defining the early stages of type 1 diabetes

October 10, 2014
Bethesda, MD

Purpose of the Workshop

- Discuss the current understanding of the natural history of type 1 diabetes (T1D) prior to the onset of symptomatic disease
- Inform clinical trial design for interventions in early stages of T1D
- Encourage product development for early stages of T1D
- Aid regulatory decision-making


defining the
early stages of
type 1 diabetes
T1D


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IMPROVING
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DIABETES.


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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AACE

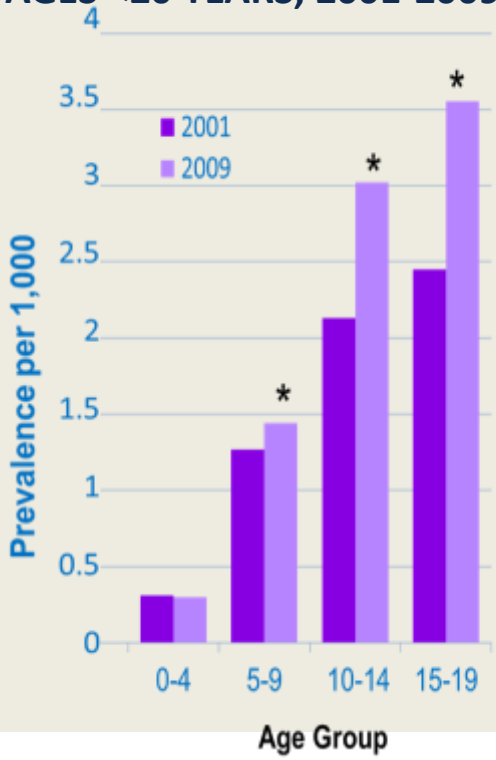

ISPAD
International Society for Pediatric
and Adolescent Diabetes


ENDOCRINE
SOCIETY

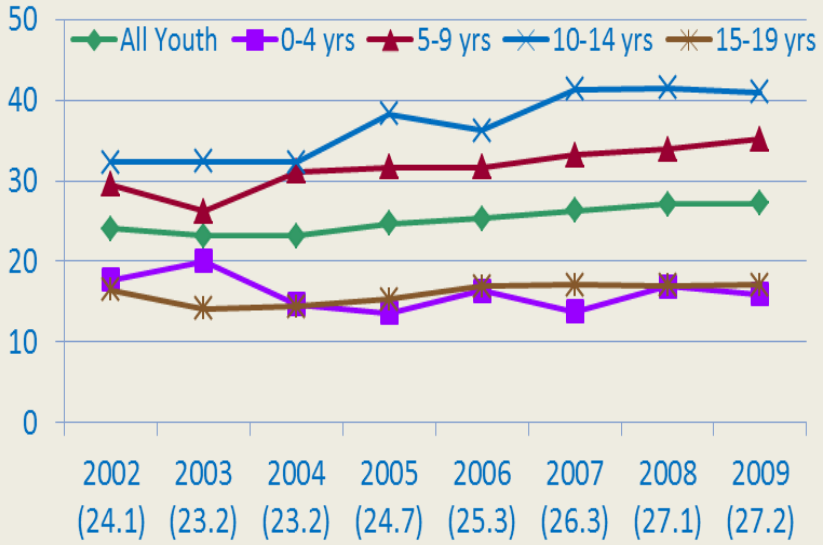
T1D UNMET NEED

T1D is Growing Significantly in the United States

T1D PREVALENCE ROSE 21%
AGES <20 YEARS, 2001-2009

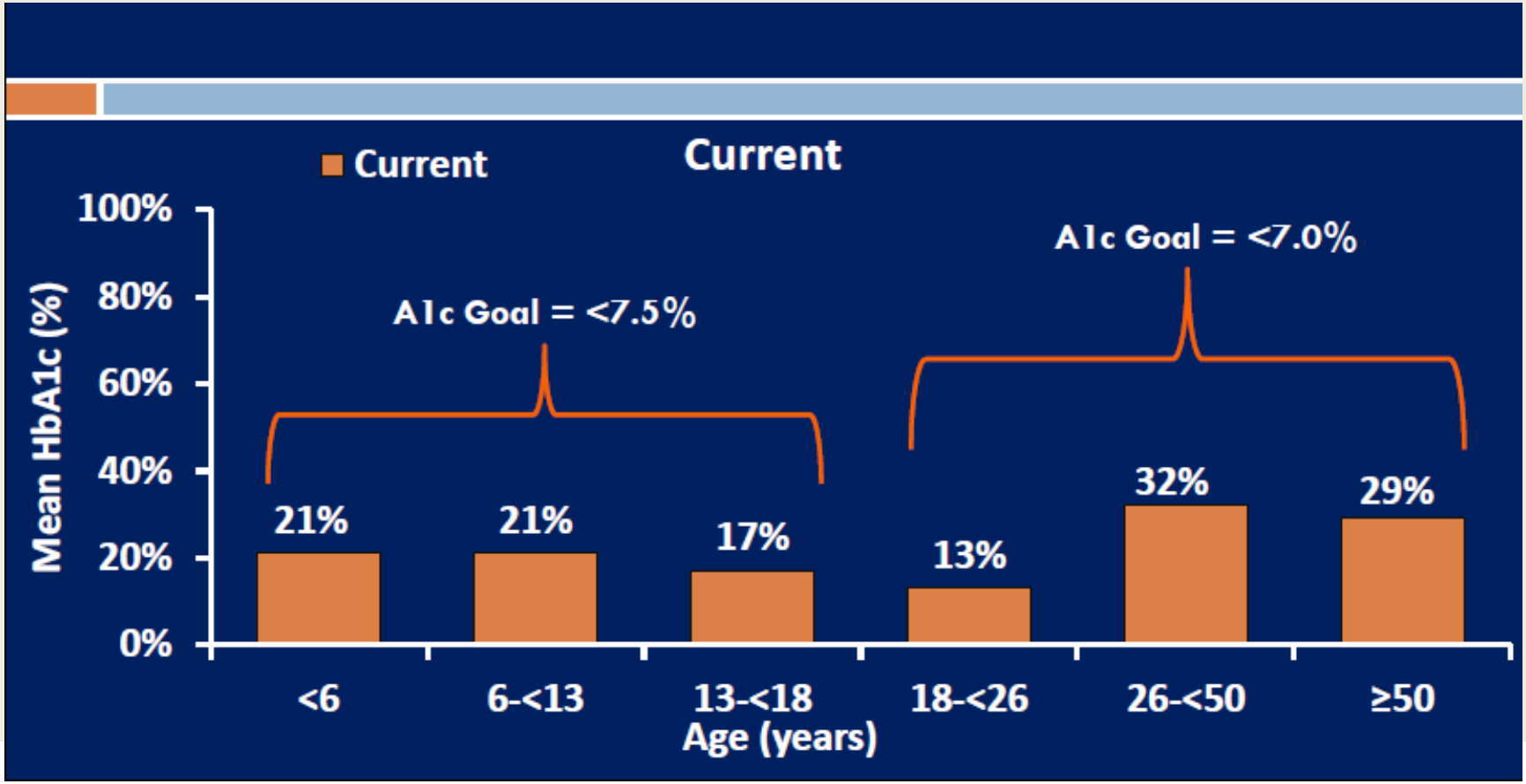


T1D INCIDENCE INCREASED 2.6% PER YEAR



Sources: 1. Dabelea D, et al. Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009. JAMA. 2014;311(17):1778-1786.; 2. Sources: CDC/NIH Study – Mayer-Davis EJ et al. and Lawrence JM et al. ADA 72nd Scientific Sessions, Phil, PA June 8-12, 2012

With Current Tools, Most Not Meeting A1C Targets

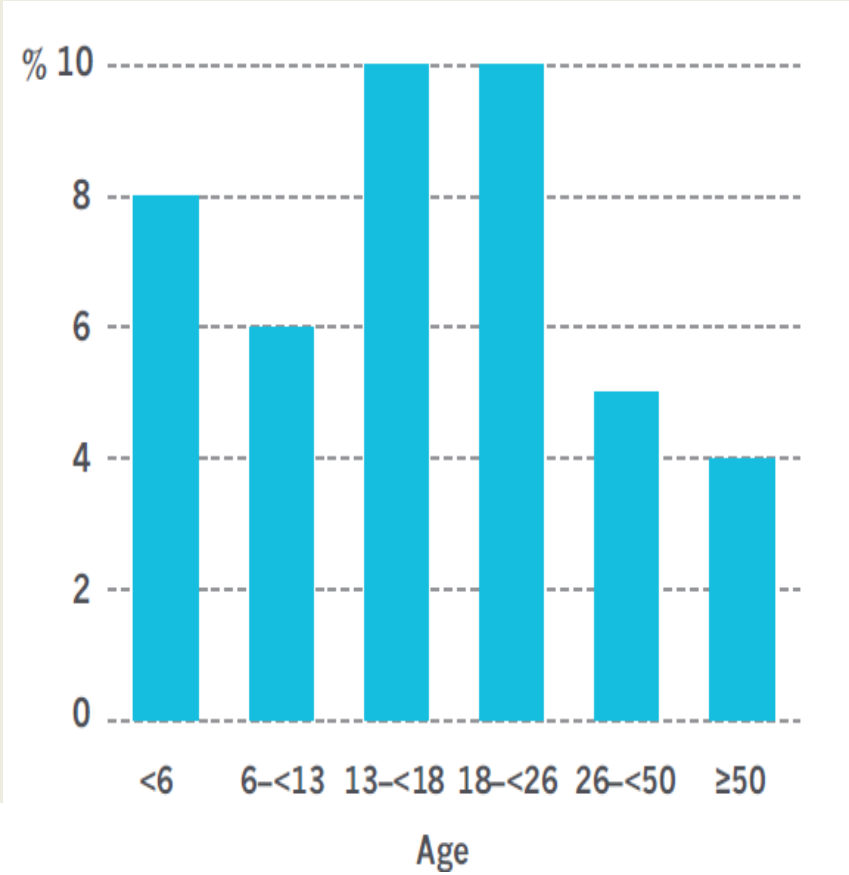


Source: T1D Exchange

T1D UNMET NEED

Rates of DKA and Severe Hypo Are Too High

12 MONTH FREQUENCY OF DKA



12 MONTH FREQUENCY OF SEVERE HYPO

Source: T1D Exchange

Objectives of the Workshop

- Garner common understanding of current data on T1D risk detection, staging, and progression
- Discuss the design and optimization of intervention trials in the early stages of T1D
- Identify tools to improve staging and predict progression of T1D
- Discuss approaches to validate existing tools and develop new tools

Scientific Framework of the Workshop

- T1D is a disease continuum that begins prior to its phenotypic, symptomatic disease
- Risk of developing T1D can be identified and quantified
- T1D has well-defined, reproducible early stages that reach a point of inevitability of symptomatic T1D
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy
- The ability to screen for risk and stage T1D prior to symptomatic T1D has benefit today, and in the future, will provide a unique opportunity to intervene to delay, and ultimately prevent, the onset of clinical symptoms and life-long insulin dependence

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Overview of Workshop Agenda

- State of Type 1 Diabetes Today
- Screening, Natural History and Risk Detection of the Early Stages of Type 1 Diabetes
- Biomarkers in the Early Stages of T1D
- Recommendation for Classification of Early Stages of Type 1 Diabetes
- Opportunities for Future T1D Prevention Research
- Conclusions and Next Steps

Desired Outcomes of the Workshop

- Provide a new standardized taxonomy and staging approach for human T1D
- Accelerate clinical development of therapies to prevent symptomatic T1D
- Aid design of clinical trials through use of risk profiles, subject stratification, and stage-specific trial endpoints
- Promote precision medicine: Tailoring of optimal therapies to specific individuals at specific stages of T1D
- Provide an approach for the benefit/risk framework in the early stages of T1D

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Epidemiology of Type 1 Diabetes

Dana Dabelea, MD, PhD

Professor of Epidemiology and Pediatrics

University of Colorado Denver

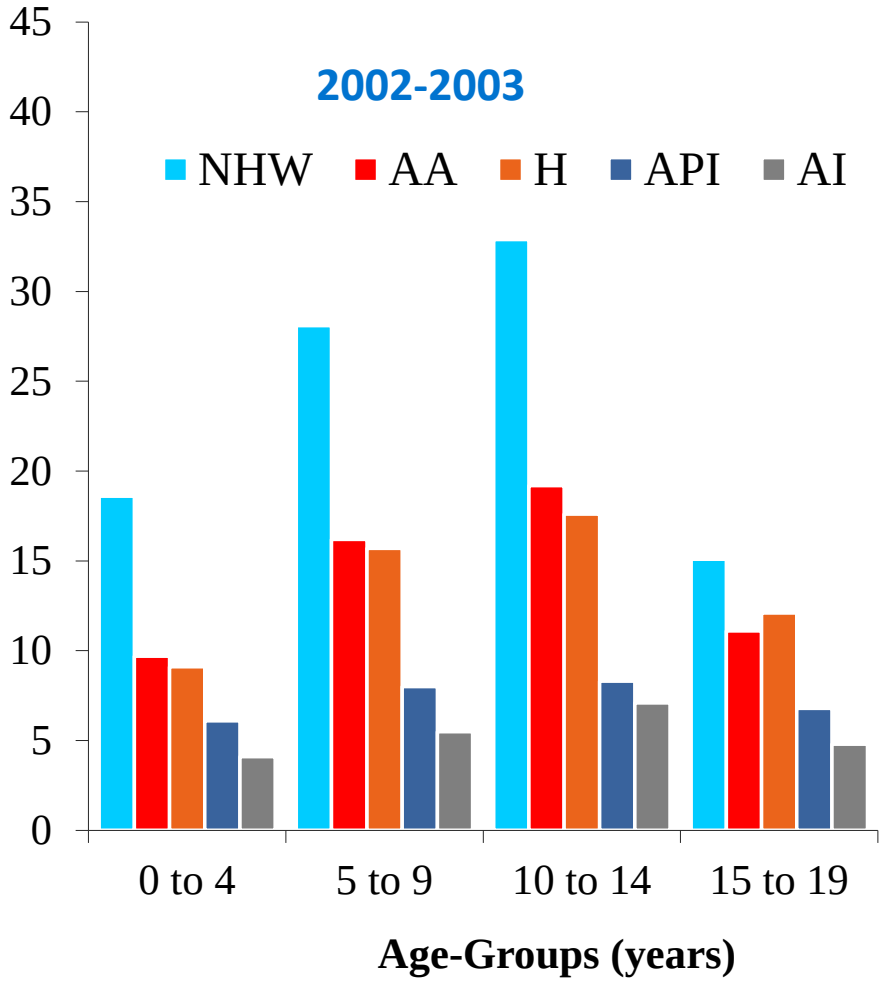
Background

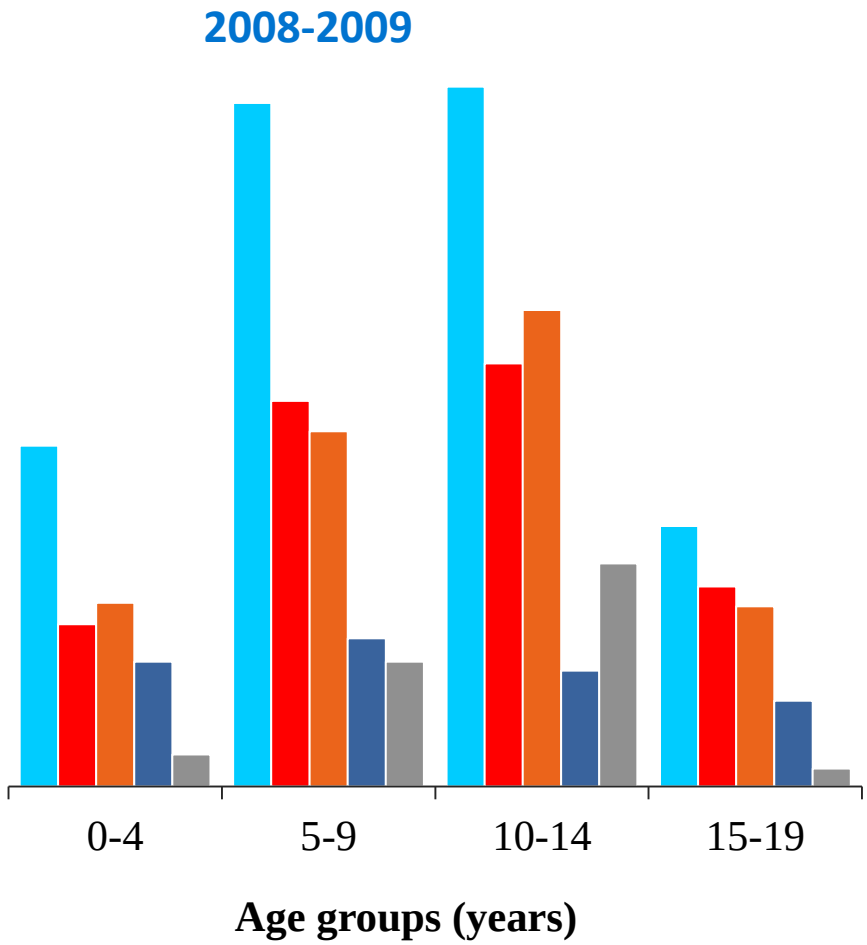
- Start of 20th century – T1D was rare and rapidly fatal
- Youth were thin, usually white race/ethnicity
- Incidence in 1900 ~ 2/100,000 rising to 7/100,000 by 1920 (Norway)
- International rise in incidence began in mid-20th century
- Incidence from 1960-1996 increased in 24/37 studies averaging 2-4% per year; recent levelling off in Scandinavia countries
- Limited US data- SEARCH registry

