JDRF

IMPROVING LIVES. CURING TYPE 1 DIABETES.

STAGING PRESYMPTOMATIC TYPE 1 DIABETES: WHY BOTHER?

Presented by Lynn Bartholow, Clinical Trials Program Manager

Learning Objectives

- By the end of this presentation, participants should:
  - Be able to identify the three stages of T1D
  - Be able to identify the key characteristics of each stage
  - Understand the reasons why this staging criteria is beneficial for relatives of those with T1D and people with T1D
  - Understand why those who are relatives of those with T1D are at greater risk for developing the disease.

Agenda

- JDRF and our mission
- Prevention Program
- Staging System
- Why It's Important
- Other initiatives within Prevention

WHO WE ARE AND WHAT WE DO

IMPROVING LIVES. CURING TYPE 1 DIABETES.

Who We Are

JDRF is the leading global organization funding type 1 diabetes (T1D) research. Our goal is to eventually cure and prevent T1D entirely.

Along the way to a cure, we will continue to drive scientific progress that delivers new treatments and therapies that make day-to-day life with T1D easier, safer and healthier.

About JDRF

OUR VISION

A world without type 1 diabetes

OUR MISSION

Accelerating life-changing breakthroughs to cure, prevent and treat type 1 diabetes and its complications

TYPE 1 DIABETES:

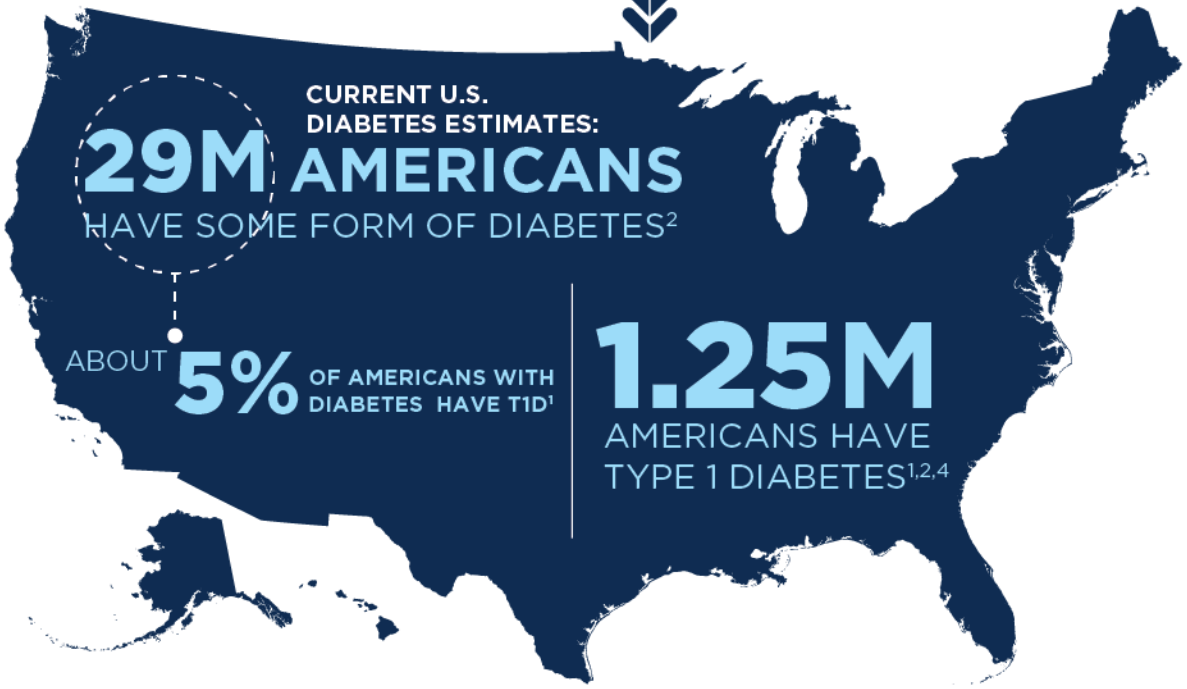
A Status Report

21% INCREASE
IN NUMBER OF U.S. YOUTH WITH T1D BETWEEN 2001 AND 2009[3]

5M PEOPLE
ARE EXPECTEDTO HAVE T1D[2,3]

2001 — 2009 — 2012 — 2050

THIS INCLUDES A
3-FOLD GROWTH
IN YOUTH WITH T1D TO NEARLY
600,000[2]



84%
OF THE PEOPLE WITH T1D ARE ADULTS[1]

40,000
PEOPLE ESTIMATED TO BE DIAGNOSED WITH T1D EACH YEAR IN THE U.S.[1,2]

$14B
T1D-ASSOCIATED U.S. HEALTHCARE COST

Less than one-third of people with T1D in the U.S. are achieving target blood glucose control levels[5]

T1D is associated with an estimated loss of life expectancy of up to 13 years[6]

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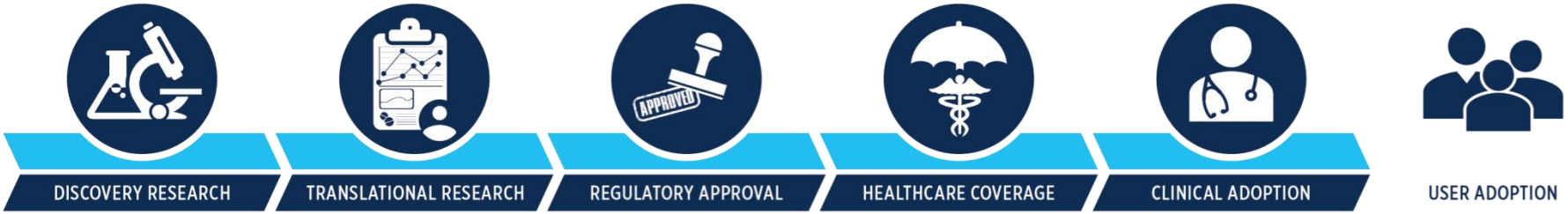
[1] CDC National Diabetes Statistics Report, 2014
[2] Impreatore, et al. 2012. Diab Care 35: 2515-2520
[3] Dabelea, et al. 2014. JAMA 311: 1778-1786
[4] JDRF Estimations
[5] T1D exchange data
[6] Jama 2015; 313(1):1-9)

4/5/2017

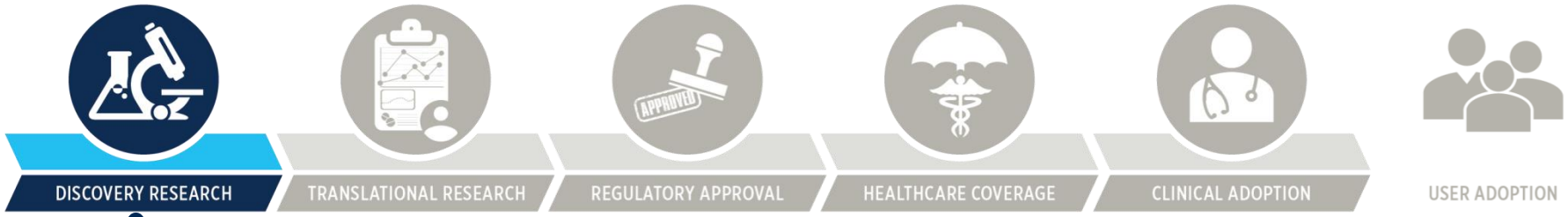
THE PLAN

Accelerating Progress Across the Pipeline



THE PLAN

Accelerating Progress Across the Pipeline



Identifying new approaches to cure, prevent and treat T1D and its complications

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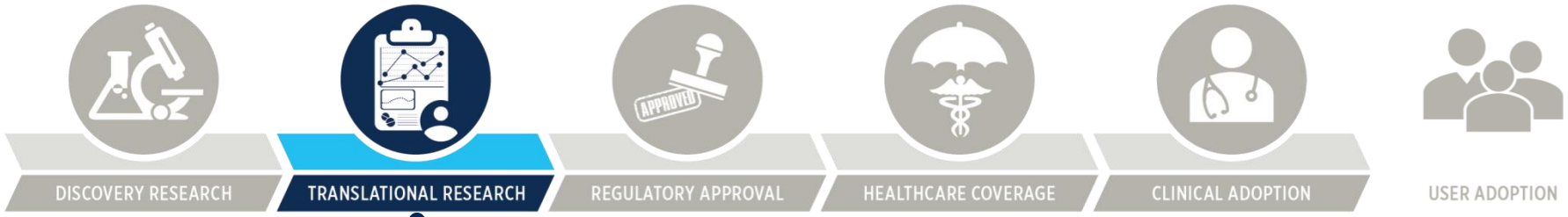
Accelerating Progress Across the Pipeline



Moving scientific discoveries from the laboratory to the real world (Clinical Trials)

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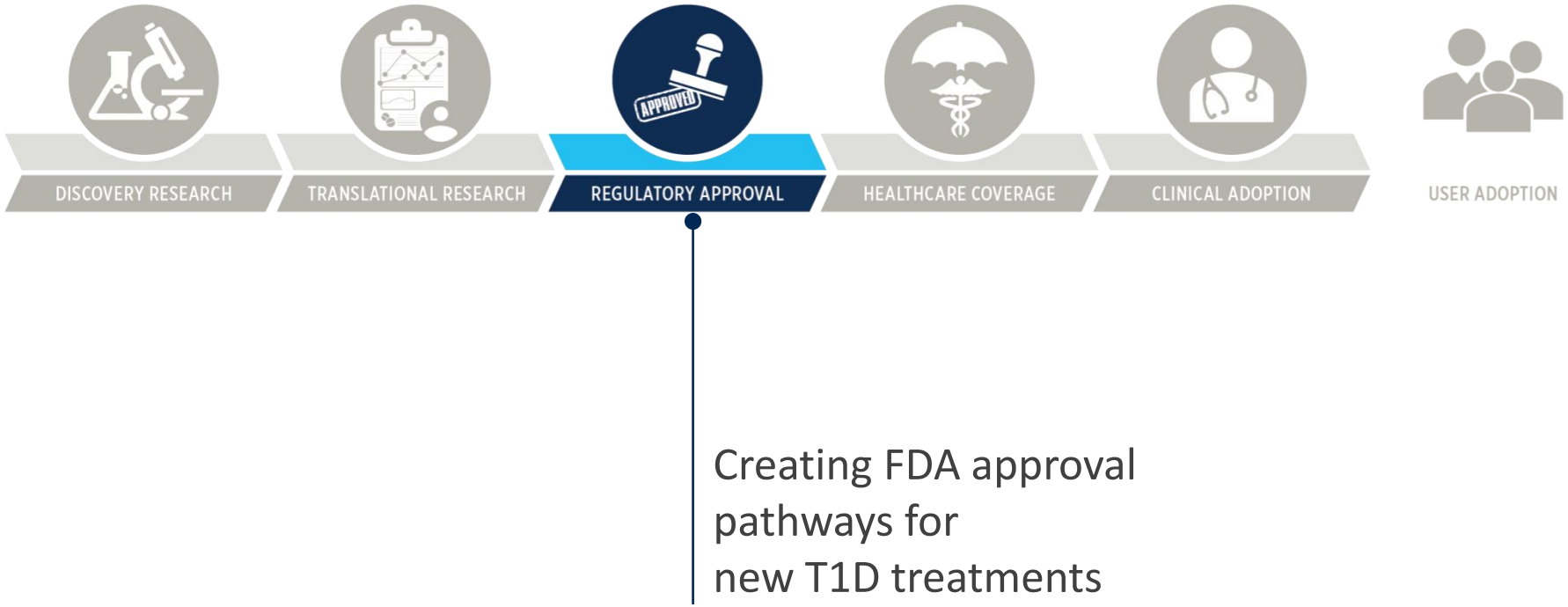

