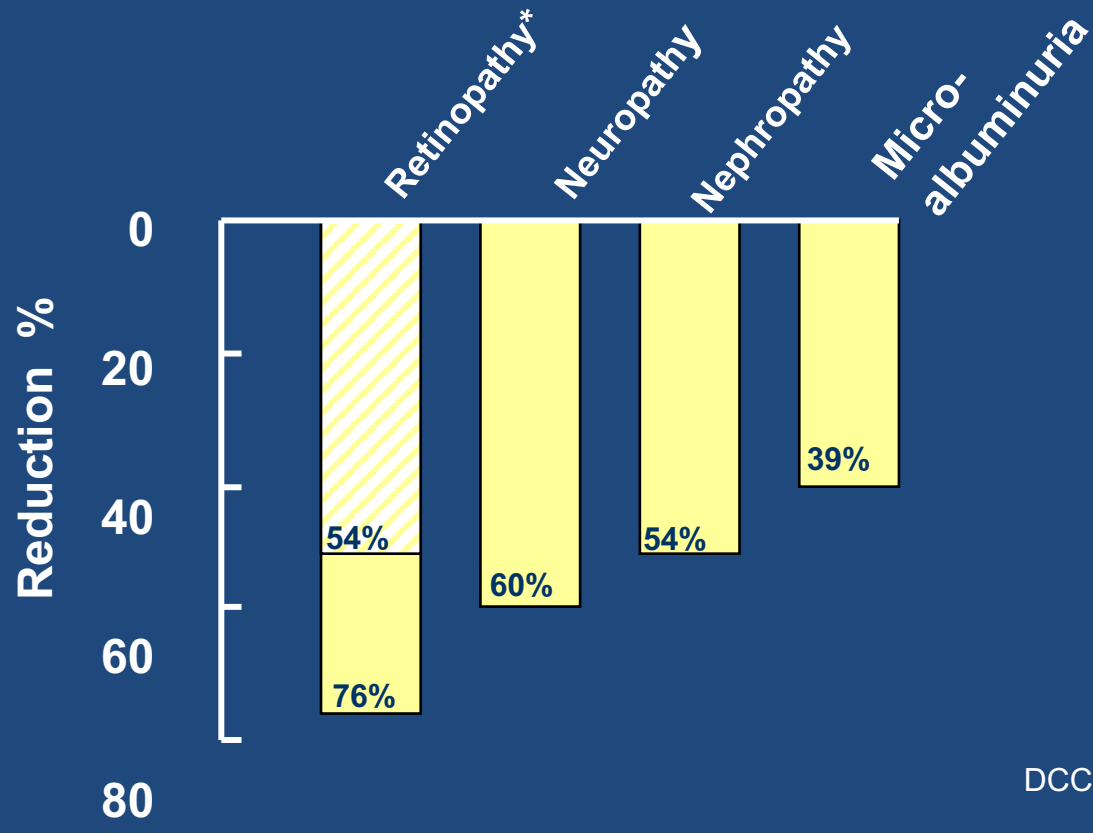
DCCT: intensive control reduces complications in type 1 diabetes

Conventional versus intensive insulin therapy (n = 1441)



DCCT Research Group. *N Engl J Med* 1993; **329**:977–986.