Gale EA:. *Diabetes* 51(12):3353-3361, 2002

Burden of Type 1 Diabetes Worldwide and in the US

Incidence of T1D, by Age and Race/Ethnicity

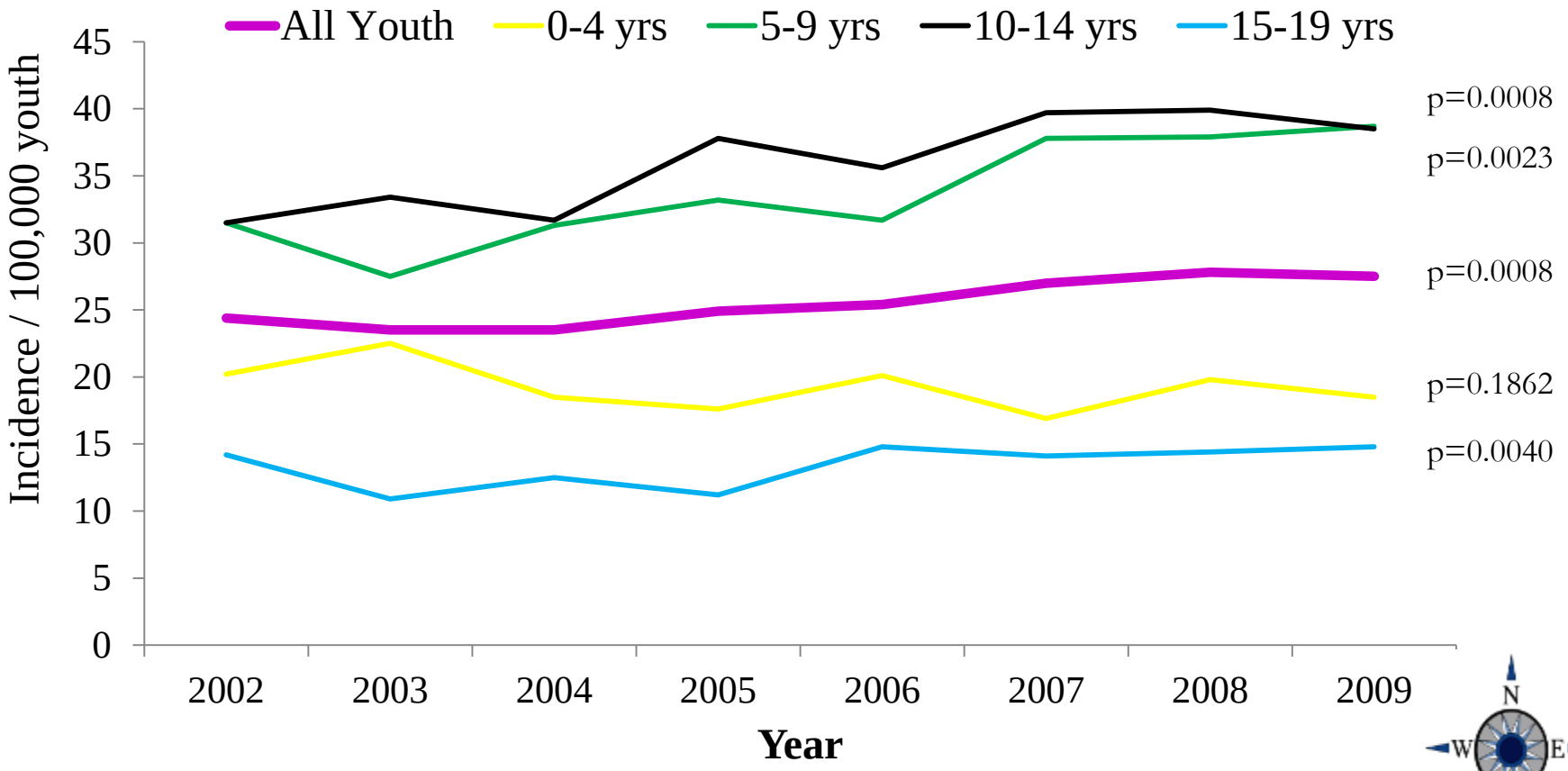




SEARCH Study Group, *JAMA* 297(24), 2716, 2007

Trends in Incidence of T1D Among NHW Youth, 2002-2009

Average annual percent increase:
Males: 2.84% (1.12-4.58%)
Females: 2.57% (0.68-4.51%)



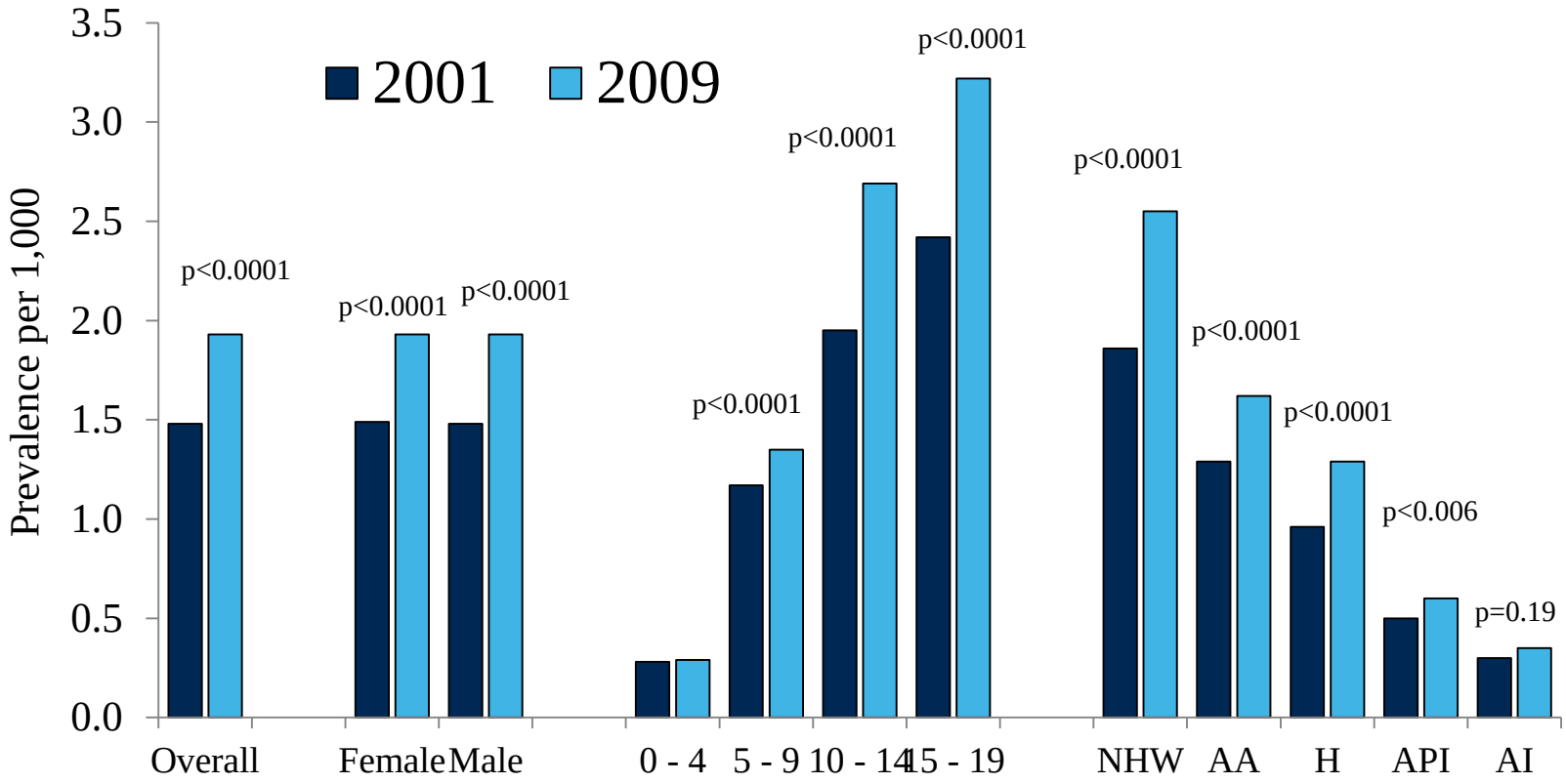
Lawrence, et al. *Diabetes* 2014, in press

SEARCH For Diabetes in Youth

defining the early stages of type 1 diabetes T1D

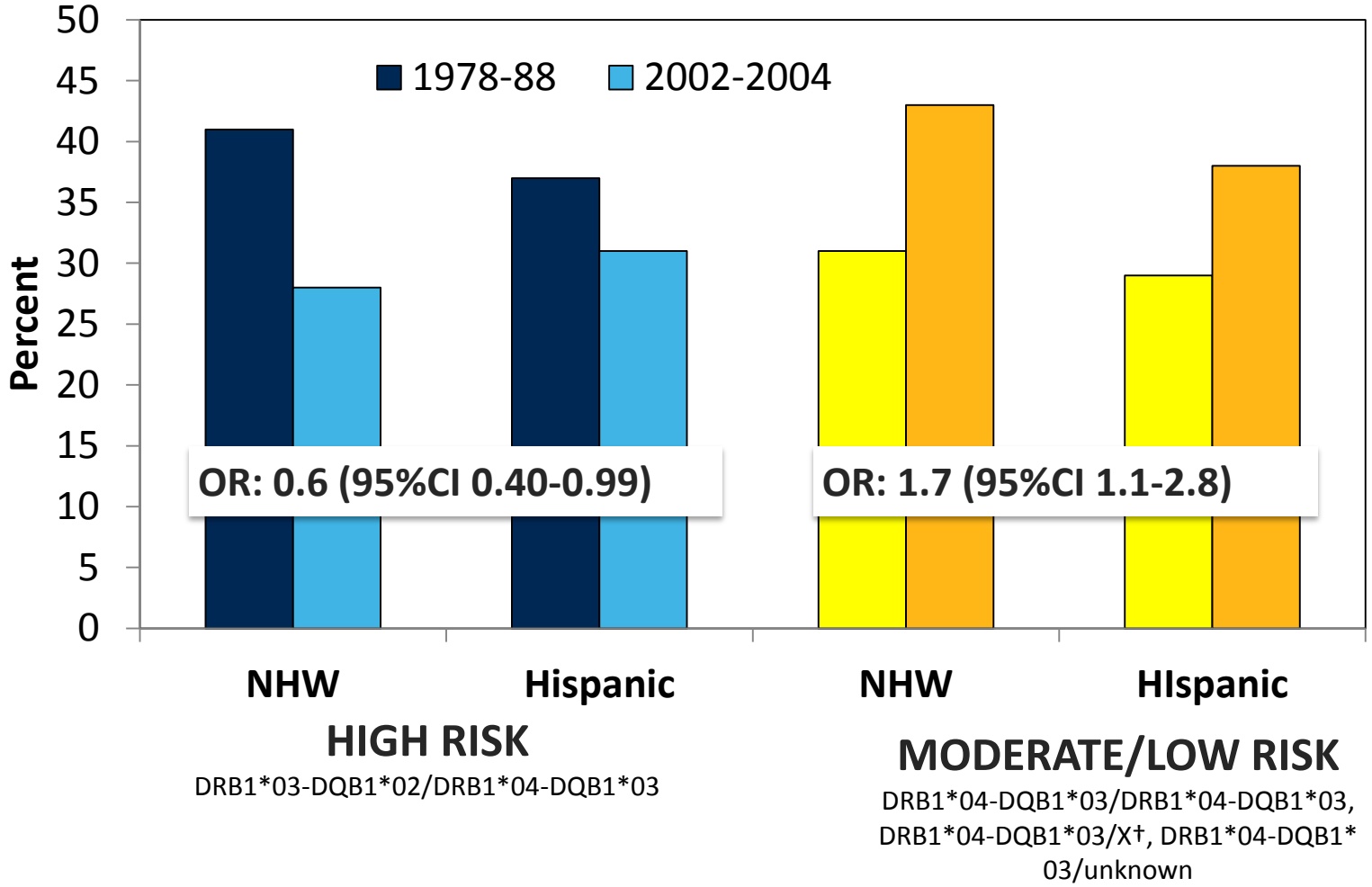
Trends in T1D Prevalence, 2001-2009, by Sex, Age, and Race/Ethnicity