Creating FDA approval pathways for new T1D treatments

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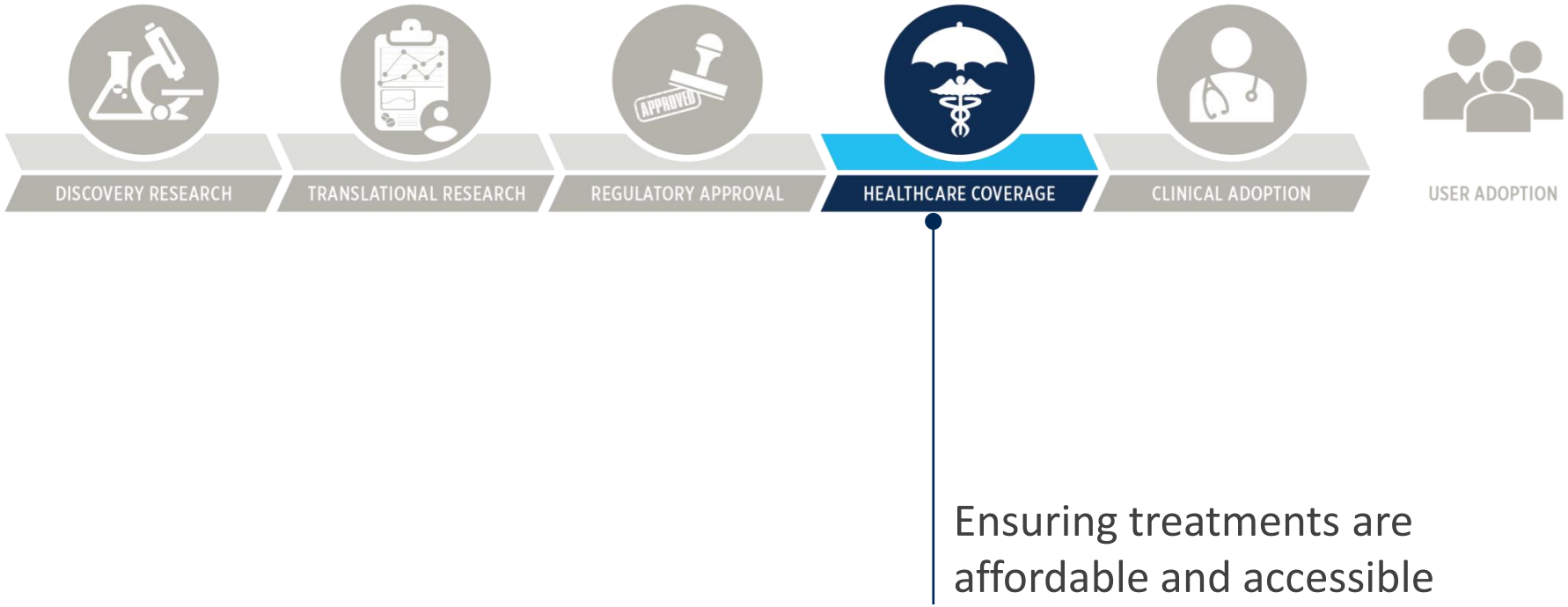

Ensuring treatments are affordable and accessible

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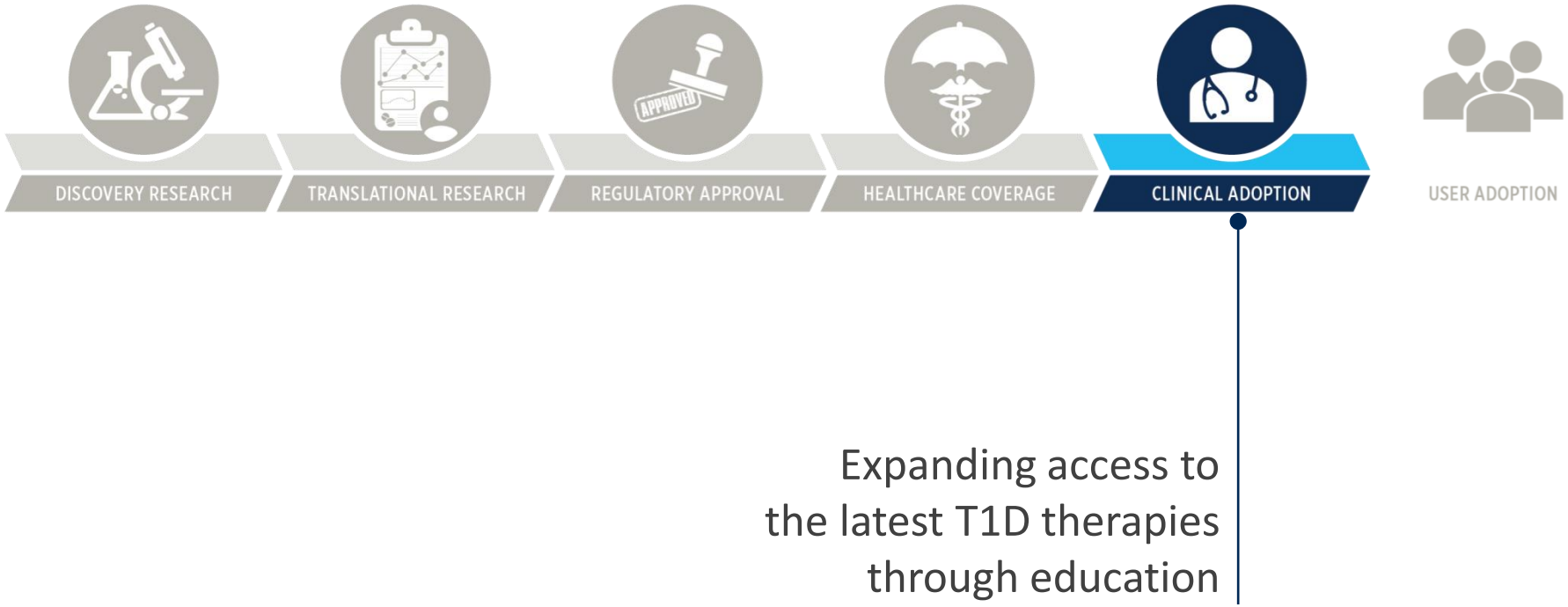
Accelerating Progress Across the Pipeline



Expanding access to the latest T1D therapies through education

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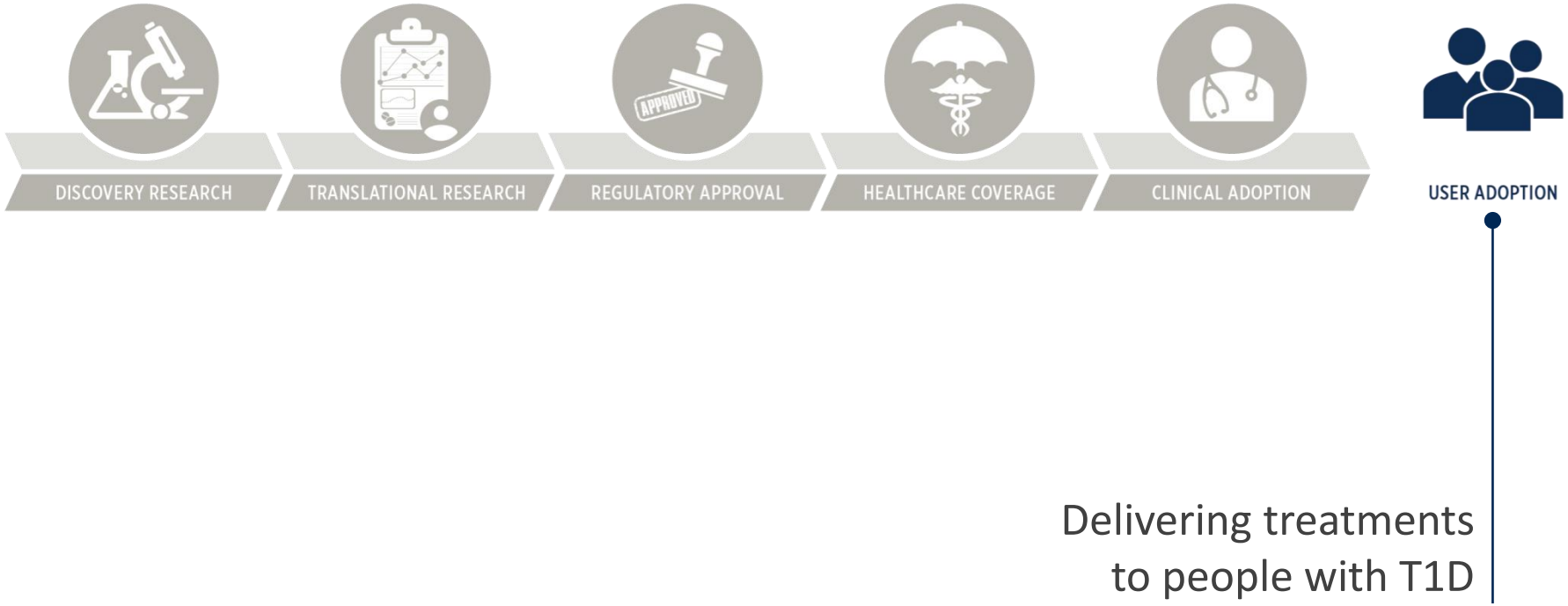
Accelerating Progress Across the Pipeline