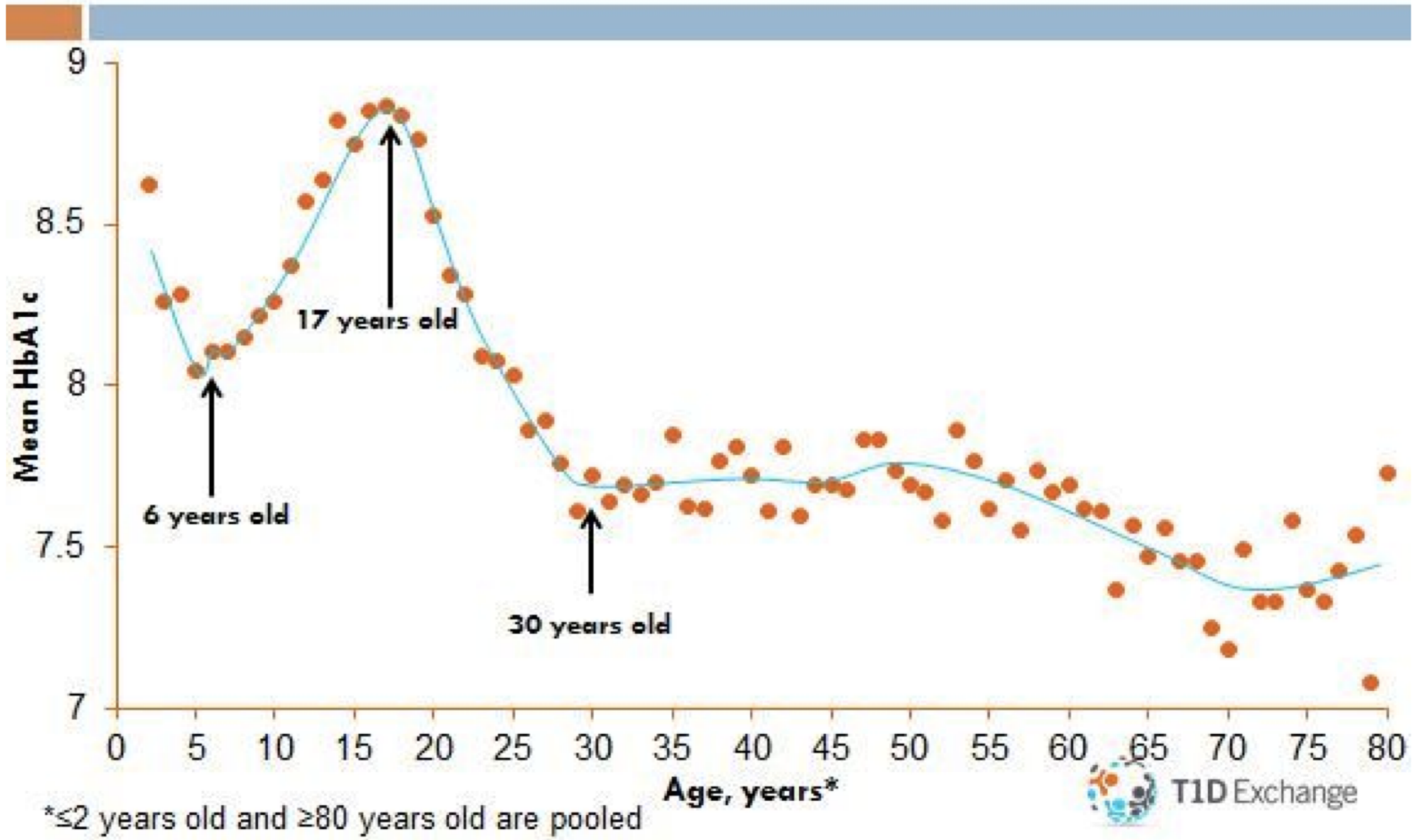
DCCT: intensive control reduces complications in type 1 diabetes



DCCT Research Group. *N Engl J Med* 1993; **329:**977–986.

A1C%	eAG mg/dl
5	97
5.5	111
6	126
6.5	140
7	154
7.5	169
8	183
8.5	197
9	212
9.5	226
10	240
10.5	255
11	269
11.5	283
12	298