21.2% relative increase



Dabelea & Mayer-Davis, et al., *JAMA,* 311 (17), 1778, 2014

Trends in High and Moderate/Low Risk HLA Alleles Colorado 1978 - 2004



Vehik et al,, *Diab Care:* 31 (7), 2008

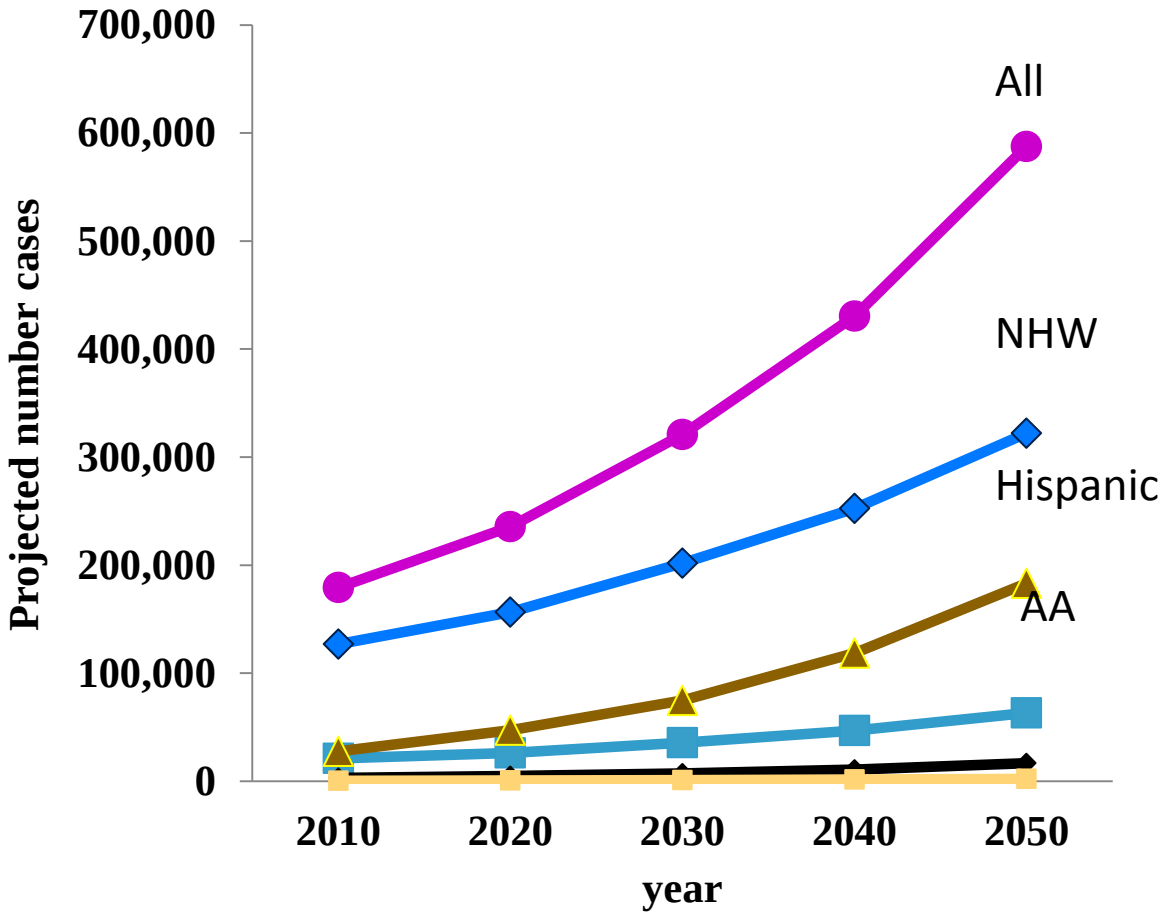
Estimated Number of T1D cases in the US, by Race/Ethnicity, 2009

Race/Ethnicity	N of US Population < 20 yrs. In 2009	Type 1 Diabetes N
Total	83,280,391	166,984
Non-Hispanic White	46,859,149	119,387
Hispanic	18,609,959	23,915
Non-Hispanic Black	12,791,402	20,887
Asian/Pacific Islander	4,158,522	2,493
American Indian	861,359	303

Pettitt et al., *Diabetes Care:* 37(1), 402, 2014

Projections of future burden

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



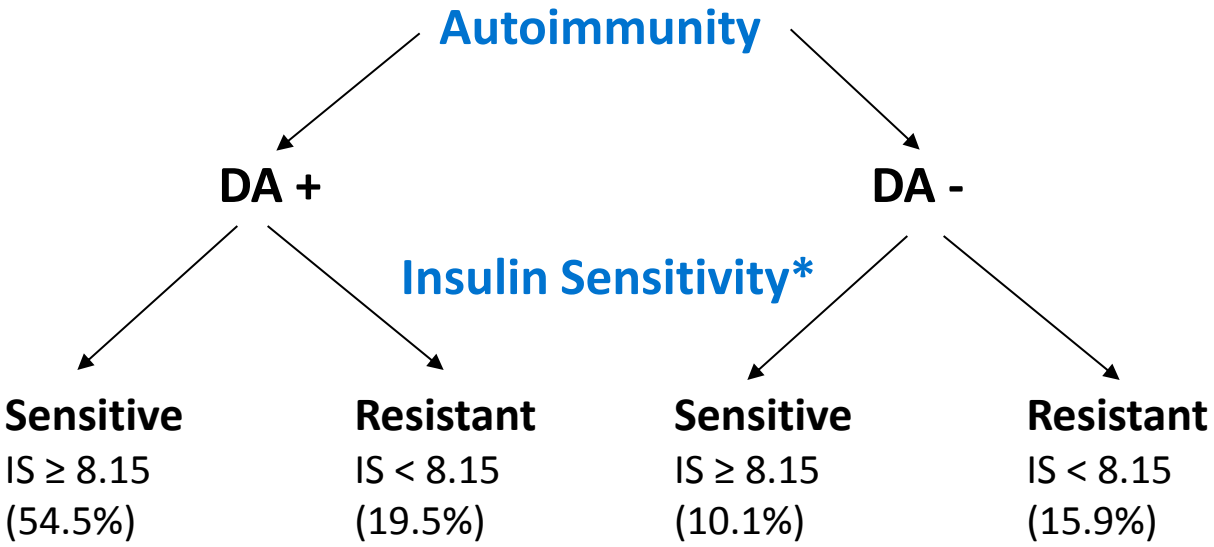
- Number of US youth with T1D projected to increase 3.3-fold by 2050
- Highest among NHW youth (7.04/1000 in 2050)
- Largest relative increase among Hispanic youth (6.6-fold increase)
- US health care systems need to be prepared

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

Presentation and Definition of Diabetes Type

With increasing obesity, youth with T1D are increasingly overweight or obese, causing confusion about the correct diagnosis

Classification of Diabetes Type based on Autoimmunity and Insulin Sensitivity



DA+ Positive for IA2 or GAD65 autoantibody

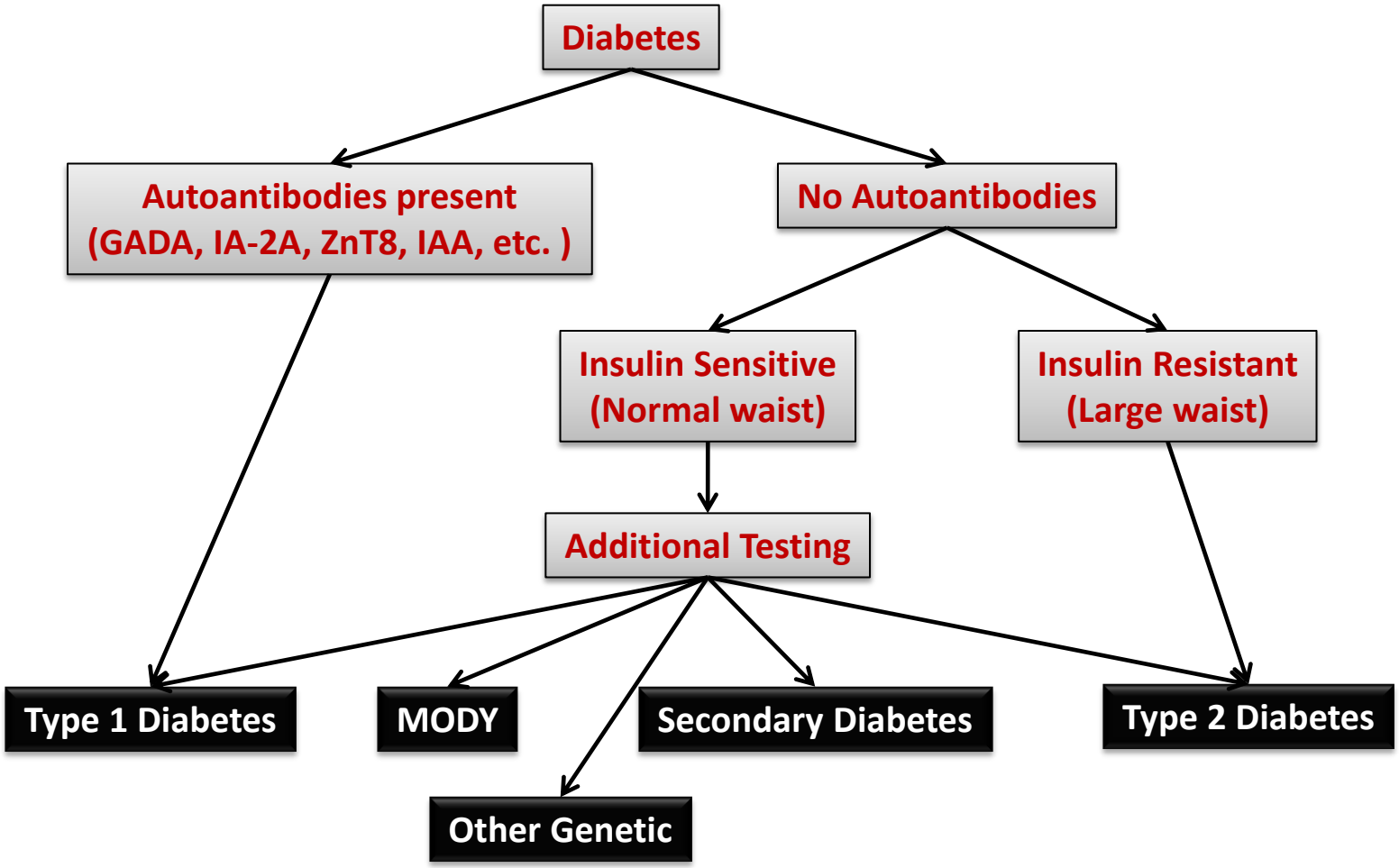
* Insulin Sensitivity = exp [4.64725 - 0.02032*(waist, cm) - 0.09779*(HbA1c, %) - 0.00235*(TG,mg/dl)];

Resistant = IS index below the 25th percentile for NHANES youth

Sensitive = IS index $\geq$ the 25th percentile for NHANES youth

Dabelea et al, *Diabetologia* 54: 78, 2011

Algorithm for Classification of Pediatric Diabetes



Baseline FCP and Estimated Decline in FCP According to Etiologic Diabetes Type

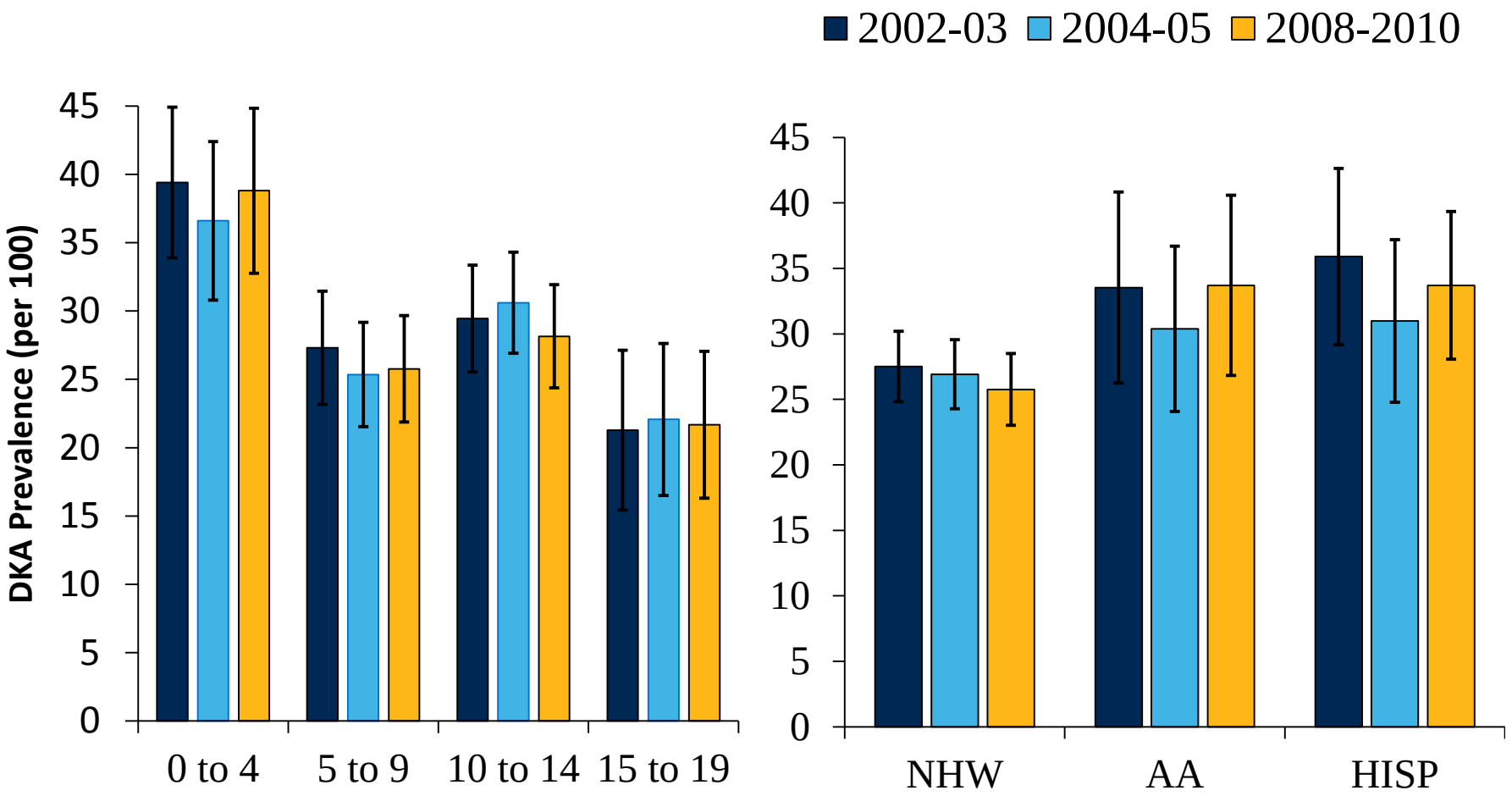
	Number	Baseline FCP (ng/ml) [median (IQR)]	FCP Decline (% per month)
Autoimmune + insulin sensitive	688	0.5 (0.7)	4.0 (3.8-4.3)%
Autoimmune + insulin resistant	212	0.8 (1.3)	4.2 (3.8-4.7)%
Non-Autoimmune + insulin sensitive	122	0.7 (1.0)	2.4 (1.8-2.9)%
Non-Autoimmune + insulin resistant	189	3.4 (2.9)	0.7 (0.3-1.2)%