Delivering treatments
to people with T1D

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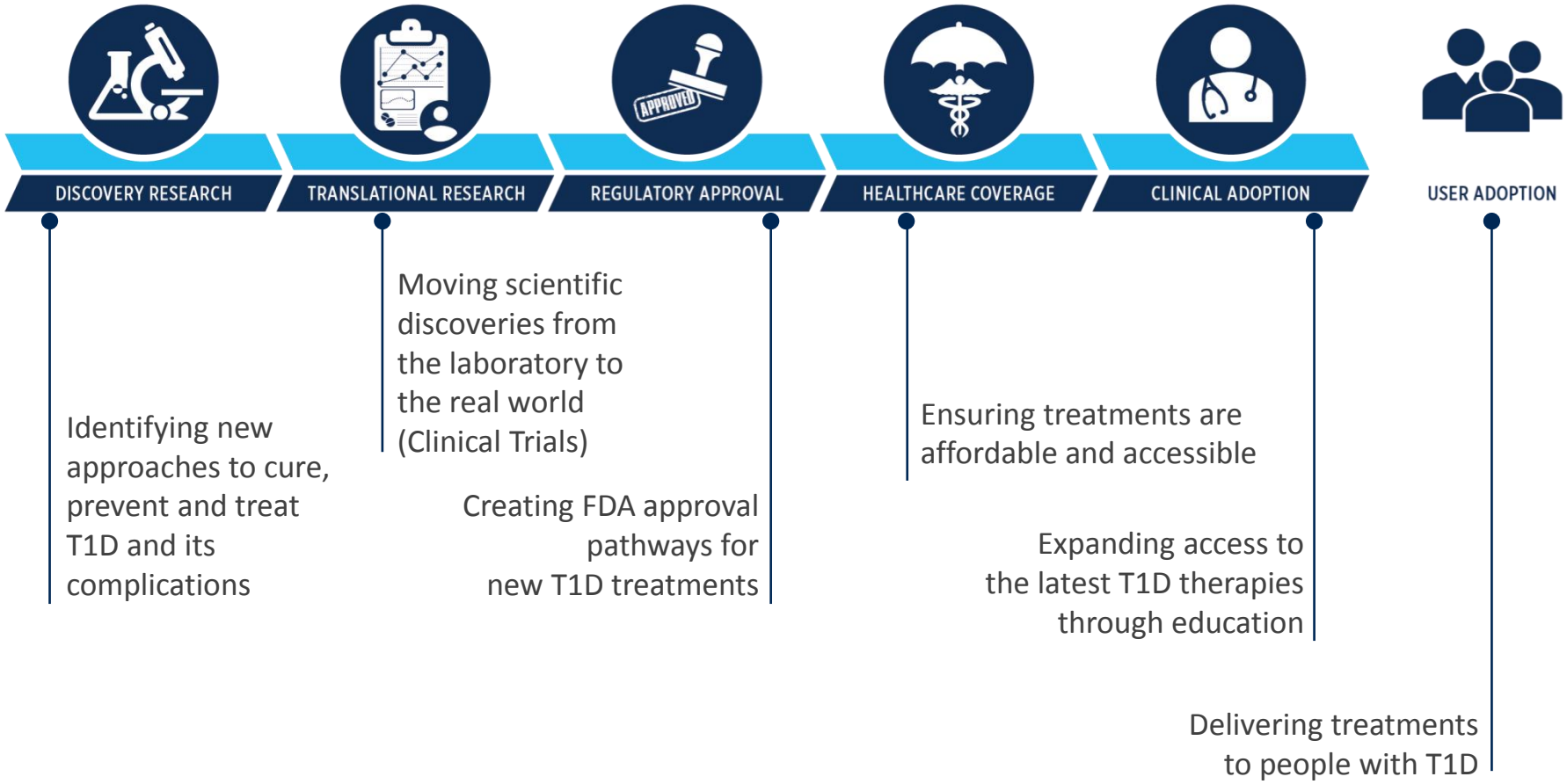
Accelerating Progress Across the Pipeline



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THE PLAN

Accelerating Progress Across the Pipeline

TO DELIVER LIFE-CHANGING BREAKTHROUGHS

CURE
Restoring Insulin Independence

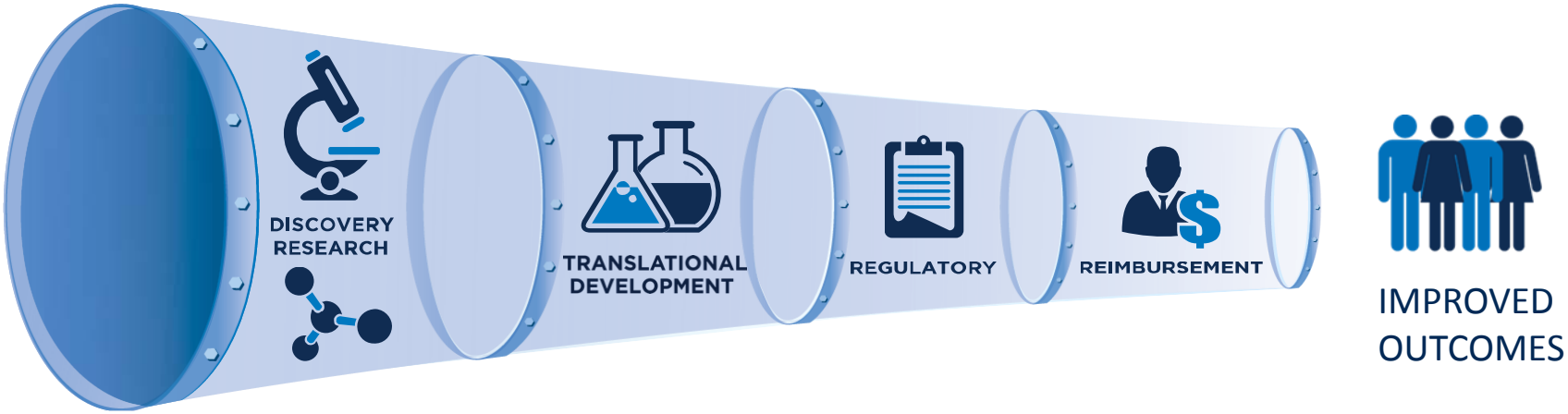
PREVENT
Preventing Symptomatic T1D

TREAT
Improving Glucose Control

JDRF'S CAPABILITIES

RESEARCH PARTNERSHIPS

INTERNATIONAL REACH (foundations)



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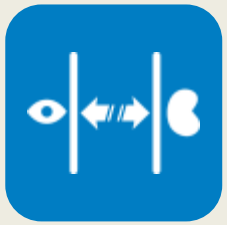
INSIDE THE PIPELINE

Continuous Therapeutic Improvements

ARTIFICIAL PANCREAS



COMPLICATIONS

ENCAPSULATION

GLUCOSE CONTROL
(INCLUDING SMART INSULIN)

RESTORATION

PREVENTION

PREVENTION

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Prevention

Our plan is to create a future where...

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A Tale of Two Families

Tommy – Age 17

- Older brother, John, diagnosed with T1D at age 8 in severe DKA
- Mom worried about Tommy so checks Tommy's blood sugar using John's meter

Emily – Age 16

- Dad diagnosed with T1D
- Intermittent blood sugar checks as well.

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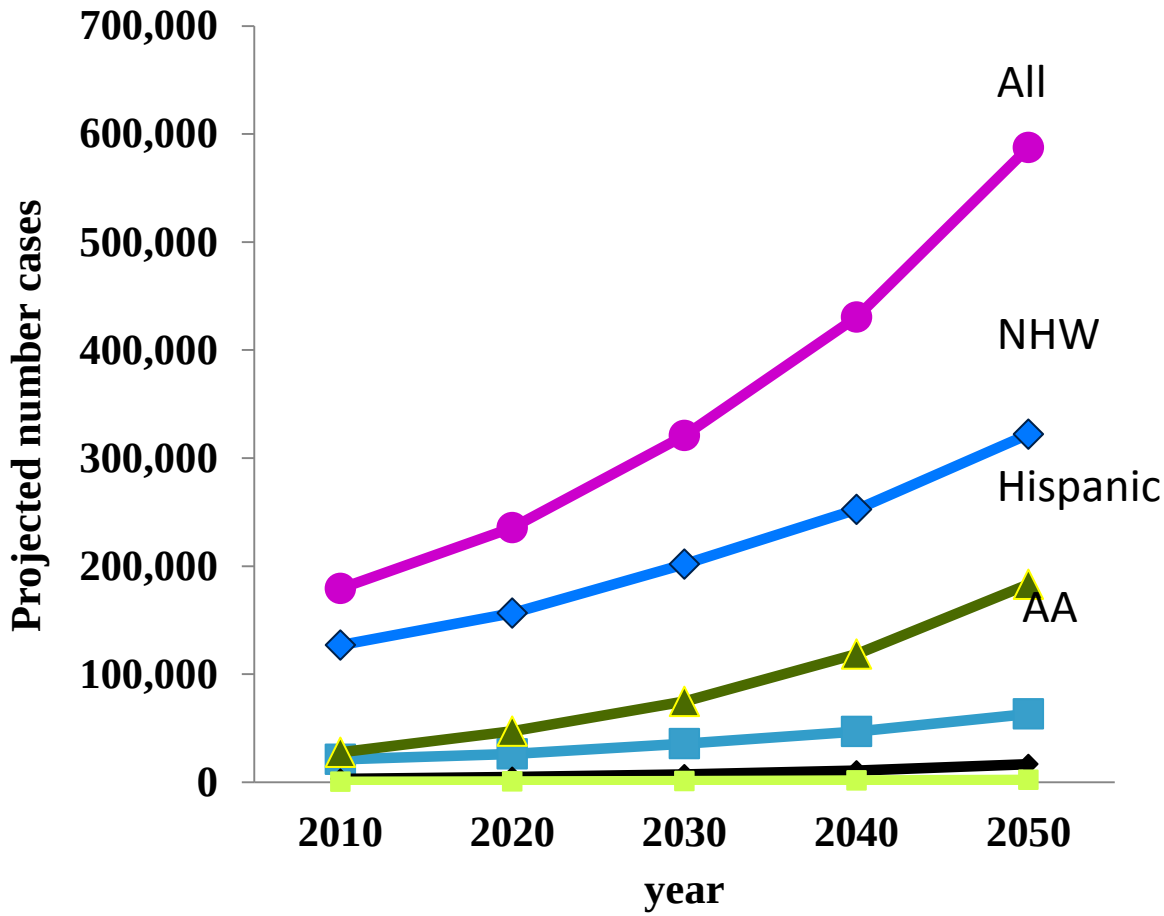
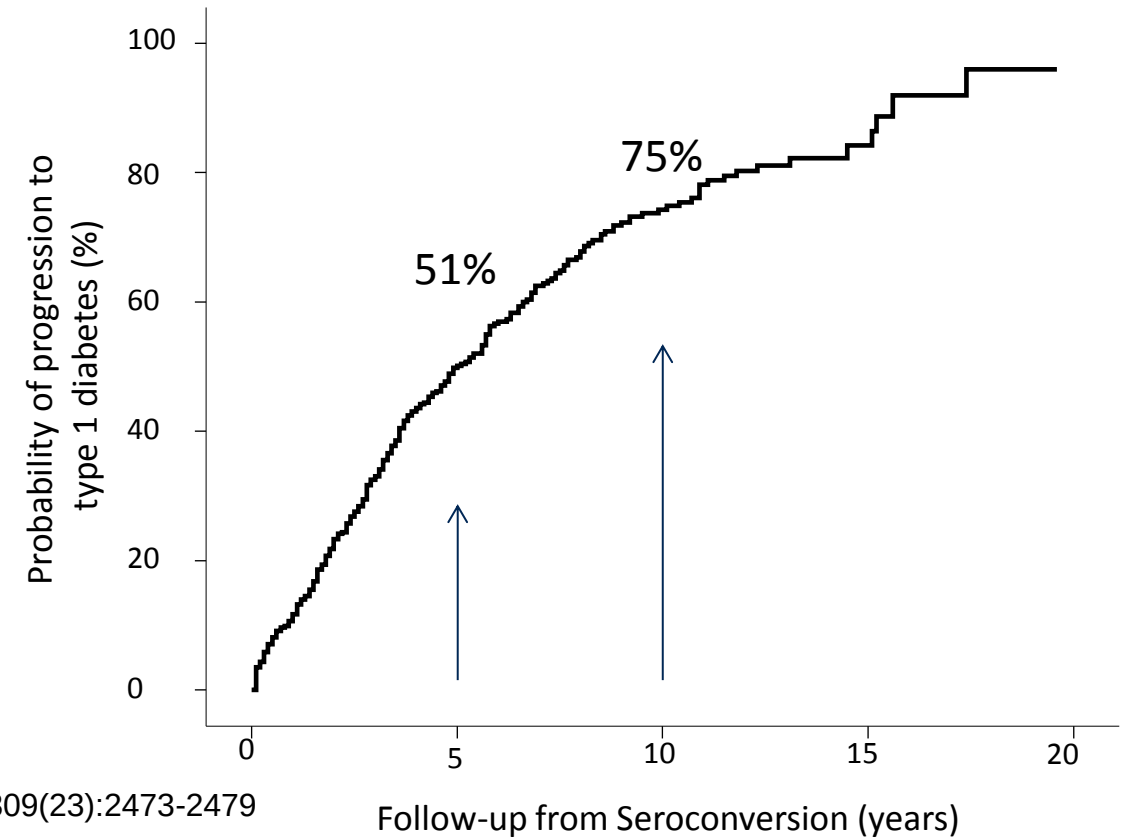
Projected Number of Youth < 20 Years With T1D: Increased Incidence Scenario