Average Hba1c By Age



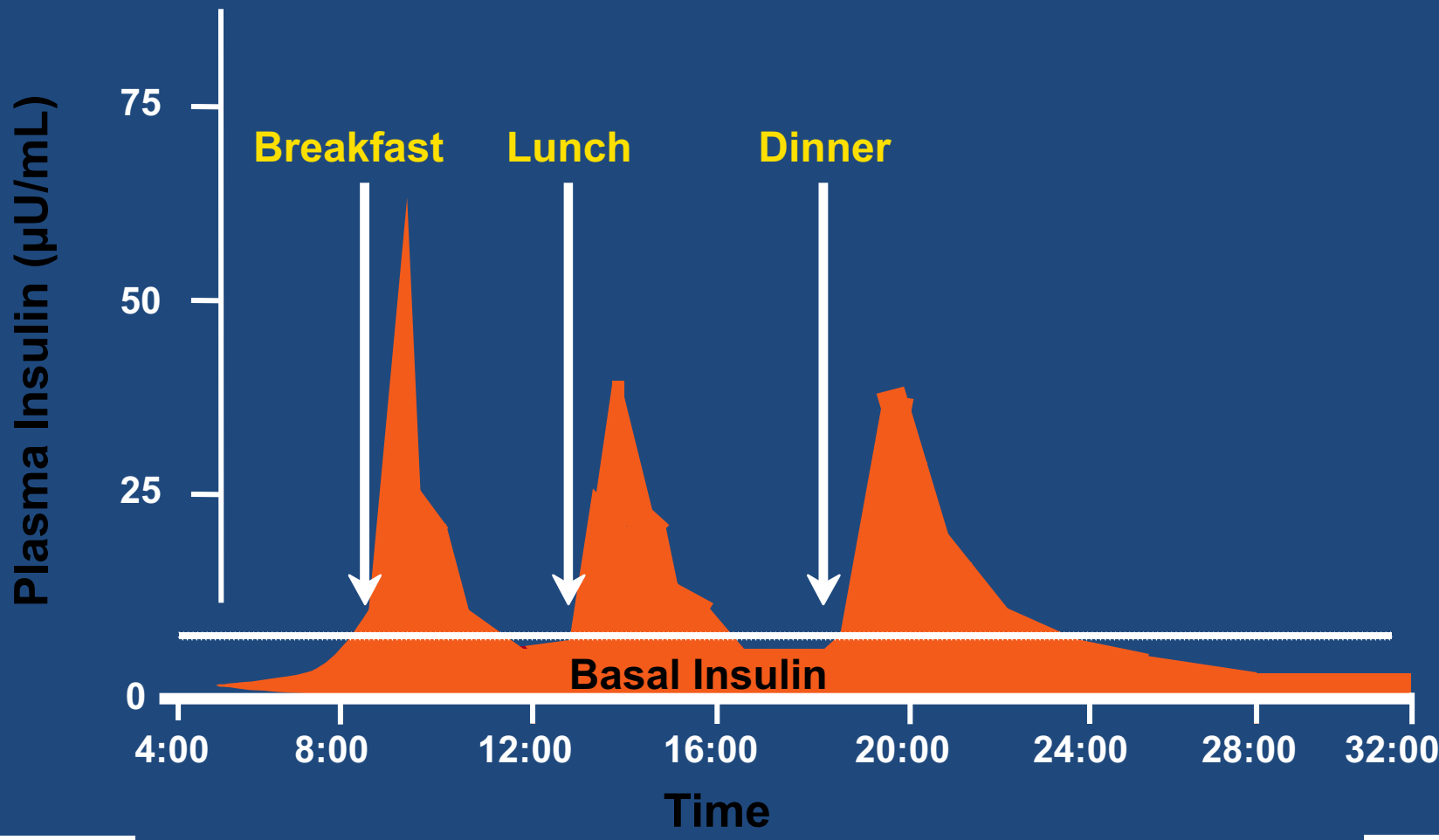
Treatment

- GOAL: Lowest A1c without significant hypoglycemia
- Monitor BG with SMBG or CGM
- Physiologic regimens whenever realistically possible including use of CSII pump therapy in all ages
- Use of CHO counting whenever possible
- Incorporating exercise/activity in plan
- Developmentally appropriate expectations

A1c goals for T1DM by age group

Age	HbA1c
Youth	< 7.5%
Adults	< 6.5% (AACE) < 7.0% (ADA)
Elderly	individualized

Normal Physiology: Basal-Bolus Insulin



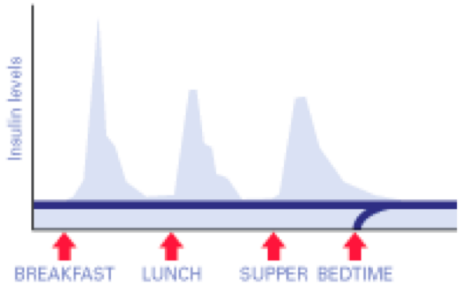
Diabetes Center
University of California San Francisco

Adapted from Polonsky KS. *N Engl J Med.* 1988;318:1231.