Dabelea et al., *Diabetologia*, 2012

Risk Factors for Poor Prognosis

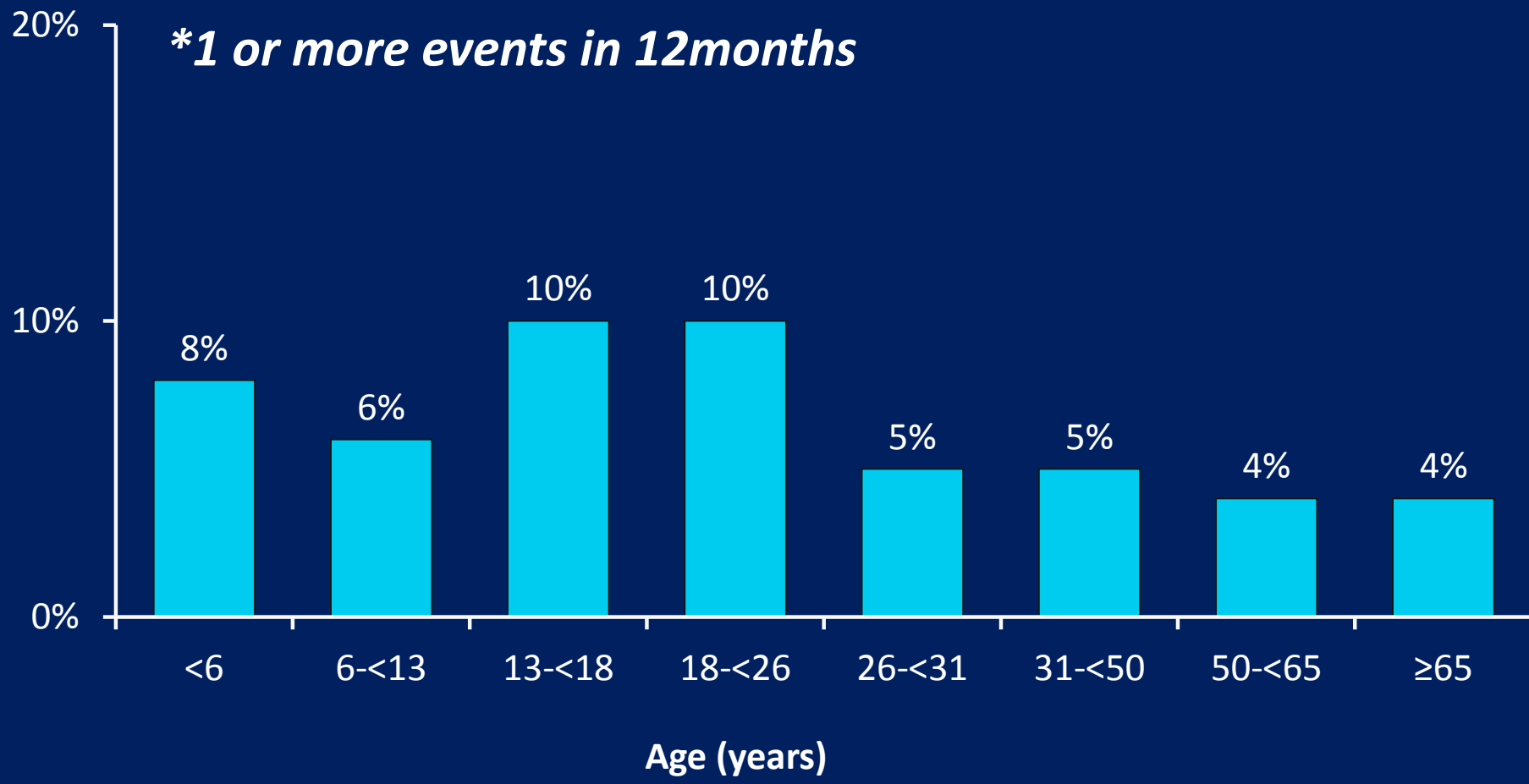
Prevalence of DKA at Onset with T1D Over Time, by Age and Race- No Trends Over Time

- **31% Prevalence overall**
- **39% Prevalence in children 0-4 yrs**

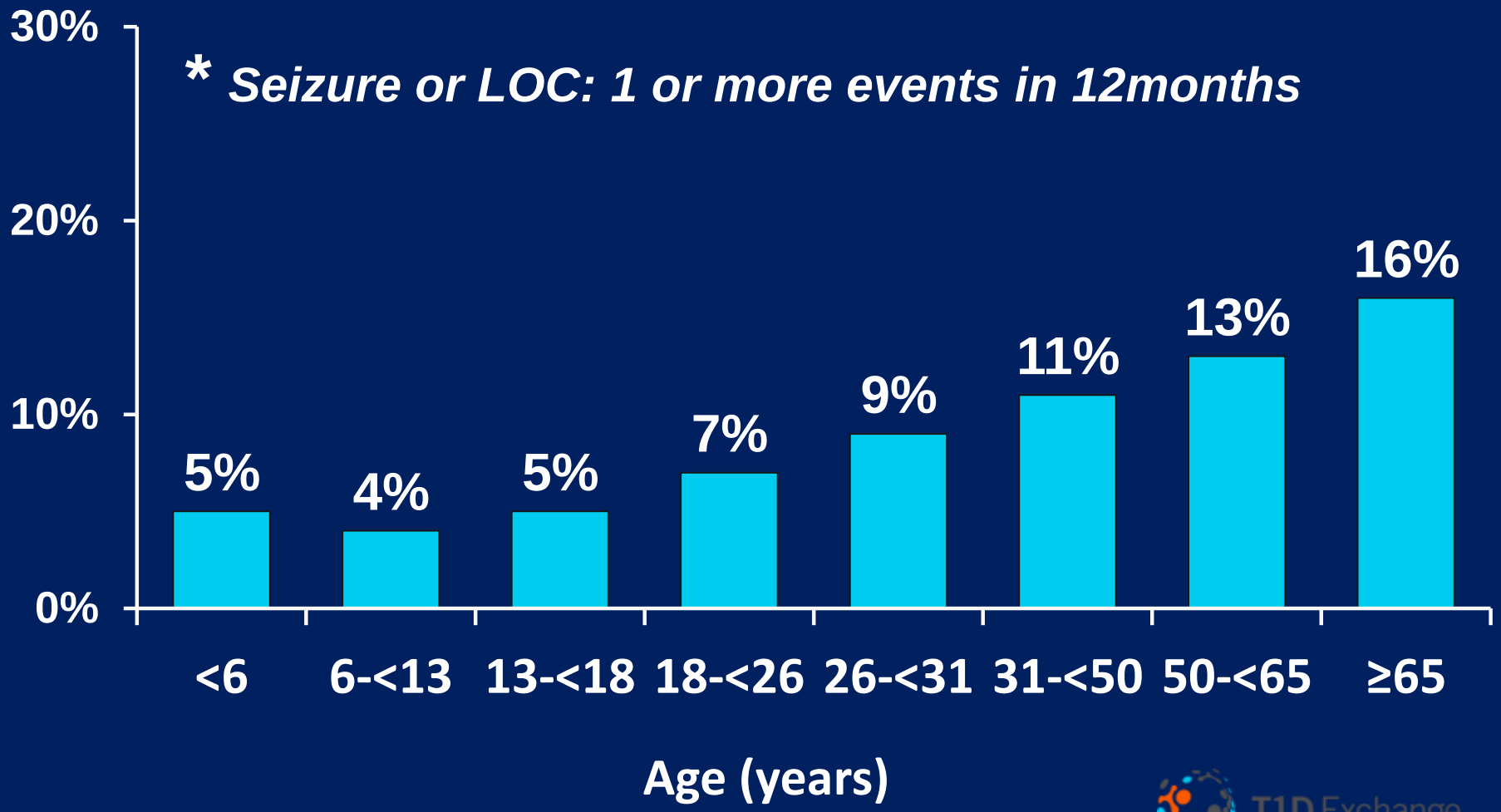


Dabelea D, *Pediatrics;* 133: 938, 2014

12-month Frequency of Diabetic Ketoacidosis* According to Age

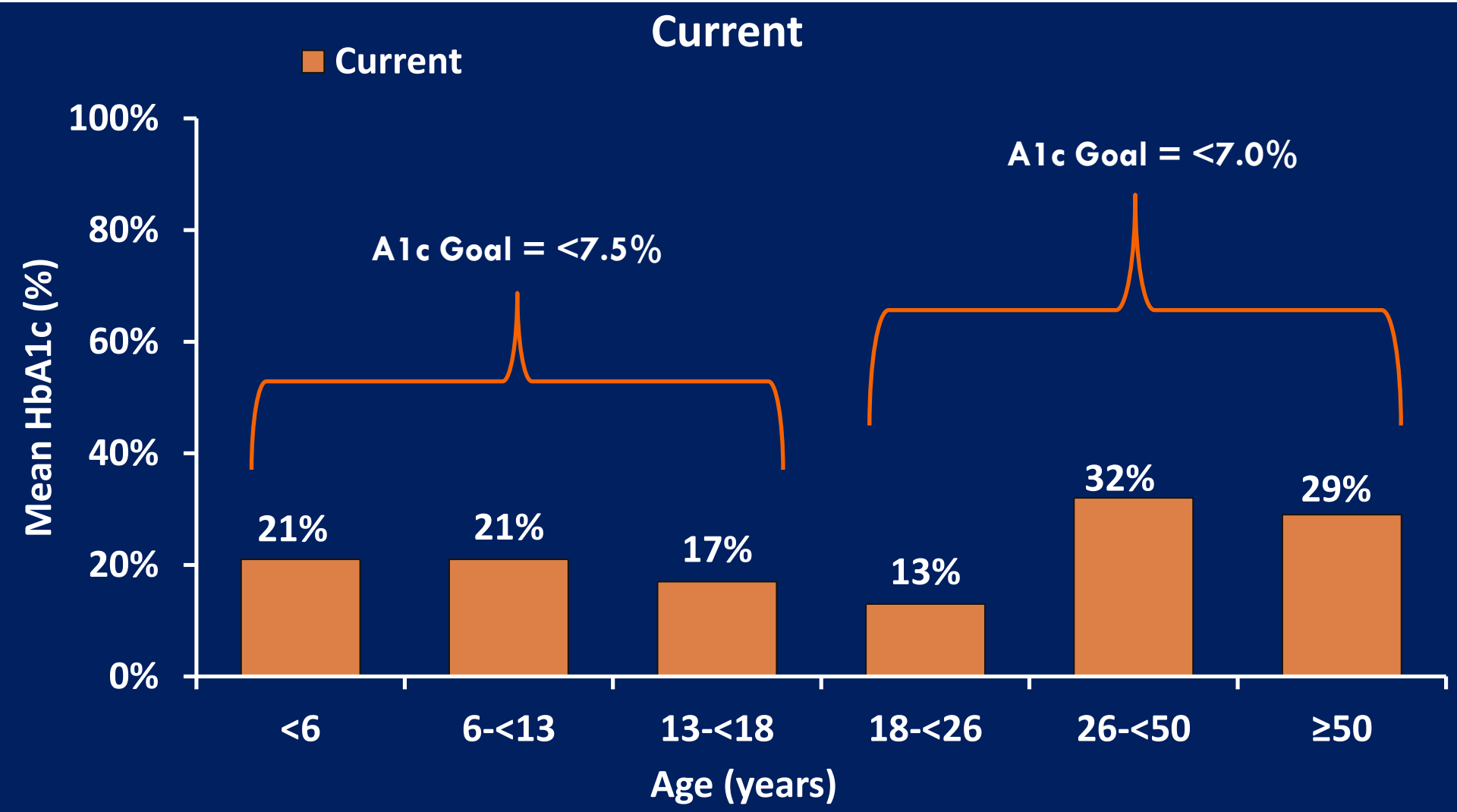


12-month Frequency of Severe Hypoglycemia* According to Age

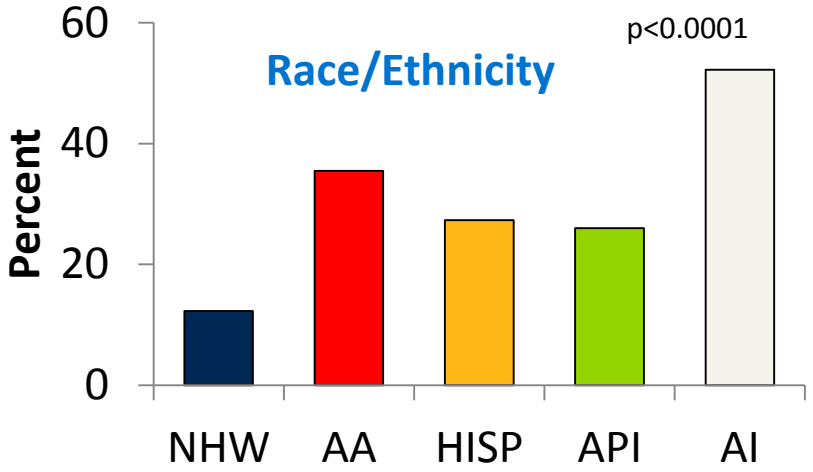


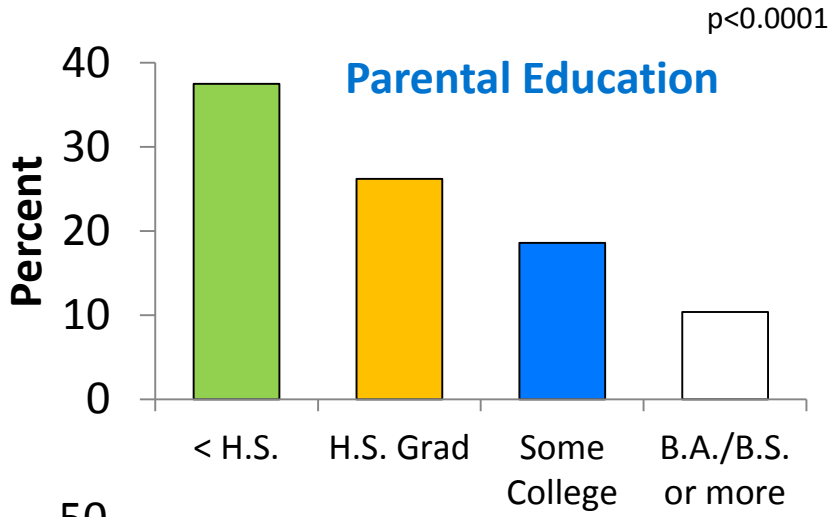
T1D Exchange

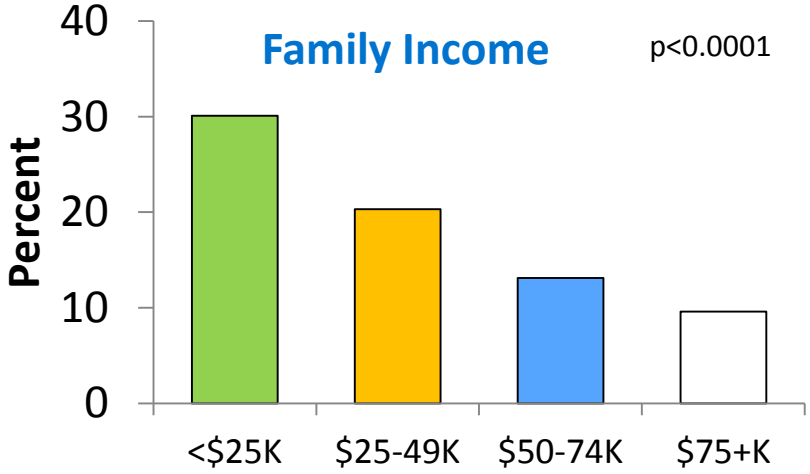
ADA HbA1c Target Met

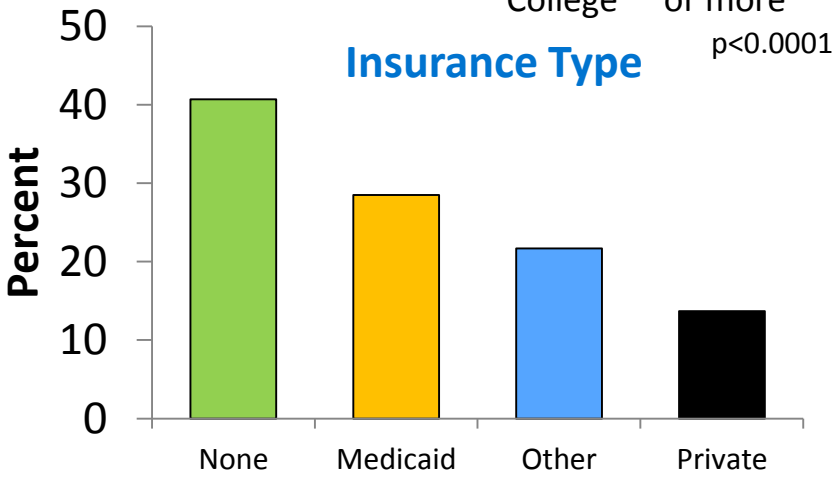


Disparities in Prevalence of Poor Glycemic Control (A1c ≥ 9.0%)