- Number of US youth with T1D projected to increase 3.3-fold by 2050
- Highest among NHW youth (7.04/1000 in 2050)
- Largest relative increase among Hispanic youth (6.6-fold increase)
- US health care systems need to be prepared

Imperatore, et al. *Diabetes Care,* 35(12), 2515, 2012

5- and 10-Year Risk of Progression to Symptomatic T1D with Multiple Islet Autoantibodies ≤ Age 5 Years is 51% and 75%



JAMA. 2013;309(23):2473-2479

And the Lifetime Risk Approaches 100%

George Eisenbarth *"The clock to T1D has started when islet antibodies are first detected".* Paradigm shift for staging of type 1 diabetes before clinical onset

JAMA. 2013;309(23):2473-2479

What is the risk for developing type 1 diabetes among family members compared to the rest of the population?

a. no difference

b. 3X greater risk

c. 15X greater risk

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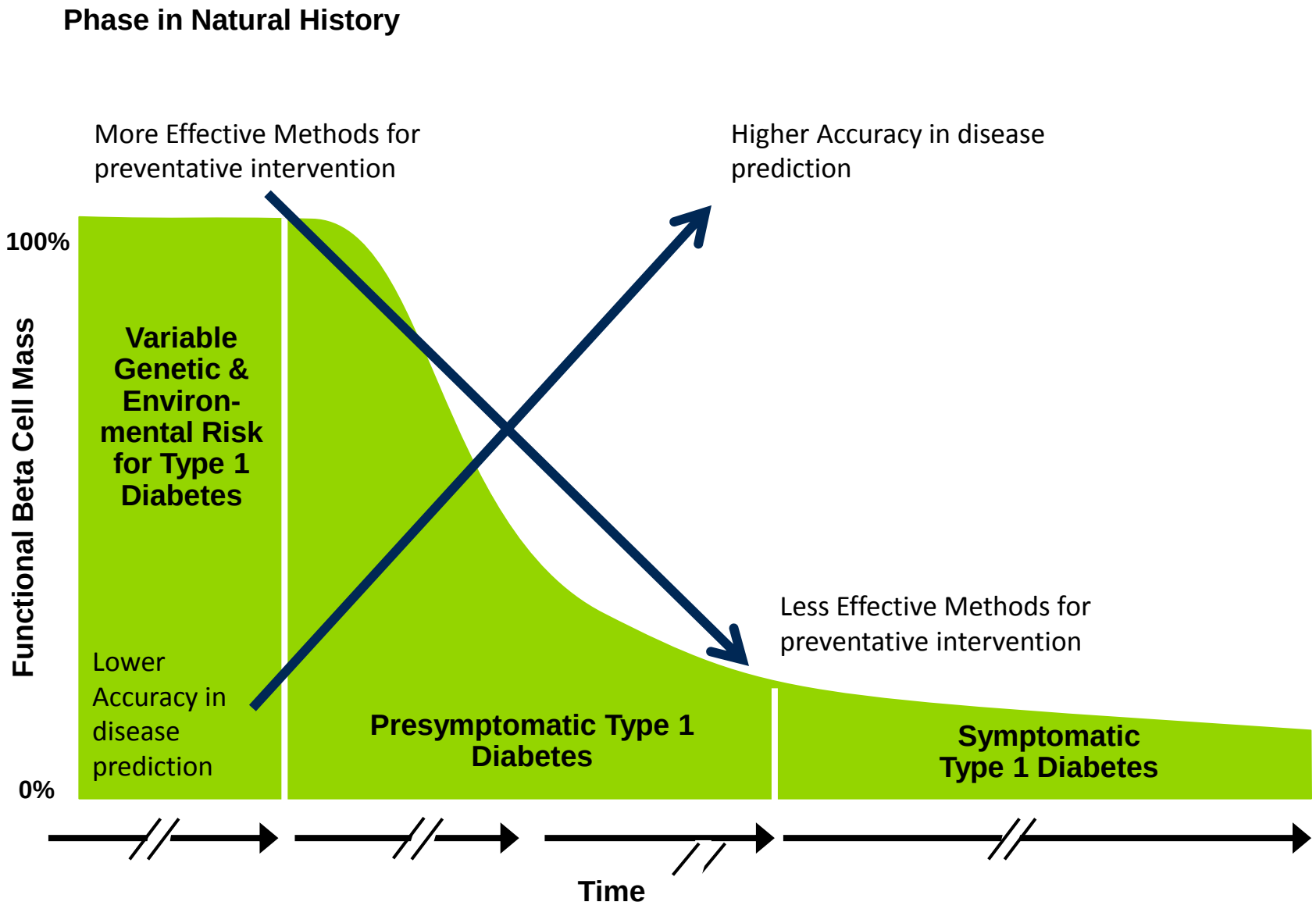
Phase in Natural History
More Effective Methods for preventative intervention
Higher Accuracy in disease prediction
100%
Functional Beta Cell Mass
Variable Genetic & Environ-mental Risk for Type 1 Diabetes
Lower Accuracy in disease prediction
Less Effective Methods for preventative intervention
Presymptomatic Type 1 Diabetes
Symptomatic Type 1 Diabetes
0%
Time

STAGING SYSTEM

defining the early stages of type 1 diabetes T1D

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American Diabetes Association

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

JDR

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AACE The Voice of Clinical Endocrinology

ISPAD International Society for Pediatric and Adolescent Diabetes

ENDOCRINE SOCIETY

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

Richard A. Insel, Jessica L. Dunne, Mark A. Atkinson, Jane L. Chiang, Dana Dabelea, Peter A. Gottlieb, Carla J. Greenbaum, Kevan C. Herold, Jeffrey P. Krischer, Ake Lernmark, Robert E. Ratner, Marian J. Rewers, Desmond A. Schatz, Jay S. Skyler, Jay M. Sosenko, and Anette-G. Ziegler

Diabetes Care 2015;38:1964–1974

The Adoption of the Staging Classification System Is Endorsed by the American Association of Clinical Endocrinologists, the International Society for Pediatric and Adolescent Diabetes, and The Leona M. and Harry B. Helmsley Charitable Trust