UCSF Benioff Children's Hospital
San Francisco

BASAL (Lantus®)

LONG-ACTING INSULIN



Onset
2-4 hours

Duration
24 hours

PRANDIAL

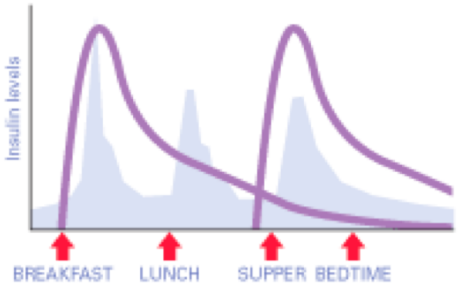
RAPID-ACTING INSULIN

Onset
~5 minutes

Duration
4-5 hours

PREMIX

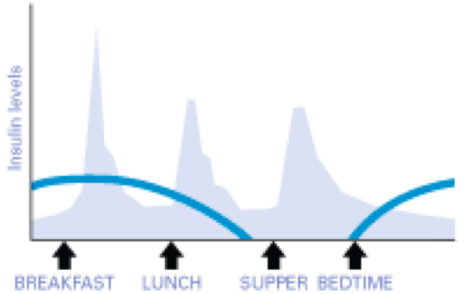
PREMIXED INSULIN (ANALOG)



Onset
5-15 minutes

Duration
10-16 hours

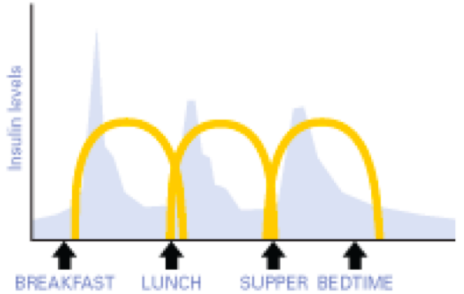
INTERMEDIATE-ACTING INSULIN (NPH)



Onset
0.5-1 hours

Duration
10-16 hours

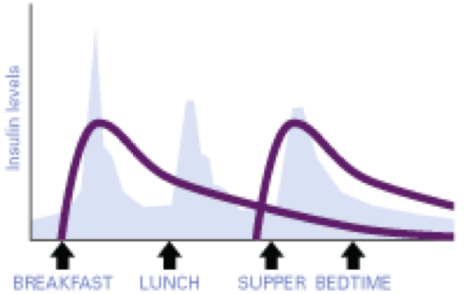
SHORT-ACTING INSULIN (RHI)



Onset
30 minutes

Duration
Up to 6 hours

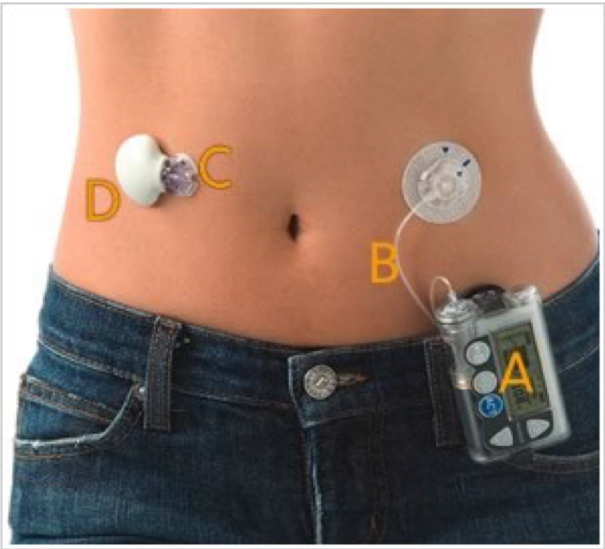
PREMIXED INSULIN (HUMAN)



Onset
5-15 minutes

Duration
10-16 hours

Optimize therapy?



A: pump
B: infusion set
C: sensor
D: transmitter

Family Protective Factors in Chronic Illness

- Family emotional closeness or connectedness
- Caregiver (parental) coping skills
- Mutually supportive relationships
- Clear family organization & decision-making
- Direct communication about the illness

Weihs, Fisher & Baird, 2005; Fisher & Weihs, 2000

Family Risk Factors in Chronic Illness

- Conflict or criticism
- Psychological trauma related to the disease
- Stressors external to the family
- Family isolation
- Disruption of developmental tasks by the disease
- Family rigidity or perfectionism