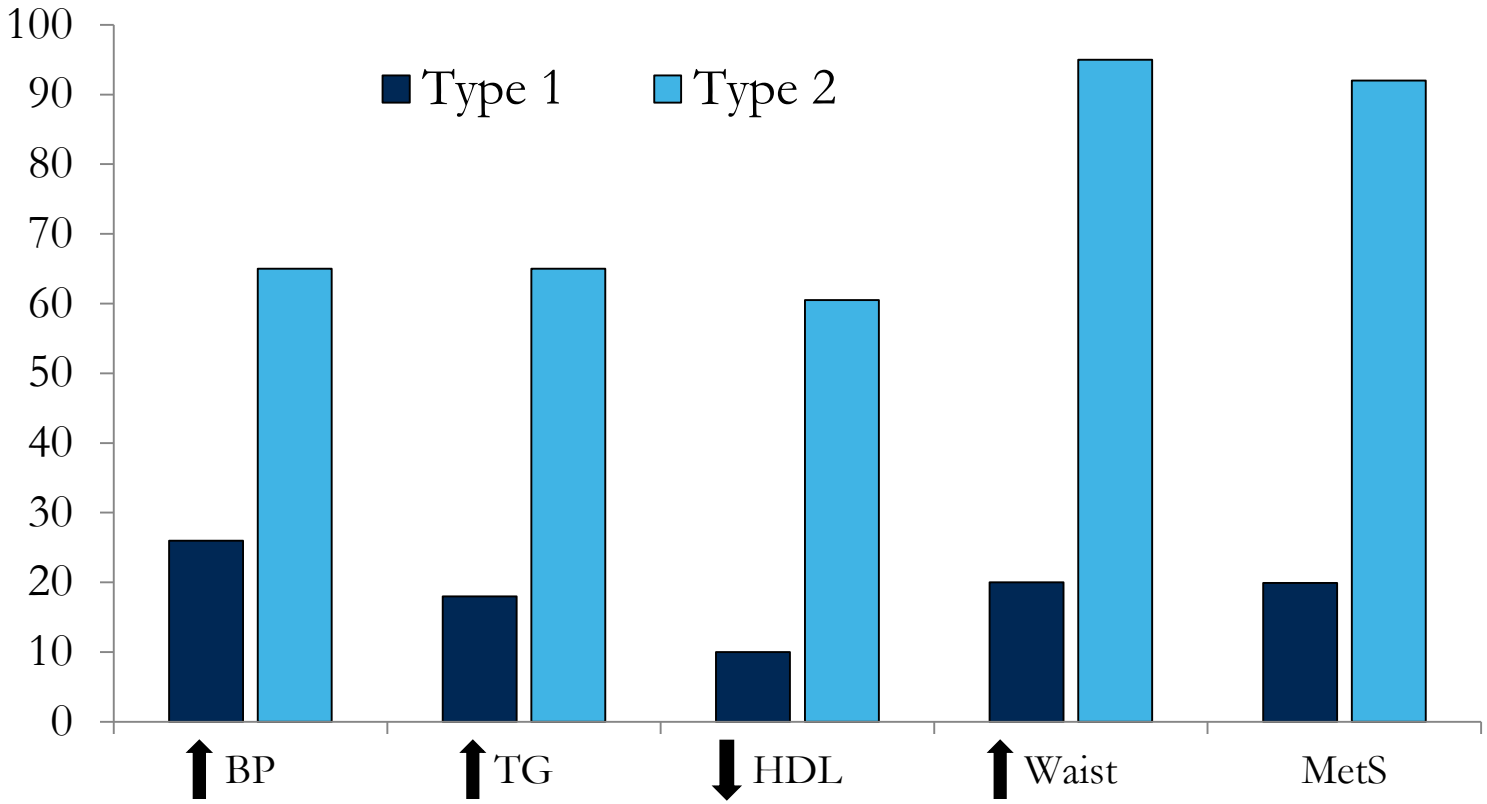






Petitti et al., *J Pediatr* 155(5):668, 2009

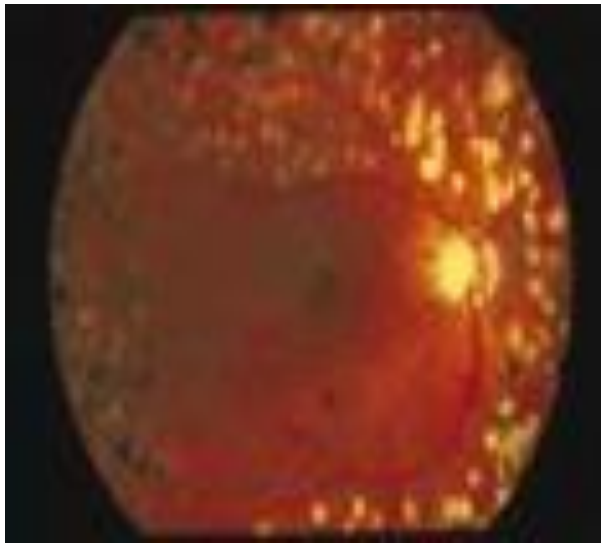
Prevalence of Cardiovascular Risk Factors in Youth with Diabetes



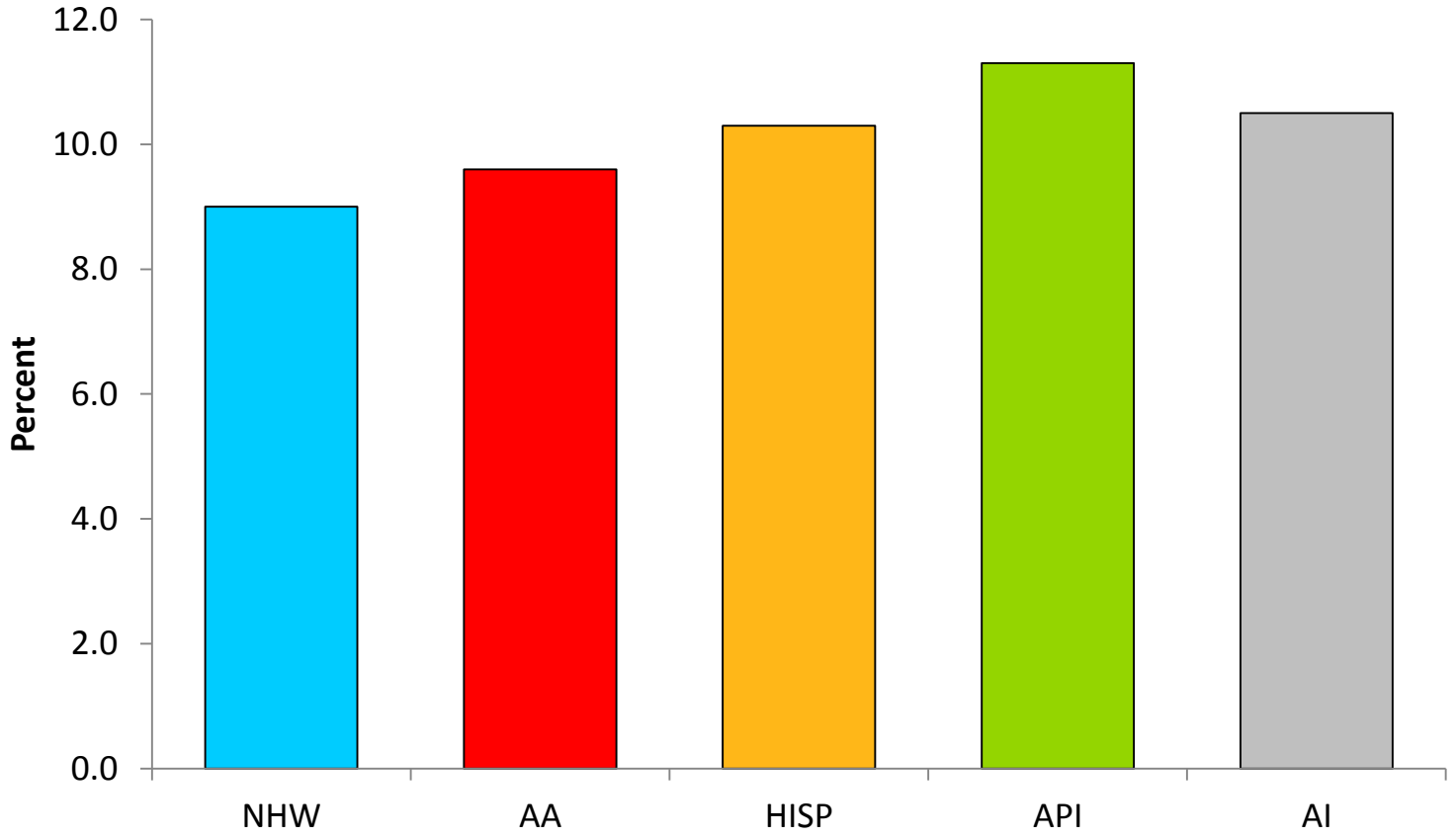
Rodriguez, et al, *Diabetes Care*, 2006

MetS: ≥ 2 CVD risk factors

Complications patterns



Elevated Albumin/Creatinine Ratio* by Race/Ethnicity Among Youth with T1D

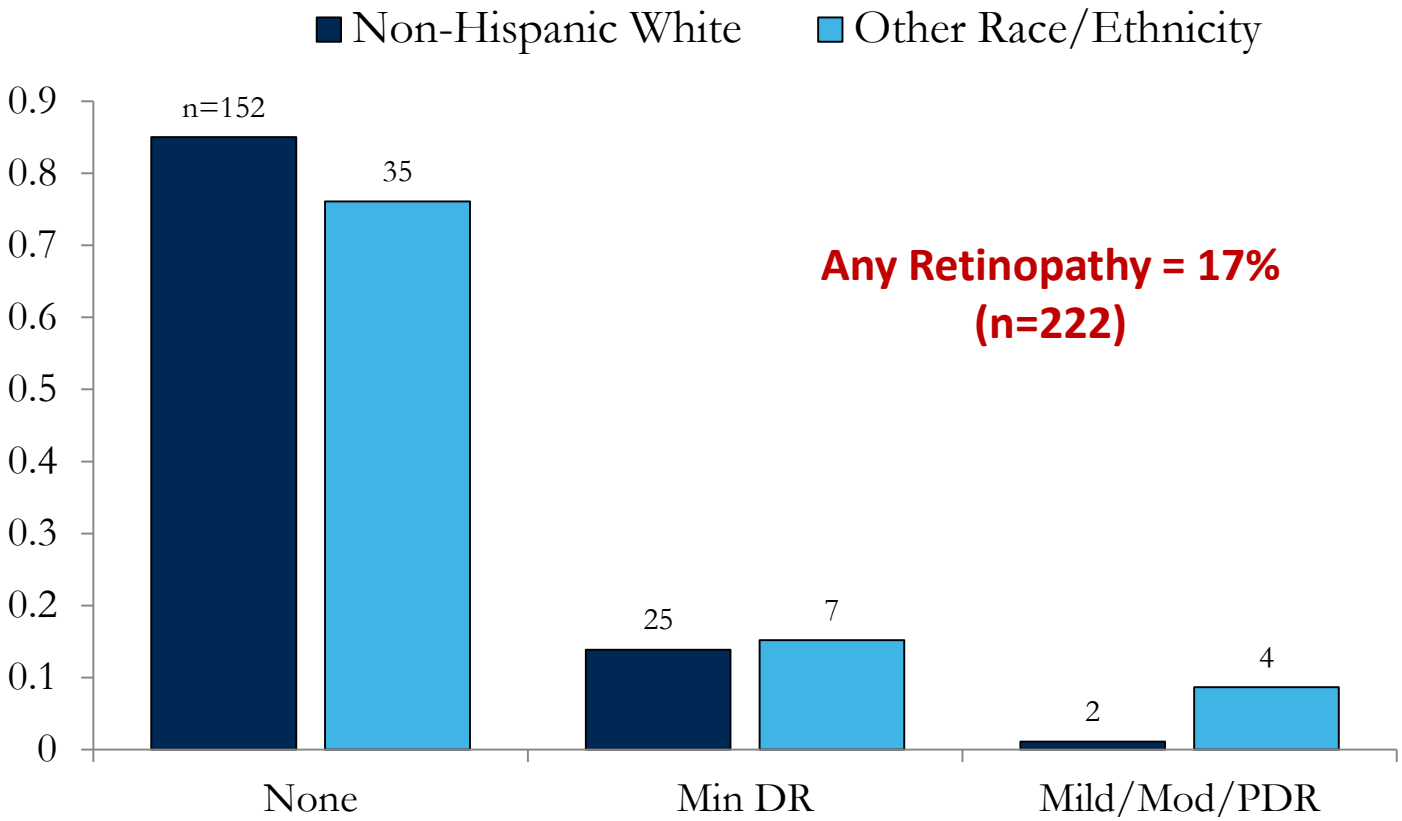


*ACR ≥ (30 g albumin/mg creatinine)

All p>0.4 vs. NHW

Maahs et al., *Diab Care* 30(10):2593-2598, 2007

Prevalence of Diabetic Retinopathy Among Youth with T1D: Pilot Study



Any Retinopathy = 17%
(n=222)

Average duration 6.8 years

Mayer-Davis et al., *Diabetic Med* 29(9):1148-1152, 2012

Complications by Diabetes Duration in adults with T1D –Type 1 Diabetes Exchange

	<20 yrs (n=1554)	20-<40 yrs (n=2269)	≥40 yrs (n=817)
Treatment for Retinopathy[a]	2.9%	19%	36%
Nephropathy[b]	5.8%	16%	25%
Neuropathy	6.2%	16%	29%
Myocardial Infarction (MI)	1.0%	1.5%	7.5%
Stroke	0.3%	0.9%	2.8%
Coronary Artery Disease, no MI	2.2%	6.7%	23%

[a]Known laser, injection therapy, or vitrectomy in either eye

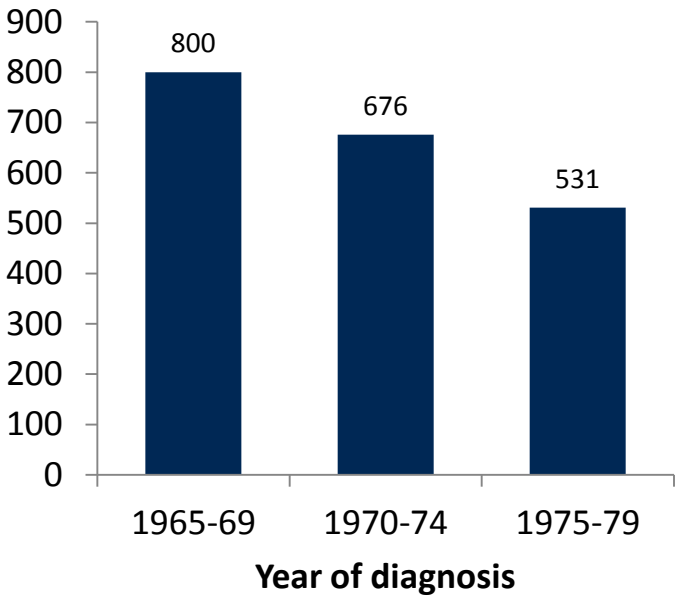
[b]Micro or macroalbuminuria, renal failure (dialysis or post-kidney transplant)