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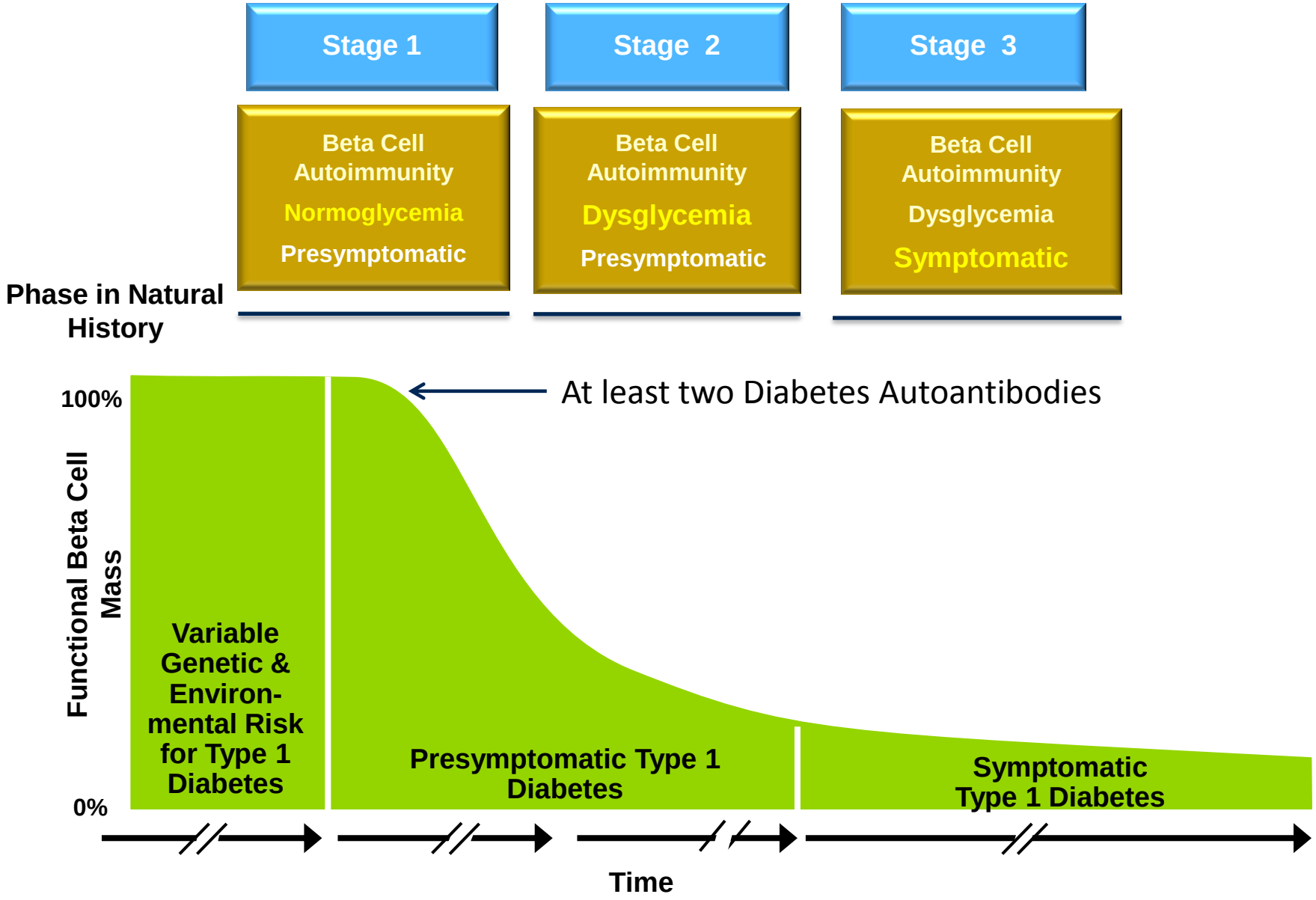
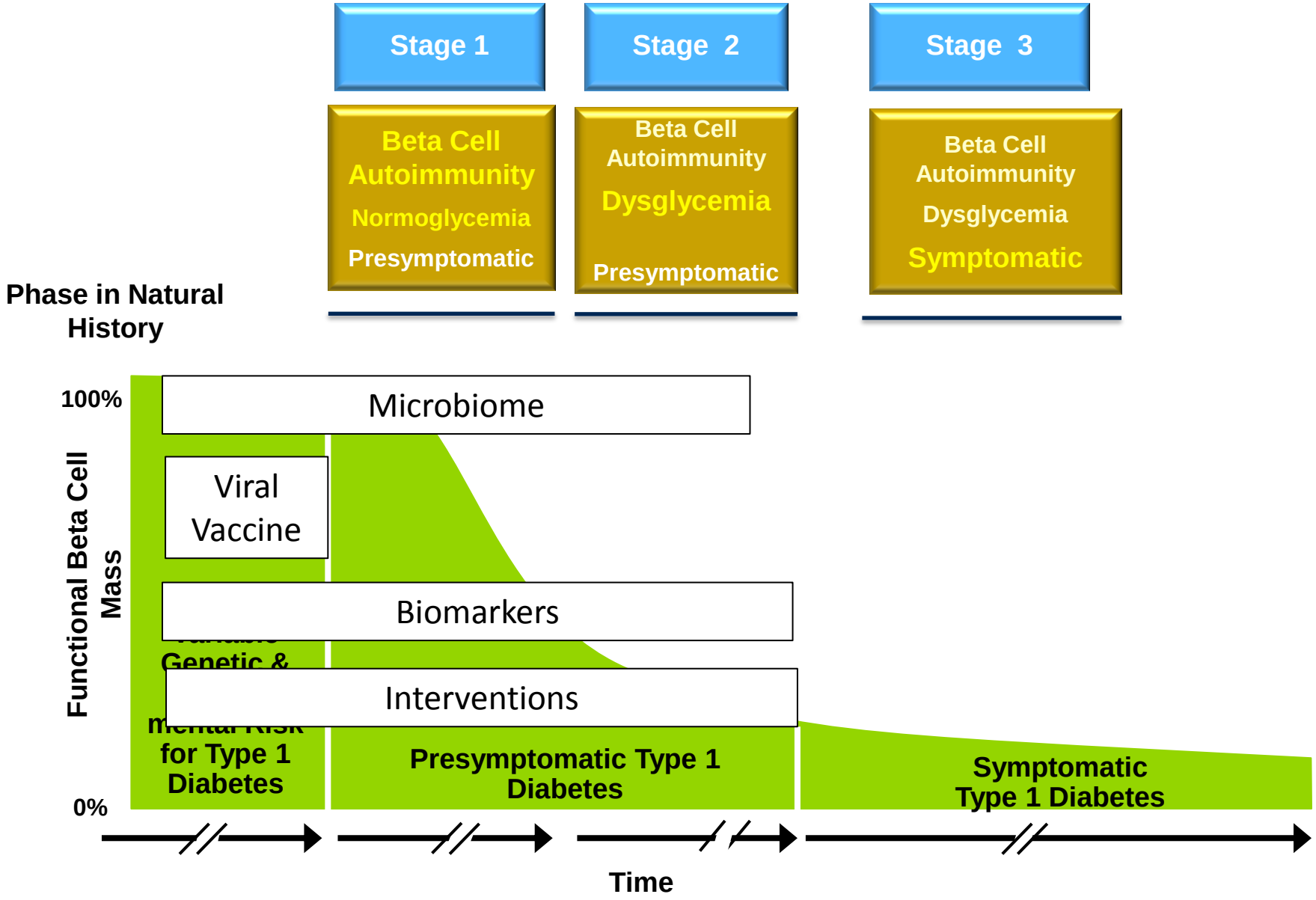
Type 1 Diabetes starts long (months even years) before symptoms occur.




Stage 1
Stage 2
Stage 3
Beta Cell Autoimmunity
Normoglycemia
Presymptomatic
Beta Cell Autoimmunity
Dysglycemia
Presymptomatic
Beta Cell Autoimmunity
Dysglycemia
Symptomatic
Phase in Natural History
100%
0%
Functional Beta Cell Mass
Microbiome
Viral Vaccine
Biomarkers
Interventions
for Type 1 Diabetes
Presymptomatic Type 1 Diabetes
Symptomatic Type 1 Diabetes
Time

Laying the groundwork

- **DIPP Study**
- **TEDDY Study**
- **FR1DA Study**
- **Other JDRF-funded projects**
- **TrialNet Pathway to Prevention Study**

DIPP (Type 1 Diabetes Prediction and Prevention Project)

- Launched in 1994 in Finland
- Finland has highest incidence of T1D
- Newborns screened for increased genetic risk of T1D
- Those with high or moderate genetic risk are recruited for follow-up examinations at 3- to 12-month intervals until the age of 15 and are screened for autoantibodies.
- Those that are autoantibody positive continue to be in follow-up
- Over 210,000 children have been screened. Of those, over 8500 children carrying genetic risk for T1D
- Over 300 have progressed to clinical diabetes

TEDDY (The Environmental Determinants of Diabetes in the Young)

- Launched in 2004 at six clinical centers in four countries (Finland, Sweden, Germany, and USA) to investigate role of environmental factors
- Newborns screened for increased genetic risk of T1D
- Those with high or moderate genetic risk are recruited for follow-up examinations at 3- or 6-month intervals and analysis of autoantibodies.
- 421,000 children screened with more than 6000 children at high-risk for T1D.
- Recruitment ended in 2010 and participating children will be followed until they have reached 15 years of age (2024)
- In TEDDY, screening newborns significantly reduced Diabetic Ketoacidosis (DKA) rates in children:
  - 16.1% vs. 39.5-54% in diabetes registries for children less than 2 yrs old

Other JDRF funded intervention studies

- TEDDY Family Follow-up (TEFA) Ake Lernmark (Finland and Sweden)
  - TEDDY family members who aren't FDRs are screened in Finland and Sweden for AAbs
  - Gluten Free Diet (GFD) + Vit D + Omega3 + probiotics in subjects with one or several islet autoantibodies without and with dysglycemia at baseline.
- adAPT Trial (autoimmune diabetes Accelerator Prevention Trial)
  - Accelerator hypothesis – both T1D and T2D are driven by demand for insulin.
  - Children age 5-16 and ≥ 2 Aabs randomized to metformin or placebo

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Impact of Early Staging of T1D on a Public Health Level

Frida

Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

- **Prevent diabetic ketoacidosis** on a population level, reducing family burden and health care cost
- Help set **new standards** for **early diagnosis** of T1D and **teaching**
- Assess the impact of **environmental determinants** for pre-T1D for which a population based approach is most suitable (air pollution, population density)
- Provide a **validation cohort** for findings from other cohorts such as TEDDY
- Provide an unprecedented **opportunity to design secondary prevention studies** to prevent insulin dependence on a broad population based level and with relatively rapid recruitment capacity.

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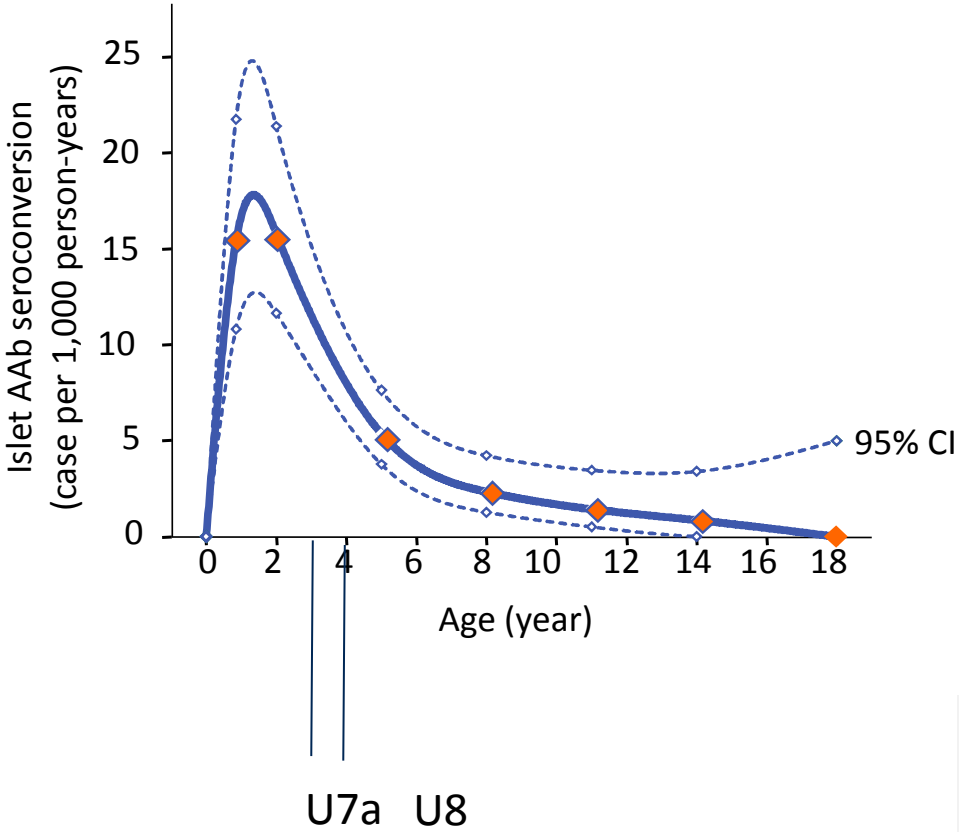
Childhood population-based risk screening: Age 3 and 4 years may be an optimal age in Germany

Incidence of islet autoantibodies in cases with multiple Abs amongst unselected FDRs



Compulsory Preventive Check-ups in Germany

U1-U6 age 0 to 12 months
U7 age 21-24 months
U7a age 34-36 month
U8 age 46-48 month
U9 age 60-64 month
U10 age 7-8 years
U11 age 9-10 years

2/3 of multiples islet autoantibodies occur before age 4 years (JAMA).