Weinstock, RS, ADA 2012

Trends in childhood-onset T1D: Mortality and life expectancy

Alleghany County, PA

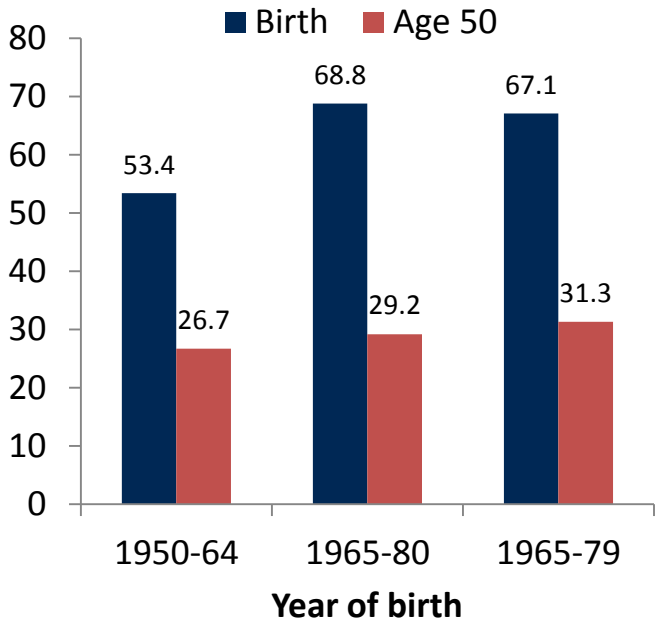
All cause mortality / 100,000/ yr



Secrest et al., Diabetes, 59, 3216, 2010

Pittsburgh, PA EDC

Life expectancy (yrs) by birth cohort



Miller et al., Diabetes, 61, 2987, 2012

defining the early stages of type 1 diabetes T1D

Conclusions

- Increasing numbers of youth with T1D, especially among minorities
- T1D now more difficult to diagnose due to increasing obesity, especially among minorities – diabetes autoantibodies are needed
- High burden of risk factors for future complications, worse in minority youth with T1D
- Subclinical complications present at young age, increasing with age and diabetes duration
- Limited data on complications & mortality in contemporary, diverse cohorts – major research need
- Shifts suggest that higher costs and greater societal burden are very likely in the next 20-30 years

defining the early stages of type 1 diabetes

T1D

Overview of Natural History of Type 1 Diabetes: Lessons for Staging

Mark Atkinson, PhD

The Departments of Pathology and Pediatrics

The University of Florida

Classic Model of Type 1 Diabetes Pathogenesis

(?Precipitating Event)

Genetic Predisposition

Overt Immunologic abnormalities

Progressive loss insulin release

Normal insulin release

Glucose normal

Overt diabetes

C-peptide present

No C-peptide

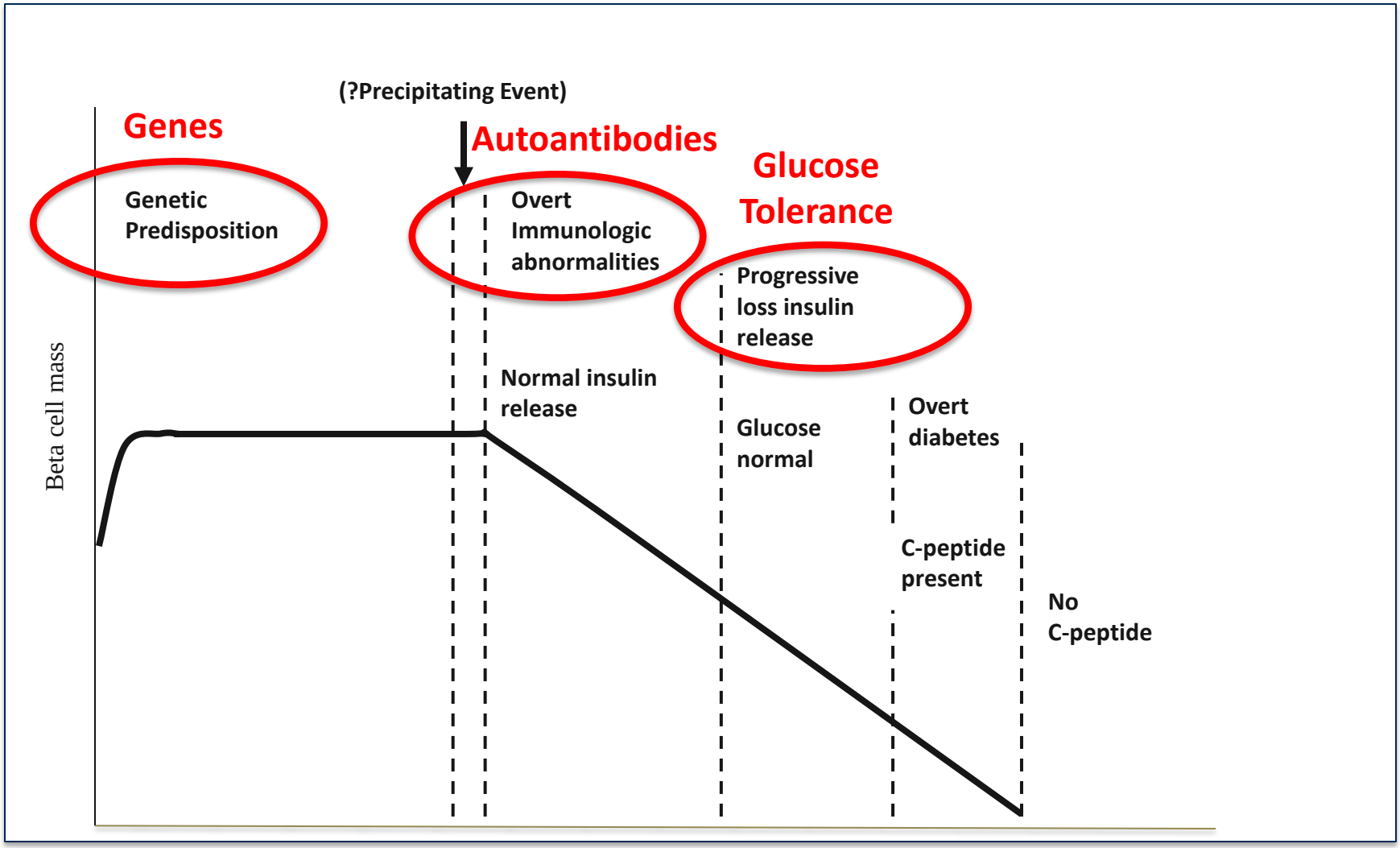
Beta cell mass

Age (years+

Eisenbarth, NEJM 1986

defining the early stages of type 1 diabetes T1D

Natural History Biomarkers Derived from the Classic Model of T1D Pathogenesis



Eisenbarth, NEJM 1986

Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

1. Precipitating events might occur in utero
2. Genetic predisposition probably the key driver or linkage to immune abnormalities
(Precipitating event)
3. Beyond precipitating, environment might influence entire natural history
5. Presence of two or more islet autoantibodies might represent asymptomatic type 1 diabetes
Genetic predisposition
6. Increasing glucose excursions as individual approaches symptomatic onset
Overt immunological abnormalities
Progressive loss of insulin release
Overt diabetes
7. Some patients produce low concentrations of C-peptide long after onset
Normal insulin release
Glucose normal
C-peptide present
No C-peptide
8. β-cell mass not always zero in longstanding patients
4. Although overall loss of β cells is potentially linear, it could show a relapsing or remitting pattern
β-cell mass
Age (years)

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Biomarkers to Refine Type 1 Diabetes Staging

Patient Stratification

Heterogeneity of T1D disease

Stratification & Response to Specific Therapy

Distinguish healthy, at-risk from not at-risk

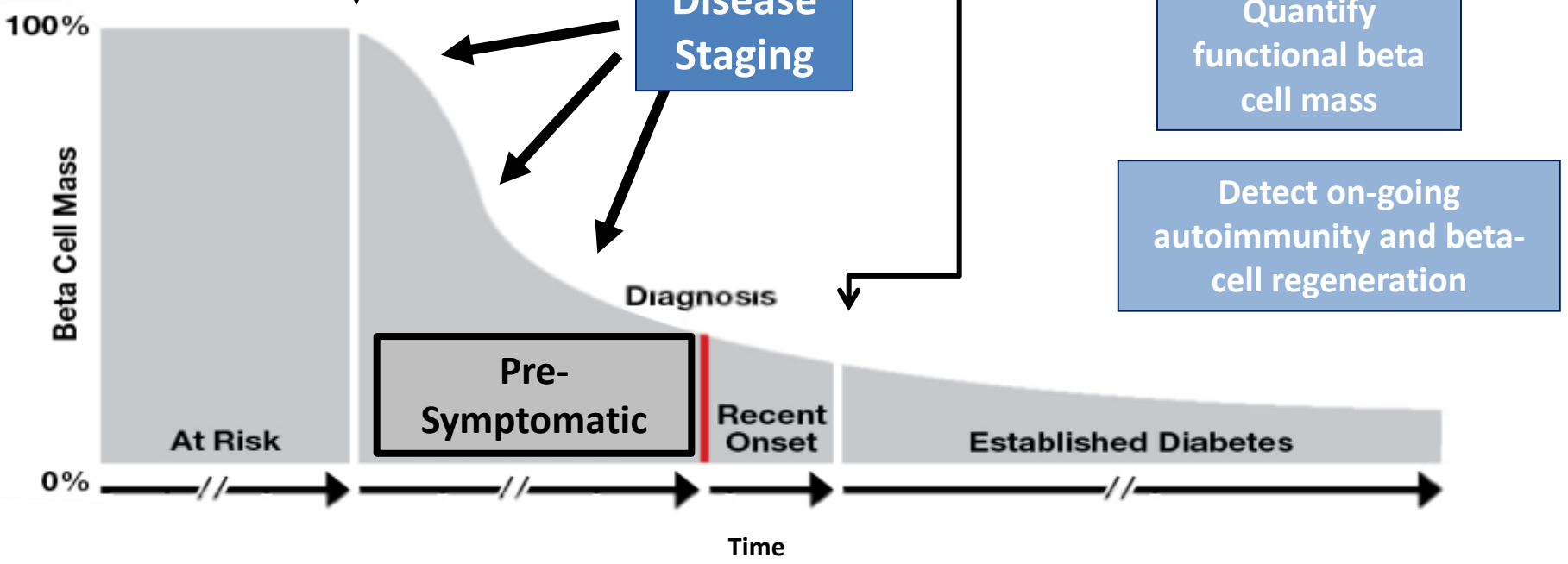
Distinguish healthy, at-risk from pre-symptomatic diabetes

Define "Degree" of Disease

Disease Staging

Quantify functional beta cell mass

Detect on-going autoimmunity and beta-cell regeneration



Practical Evolution of Biomarkers for Type 1 Diabetes

"Something is Wrong"

- Genetic Susceptibility
- Autoantibodies
- Declining Metabolic Status

"This is What is Wrong"

- Mechanistic Insights that Guide:
  - Disease State
  - Pathogenesis

"This is How we will Respond to the Wrong"

- Improved Prediction
- Therapies for Prevention/Cure
- Better Treatment Modalities

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(Precipitating event)

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Genetic predisposition

6. Increasing glucose excursions as individual approaches symptomatic onset

Overt immunological abnormalities

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Overt diabetes

7. Some patients produce low concentrations of C-peptide long after onset

Normal insulin release

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β-cell mass

Age (years)

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

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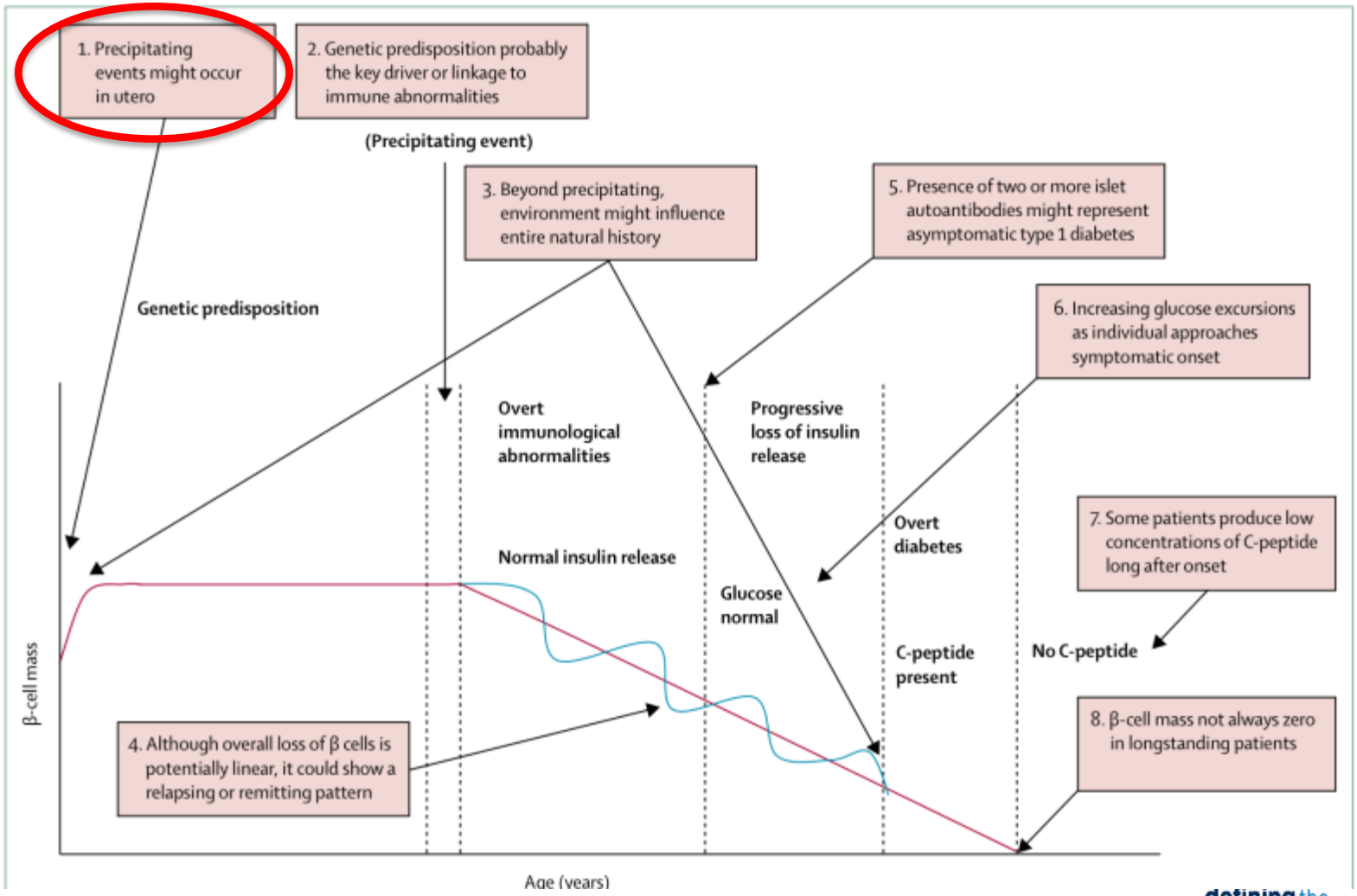
Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

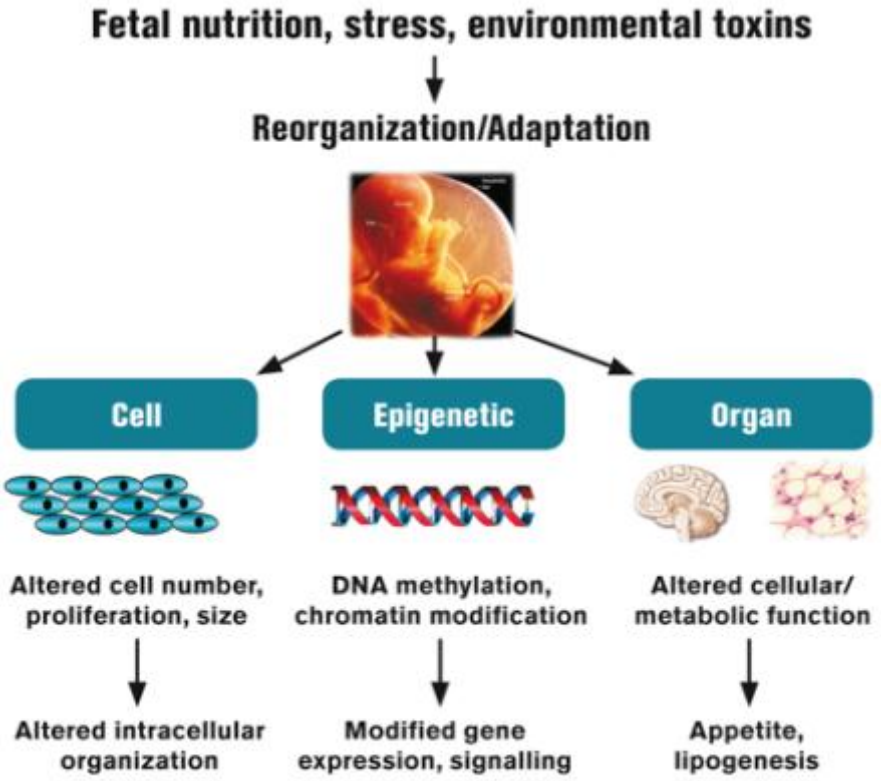
Maternal Factors



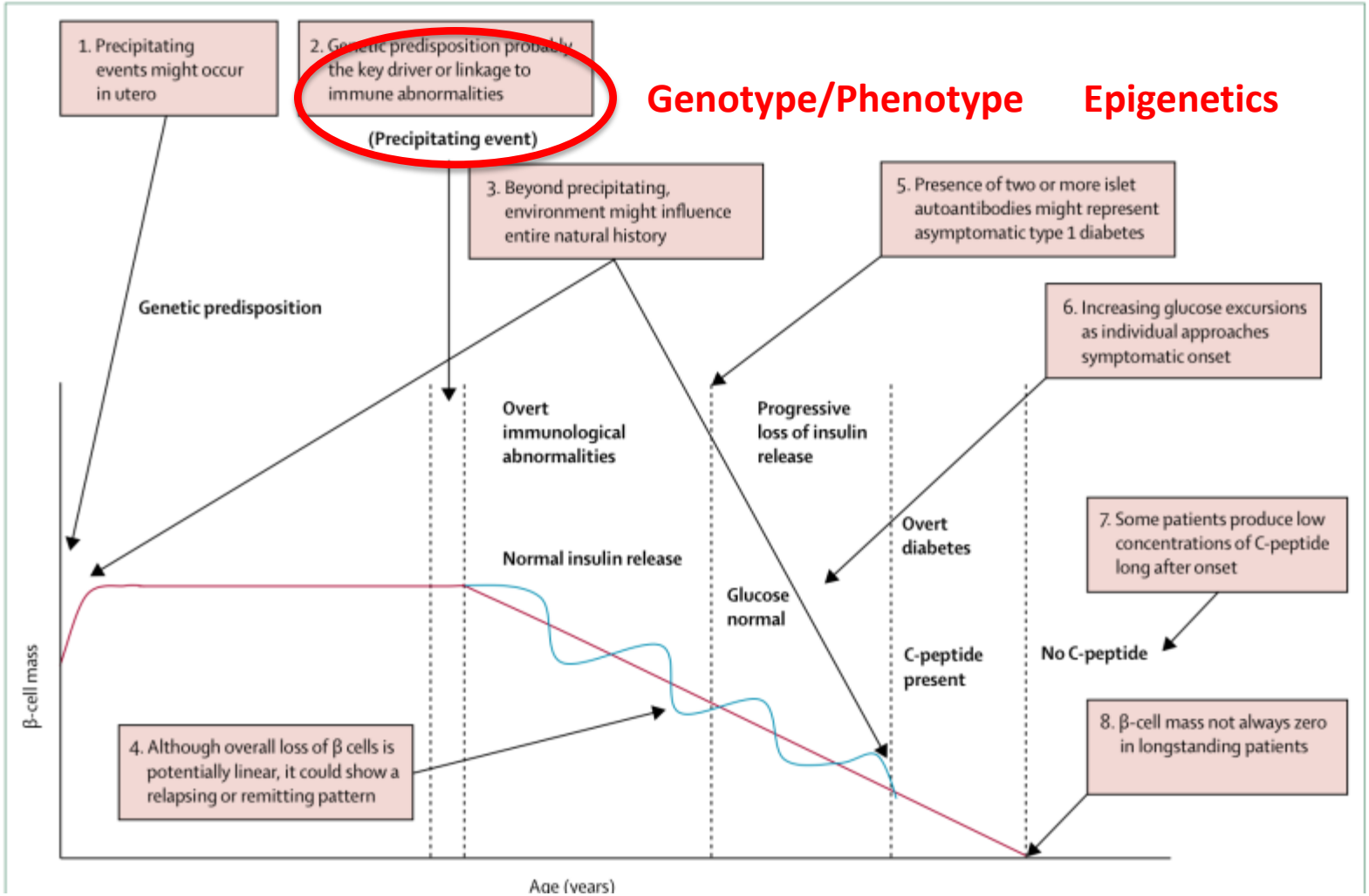
Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Precipitating Events Might Begin In-Utero

- Born to diabetic fathers vs. mothers
- Diabetic mother diagnosed less than 8 years of age vs later age
- First born
- Increased maternal enterovirus infections
- ABO incompatibility
- Increasing maternal age at delivery
- Season of delivery
- Early cessation of breast feeding

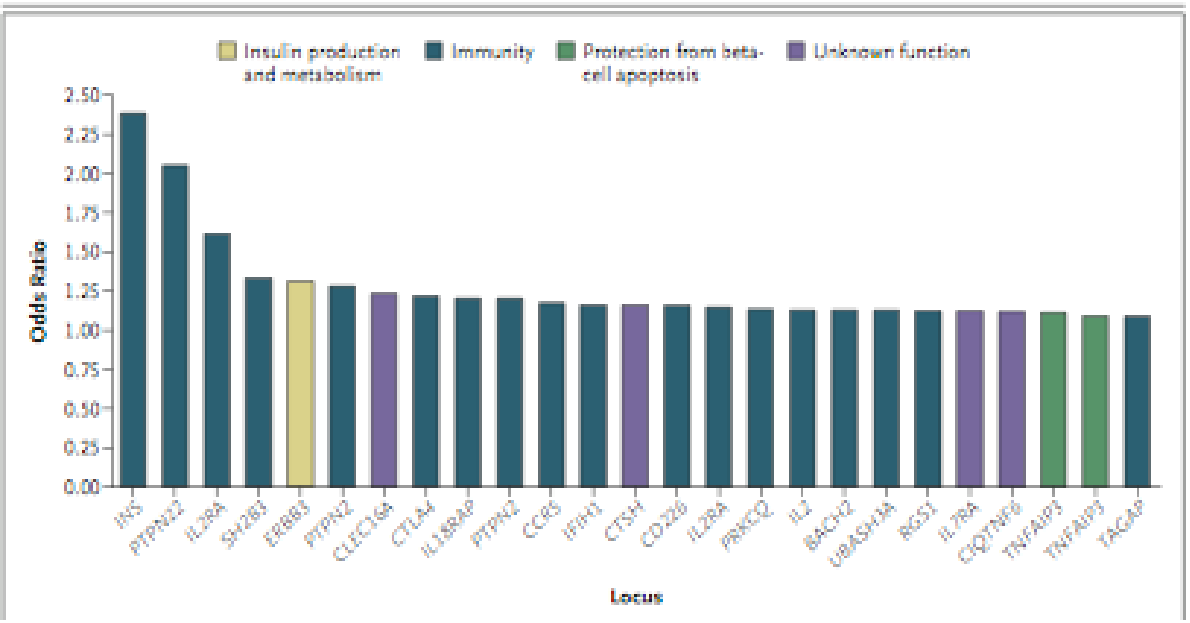


Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes



Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Genetic Linkage to T1D



Concannon P , Rich S, Nepom GT
N Engl J Med 2009;360:1646-1654

The NEW ENGLAND JOURNAL of MEDICINE

The Evolution of Type 1 Diabetes Genetics

1980's to Present – Biomarkers that Define Risk for Type 1 Diabetes

Note: Too many;
Too little OR;
Notions of GWAS
"Bust"

Future – Genotype/Phenotype Studies in Type 1 Diabetes

defining the early stages of type 1 diabetes T1D

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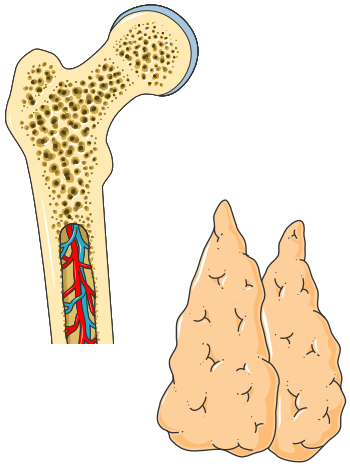
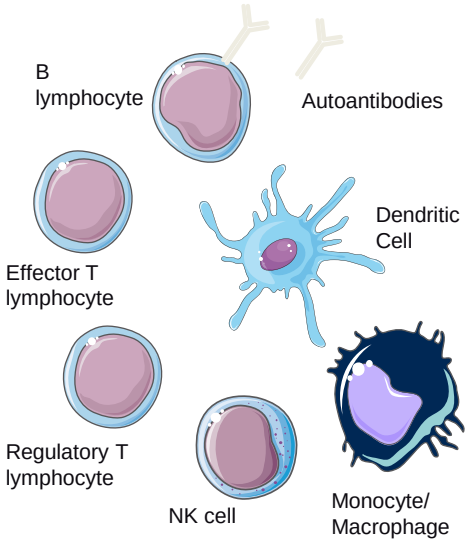
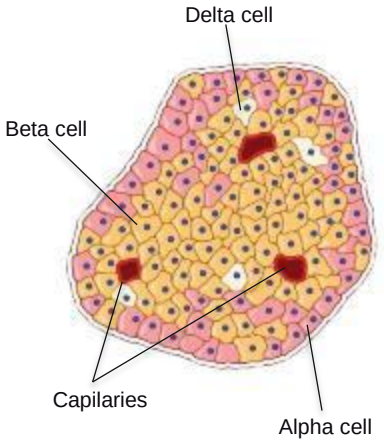
Genetic Linkage to T1D Abnormalities







Compartment #1
Bone Marrow / Thymus Contributions

- Defective thymic selection (positive/negative)
- Potential for self-antigens presented in incorrect register of MHC binding
- Influence of *Aire* and *VNTR* expression in thymus
- Mobilopathy
- Intrinsic defects in lymphocyte precursors
- Inherited genetic susceptibility
- "Niche" for persistent autoreactive lymphocytes

Compartment #2
Immune Contributions

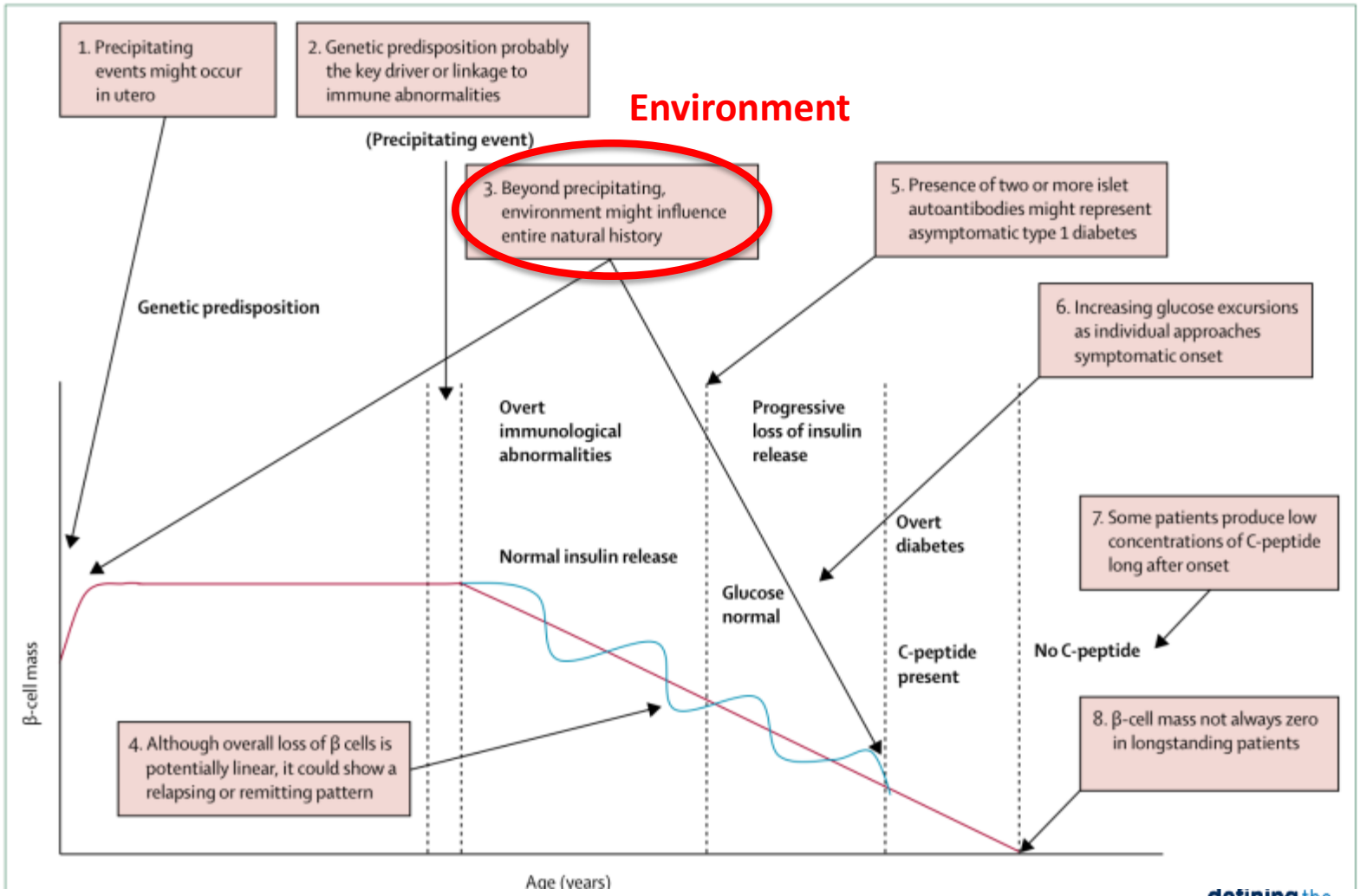
- Defective immune regulation (e.g., Teff resistance to Treg, Treg abnormalities, etc.)
- Chronic APC activation
- Autoantibody production
- Self-antigens with low affinity epitopes recognized by low avidity autoreative TCRs
- Failure to resolve autoreactive immune memory
- Abnormal cytokine production/ regulation
- Cellular trafficking/adhesion defects