~ 90% of youth T1D is after age 3 years

Ziegler, Diabetologia 2012

Metabolic staging in children with early T1D

50,029 Screened, data from November 2016

165 (0.33%) with early T1D

134 received training and education, staging(OGTT)

13 spontaneous Diabetes (glucose > 200 mg%)

18 no OGTT yet

122 (91%) Normoglycemia → **10 (7%) + 2** Dysglycemia → **2 (2%) + 4** Hyperglycemia/ Manifest T1D

61 enrolled into the Fr1da Insulin Intervention Study

Total: **31** with dysglycemia /T1D

No ketoacidosis

Other JDRF-supported screening programs

- Fr1dolin – Thomas Danne (Lower Saxony, Germany)
  - Combined AAb screening with pediatric screening for familial hypercholesterolemia
  - Expect to screen 150,000 children aged 2 to 6 years
- ASK – Autoimmunity Study in Kids – Marian Rewers (Denver)
  - General population screening program for two most frequent autoimmune diseases of childhood, pre-T1D and celiac disease (CD)
  - Children ages 2-17 years in the Denver metro area
- ENDIA – Jenny Couper (Australia)
  - Largely funded by JDRF-A and HCT
  - http://www.endia.org.au/
  - Environmental factors that may contribute to the development of T1D in pre- and peri-natal period
  - Pregnant women with T1D or other FDRs of baby
    - 1400 women in their pregnancies and the babies born from those pregnancies.

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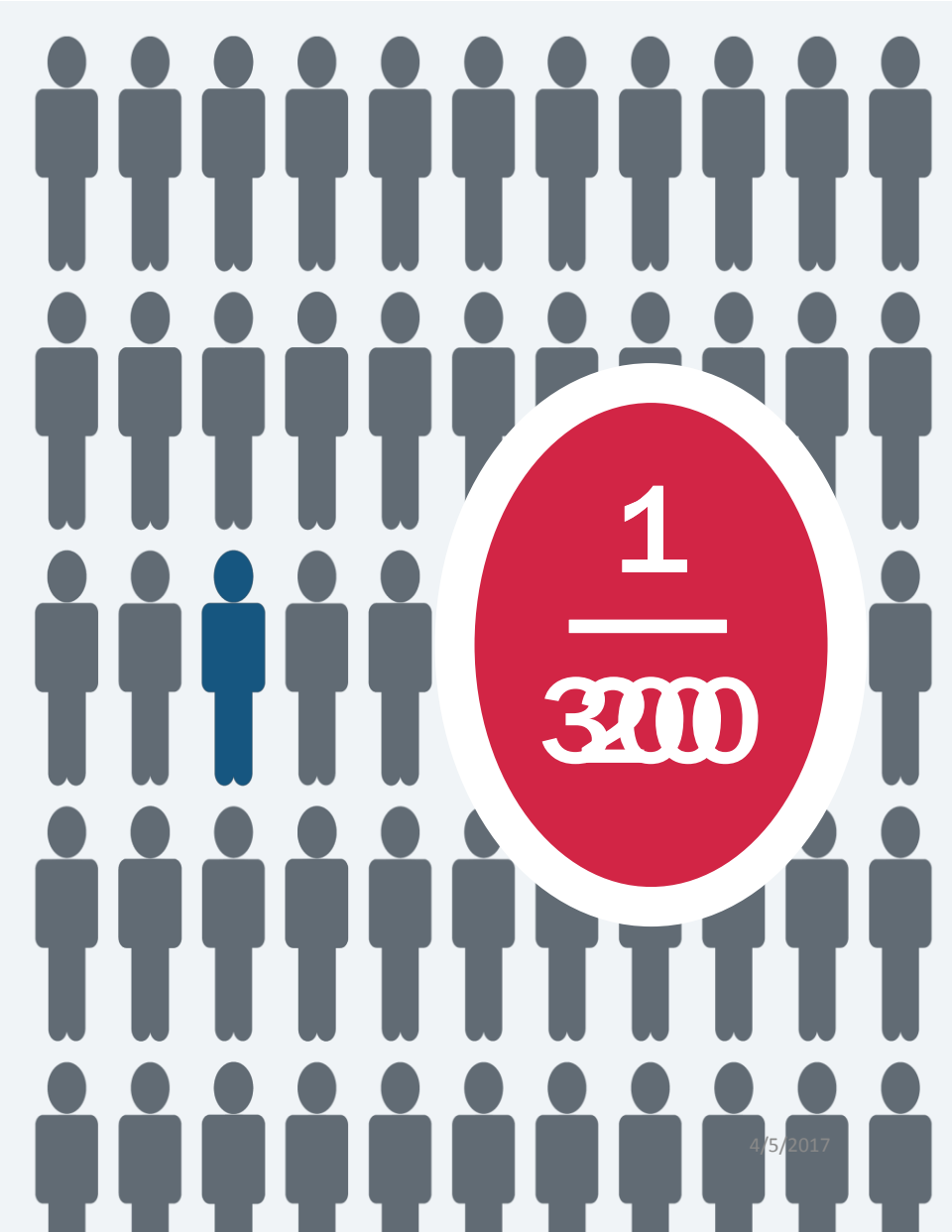
T1D Disease Progression

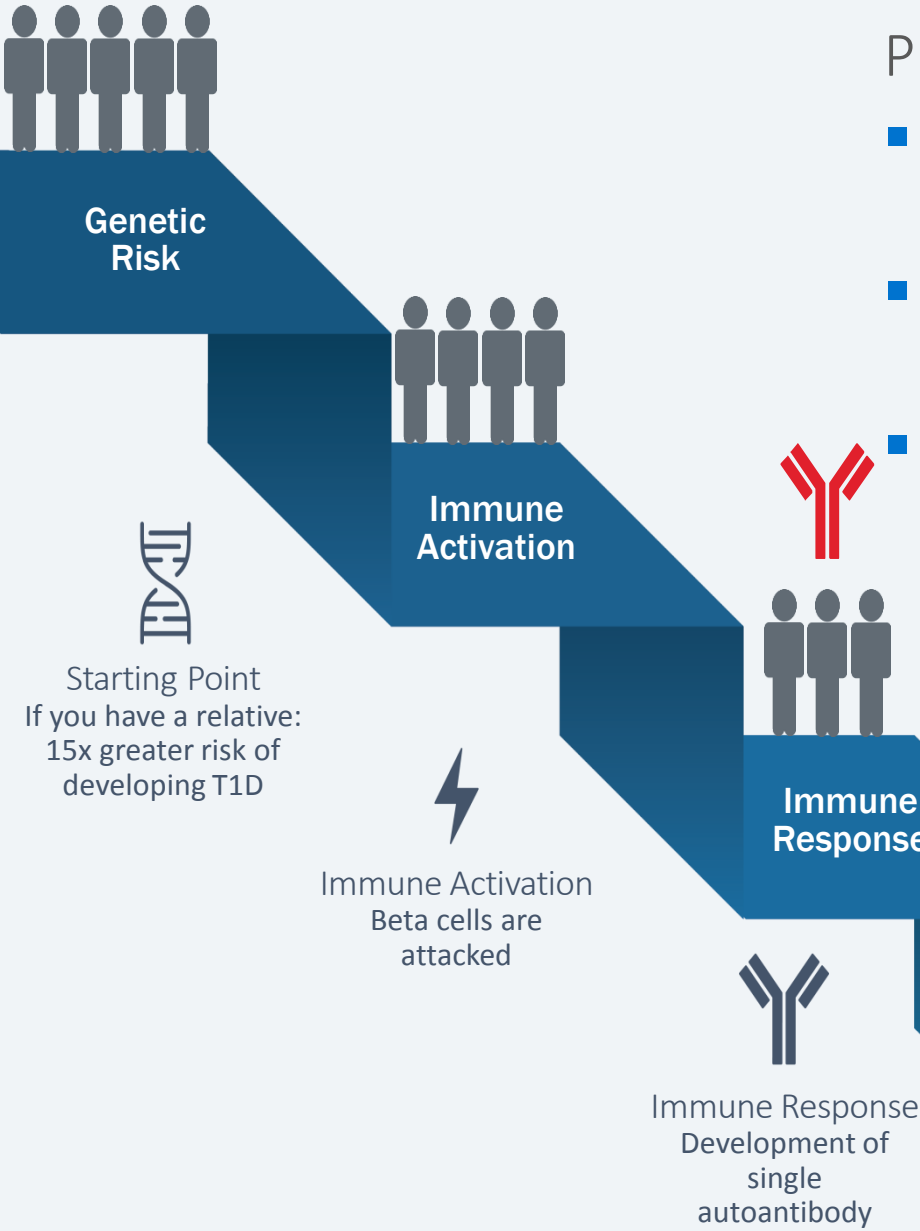
Starting Point
Genetic Risk

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

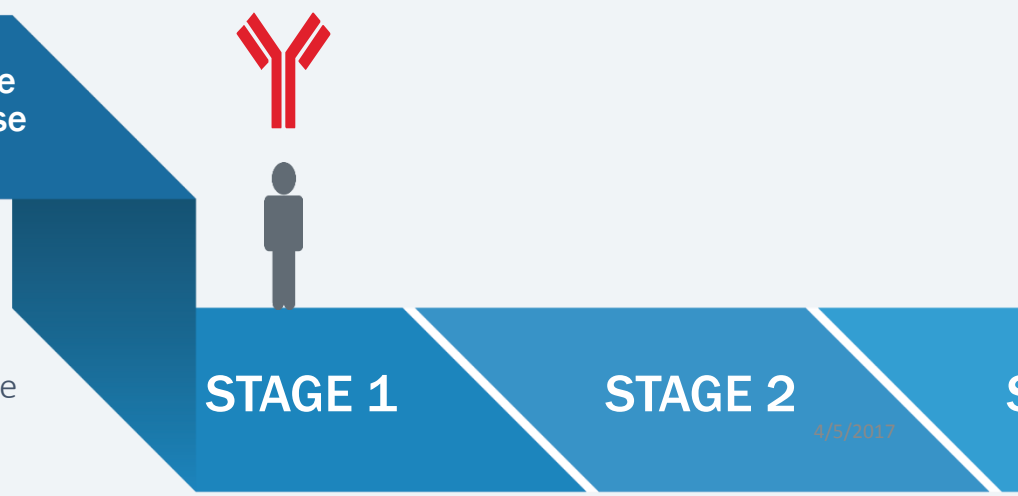


T1D Disease Progression

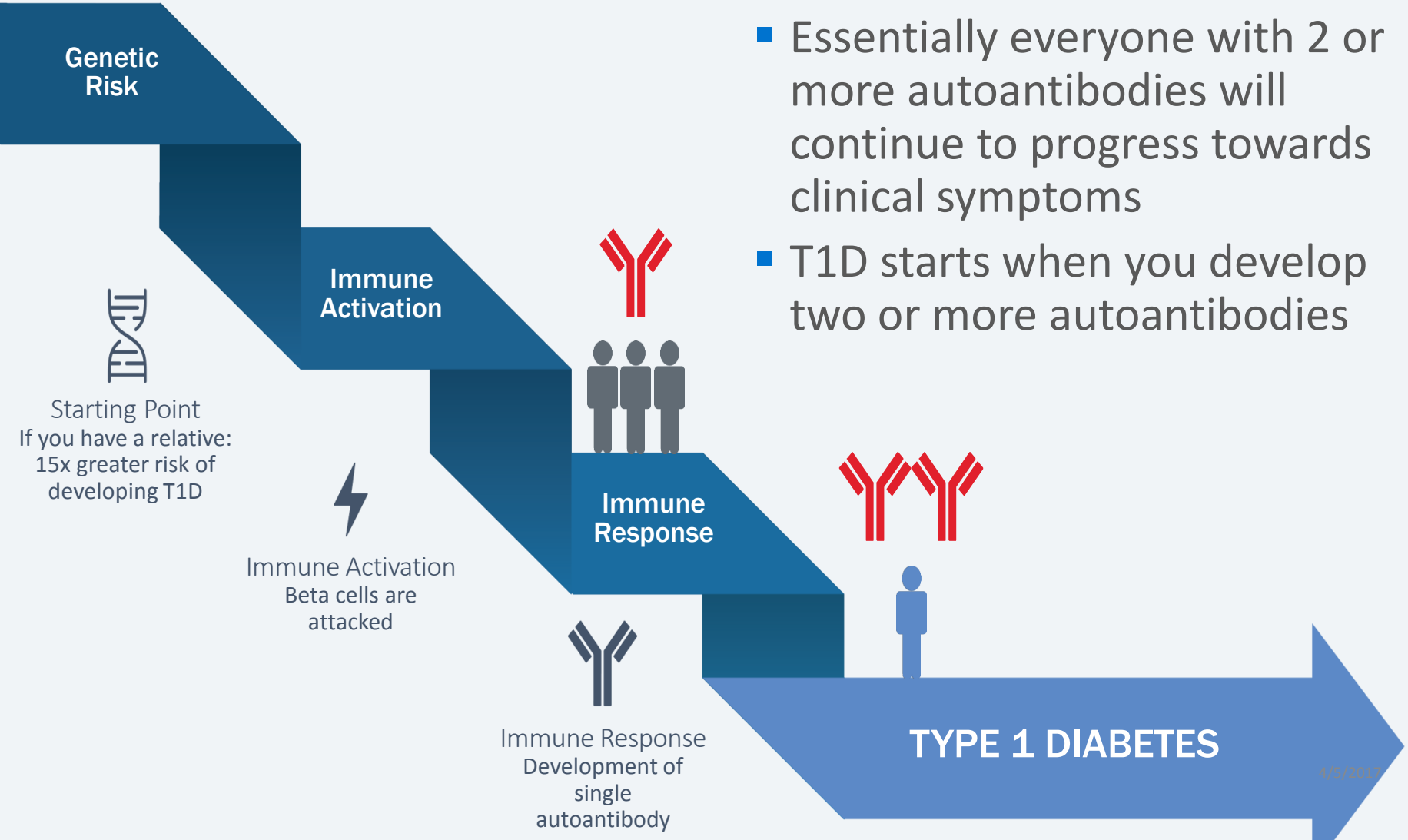


Progression by Population:

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



T1D Disease Progression

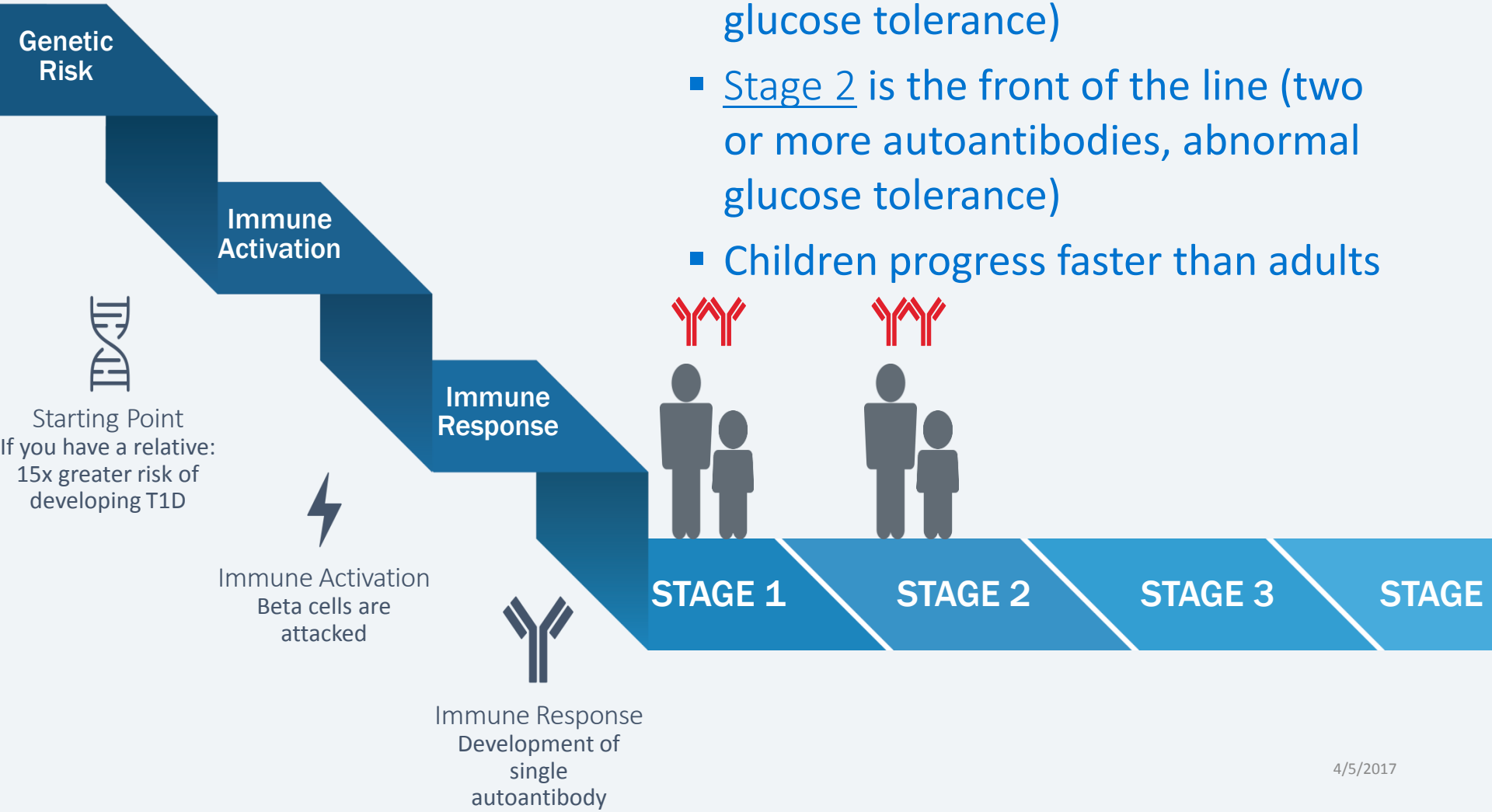


Progression by Population:

- 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 is the back of the line (two or more autoantibodies, normal glucose tolerance)
- Stage 2 is the front of the line (two or more autoantibodies, abnormal glucose tolerance)
- Children progress faster than adults



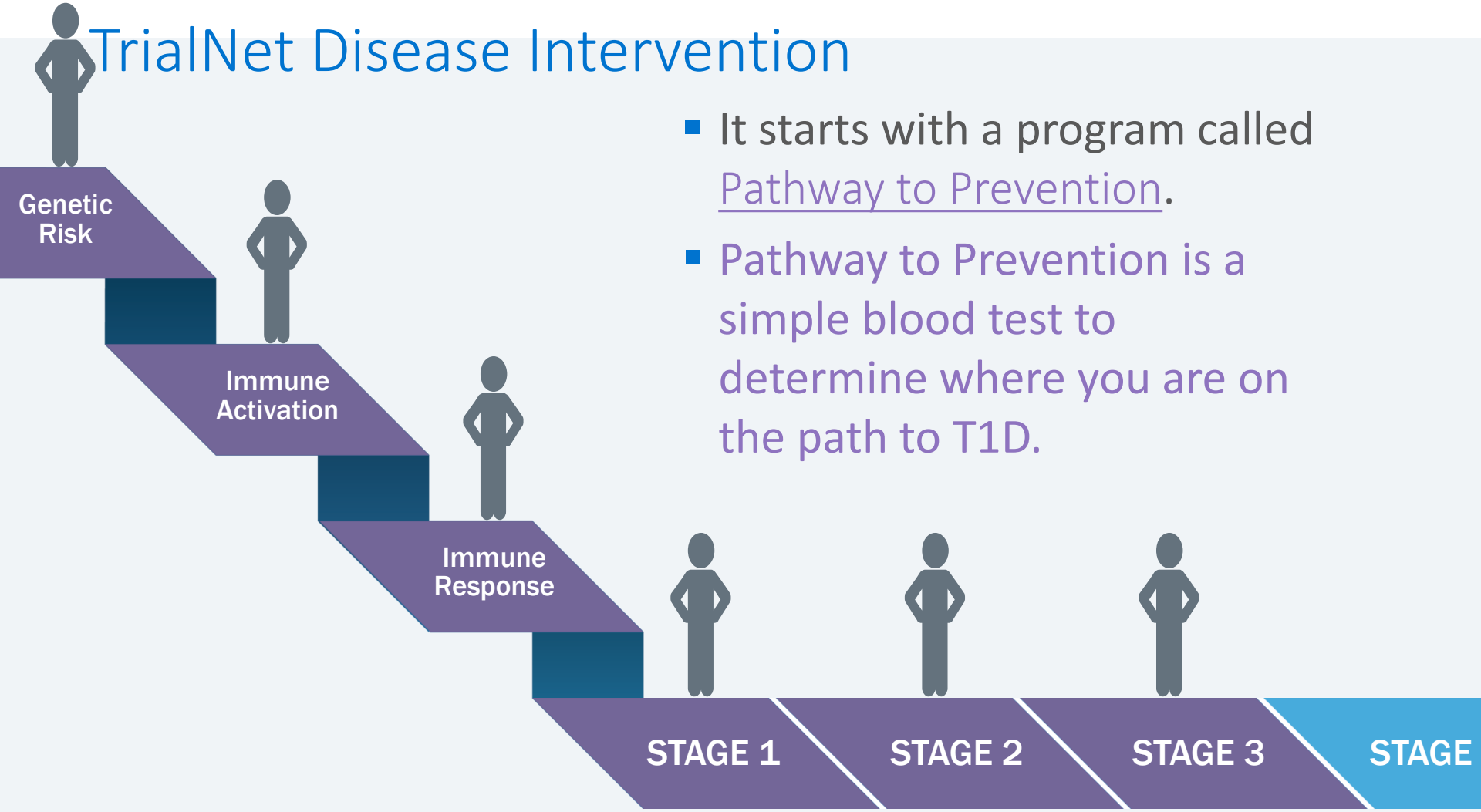
WHY IT'S IMPORTANT

T1D Disease 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

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 Disease Intervention

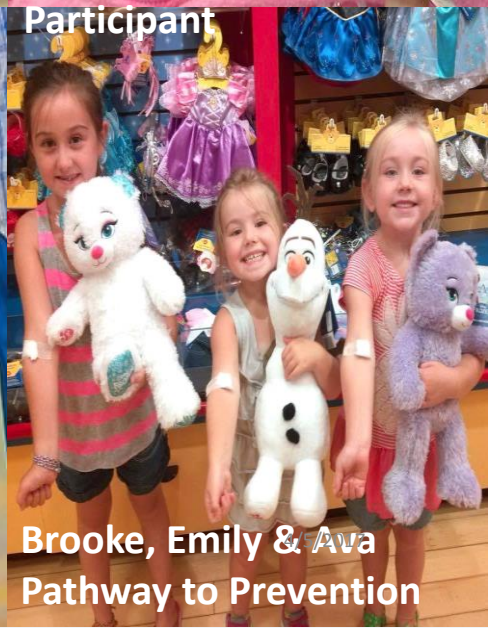
P2P
Pathway to Prevention

Determine where you are on the path

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

Scott & Adam
Pathway to Prevention
Participants

Keilyn
Pathway to Prevention
Participant



Brooke, Emily & Ava
Pathway to Prevention

TrialNet Disease Intervention

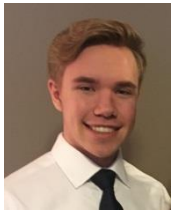
P2P
Pathway to Prevention

Eligibility Requirements

- Anyone between age 1 and 45 with a sibling, child or parent with type 1
- 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

A Tale of Two Families

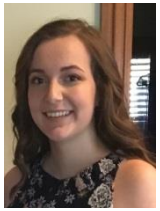


- Tommy
  - At age 3, develops one autoantibody, but is undetected.
  - At age 6, develops two autoantibodies, blood sugars in normal range, but it undetected.
  - At age 16, blood sugars intermittently outside normal range, but isn't caught with random glucose checks.
  - At age 17, at a church camp and catches stomach virus (nausea, vomiting, weight loss, drinking lots of water). Taken to PCP which reveals high glucose, in DKA with T1D, hospitalized.

Stage 1

Stage 2

Stage 3



- Emily
  - At age 7, develops one autoantibody, but is undetected.
  - At age 14, enrolls in TrialNet Pathway to Prevention study which reveals she is positive for 2 autoantibodies, blood sugars in normal range.
  - Have opportunity to participate in prevention study for Abatacept to see if it can delay or prevent progression to next stage.

Stage 1

Stage 2

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Why is screening important?

1. Identifies those at risk long before blood sugar is elevated
   - Chances are as a parent already testing using glucose meter
2. Lowers risk of Diabetic Ketoacidosis (DKA) for those diagnosed with T1D
   - Around 25-30% of children with T1D are diagnosed in DKA
   - 3-4% of children with T1D are diagnosed in DKA in Prevention studies
     - Able to identify those as risk and monitor them for early signs.
     - Likely to identify it before child is ill which can result in better glucose control and possibly fewer long term complications.
3. Better able to intervene if early in diagnosis with potential to enroll in clinical trial to preserve insulin producing cells
4. Help researchers figure out how to stop T1D from developing in the first place.

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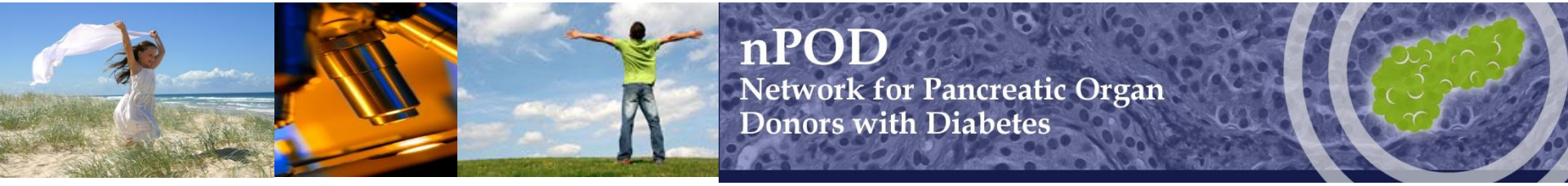
Does someone in your family have T1D?

- **Risk of T1D in relatives of individuals with T1D**
  - Identical Twin: 30-70%
  - Multiple Affected First Degree Relatives: 20-50%
  - Sibling: 8% (but if HLA risk genes identical:30-70%)
  - Offspring
    - Father: 5%
    - Mother: 3%
  - If no Family Hx- General Population: 0.4% (but if HLA risk genes: 4%) (Only 10-15% of newly diagnosed cases of T1D have a relative with T1D)

Take home messages

- Relatives are at 15X increased risk for developing T1D
- Type 1 diabetes starts with 2 or more antibodies
- Age matters. Children progress through stages of disease faster than adults
- We can change the progression of disease

- JDRF + TrialNet working together to stop type 1 diabetes
  - Join TrialNet (www.trialnet.org)
  - Spread the word (Facebook!)



The goals of nPOD are to:

- Maintain a network of procuring and characterizing, in a collaborative manner, pancreata and related tissues (spleen, lymph node, pancreatic lymph node, peripheral blood) from cadaveric organ donors with type 1 diabetes as well as those whom are islet autoantibody positive.
- Utilizing these tissues, investigators will work together to address key immunological, histological, viral, and metabolic questions related to how type 1 diabetes develops

- To find out more information about nPOD, please visit **www.jdrfnpod.org**

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The Hygiene Hypothesis/Disappearing Microbiota

- Lack of early childhood exposure to infectious agents, symbiotic microorganisms (e.g., gut flora), and parasites increases susceptibility to T1D by suppressing natural development of the immune system.
- Through modern medical practices and lifestyle changes, we our losing ancestral microbiota species which may also have effects on our immune system and T1D development.

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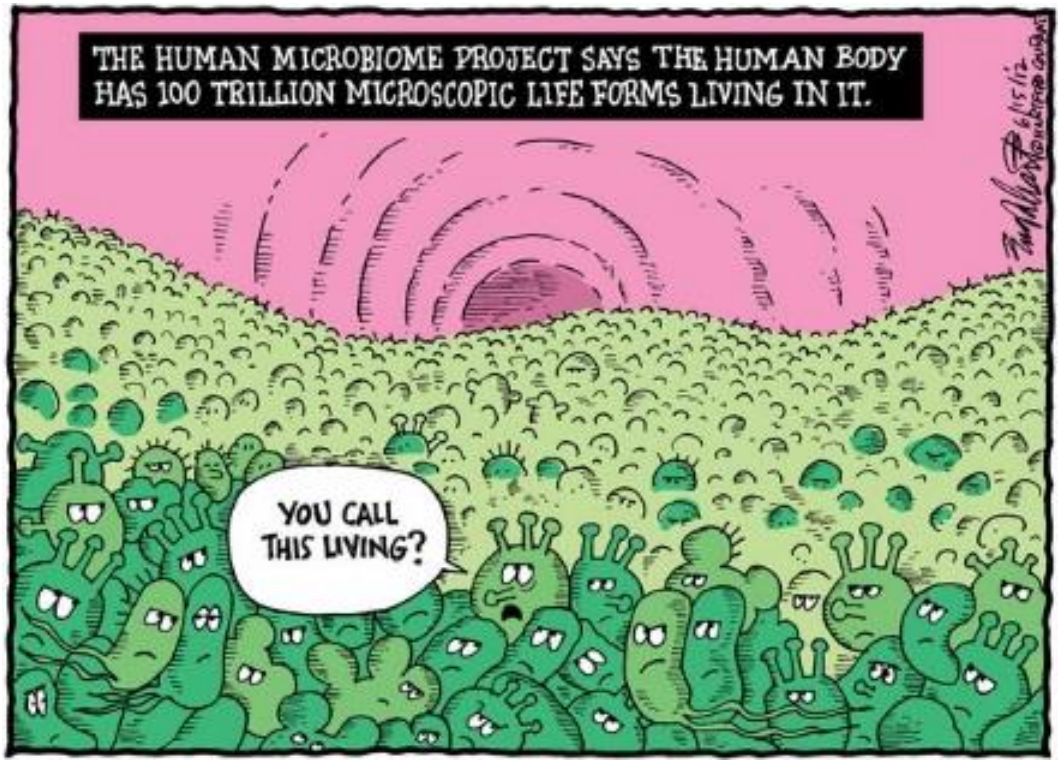
Agenda

- What is the gut microbiome?
- Why is it important?
- What does it mean for T1D?

What is the gut microbiome?



- We have 10x more bacterial cells in our bodies than human cells
- We are walking ecosystems!
- These microbes are integrated into our biology: they help us digest food, shape our immune system, alter our metabolism and evidence is even starting to show that they affect the nervous system, influencing our mood and behavior.

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Gut Microbiome in T1D Key Messages

- Our guts are made up of trillions of microbes that play important roles in our biology
- Through modern day practices, we may have altered our gut microbiomes in such a way to alter biological processes.
- The rate of T1D has been increasing worldwide and may be linked to changes in the microbiome
- If we could reset the microbiome at an early age, we may be able to prevent or delay the onset of T1D in some individuals.

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THANK YOU

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