Compartment #3
Beta Cell Contributions

- Expression of Class I MHC
- Production of cytokines and chemokines
- Free radical sensitivity
- Sensitivity to stress protein response
- Potential to present high quantities of self-antigen via Class II MHC
- Susceptibility to viral tropism/ inability to resolve inflammation
- Limited replication potential
- Rate of immune destruction influenced by metabolic activity

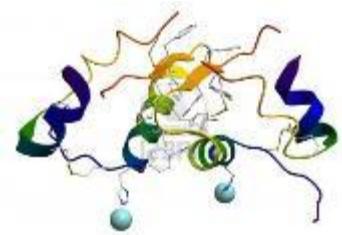
Atkinson, Eisenbarth, Michaels 2014 Lancet

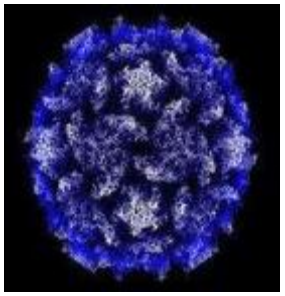
Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes



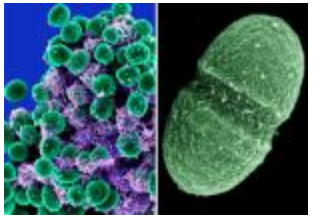
Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Beyond Triggering, Environment Likely Contributes throughout Natural History of T1D



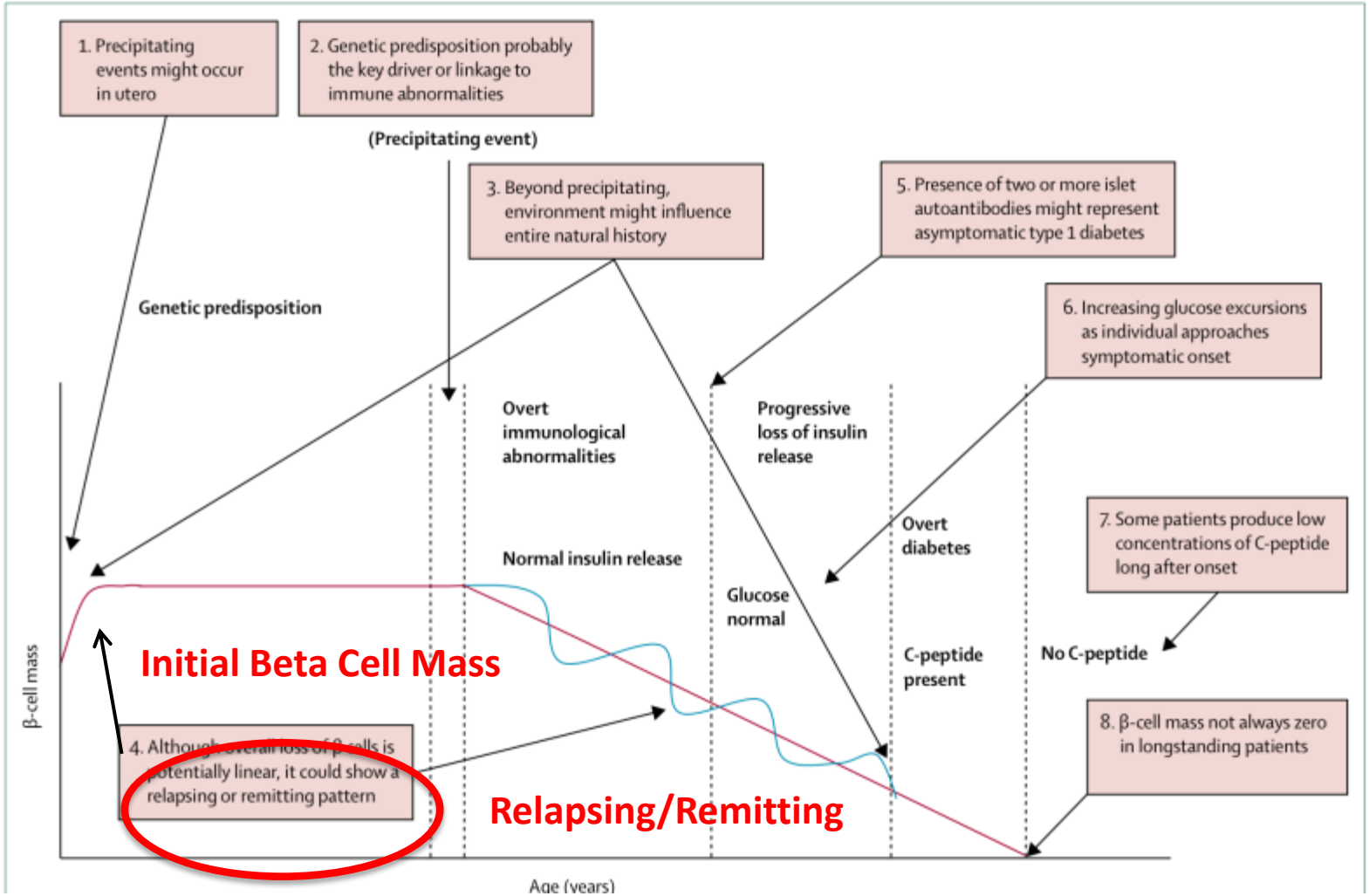


Omega-3 Fatty Acids



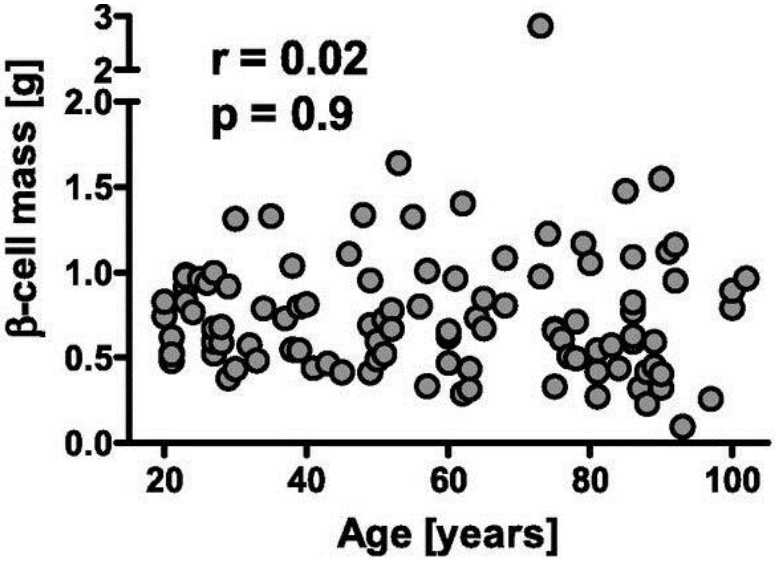
Microbiome

Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes



Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

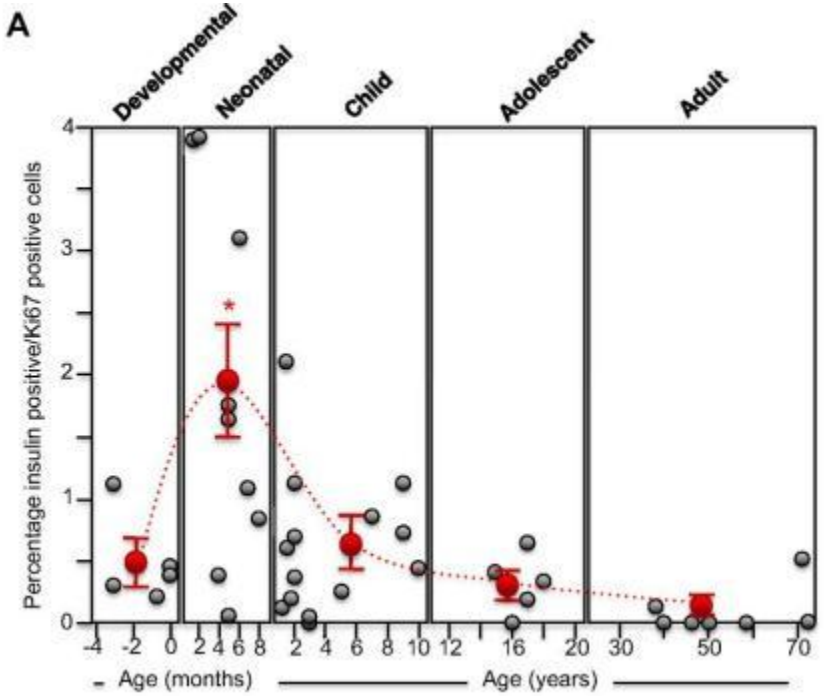
Not All Humans are "Created Equal", in terms of Beta Cell Mass nor in Their Ability to Replicate Beta Cells



Butler et al., Diabetes Care 36:111, 2013

Formation of a Human β-Cell Population within Pancreatic Islets Is Set Early in Life

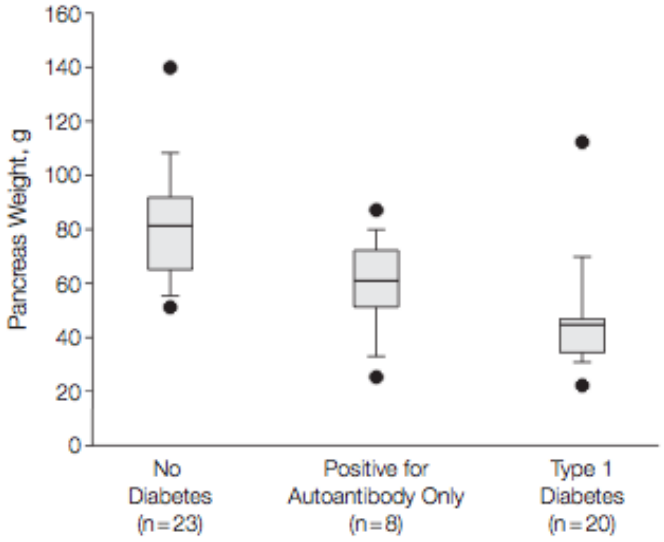
Brigid E. Gregg, Patrick C. Moore, Damien Demozay, Ben A. Hall, Mei Li, Aliya Husain, Amy J. Wright, Mark A. Atkinson, and Christopher J. Rhodes



THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Smaller Pancreas in the Natural History of T1D

Figure. Pancreas Weight of Organ Donors by Disease Status Using an Analysis of Covariance Model

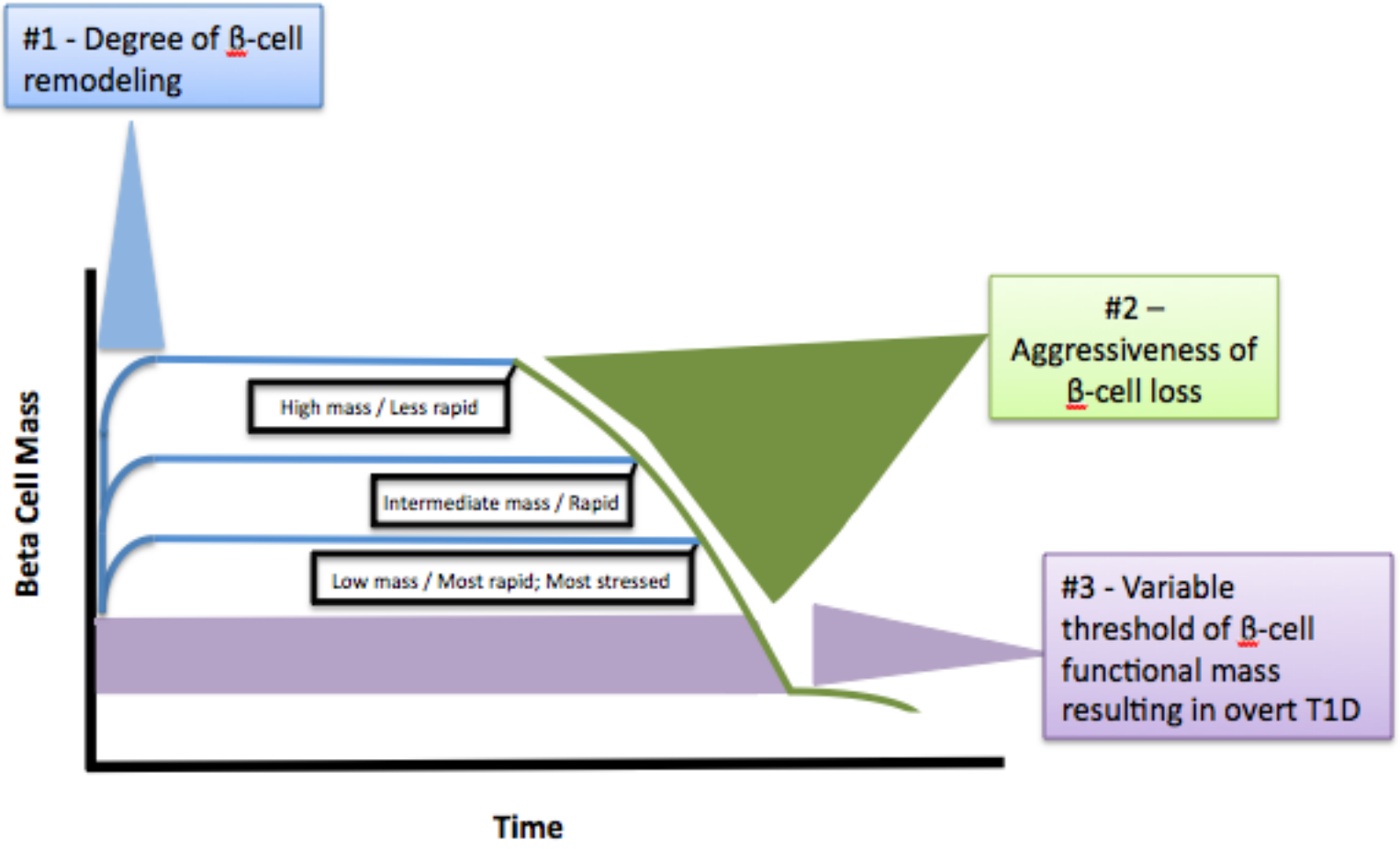


	No Diabetes (n=23)	Positive for Autoantibody Only (n=8)	Type 1 Diabetes (n=20)
Upper and lower box values	91.4 and 65.8 g	72.0 and 51.8 g	46.5 and 34.8 g
Mean value	81.4 g	61.3 g	44.9 g
95th and 5th percentiles	108.5 and 55.6 g	79.8 and 33.2 g	69.8 and 31.0 g
Upper and lower outlier values	139.0 and 52.7 g	83.8 and 25.0 g	117.4 and 23.4 g

Campbell-Thompson, JAMA. 2012

57

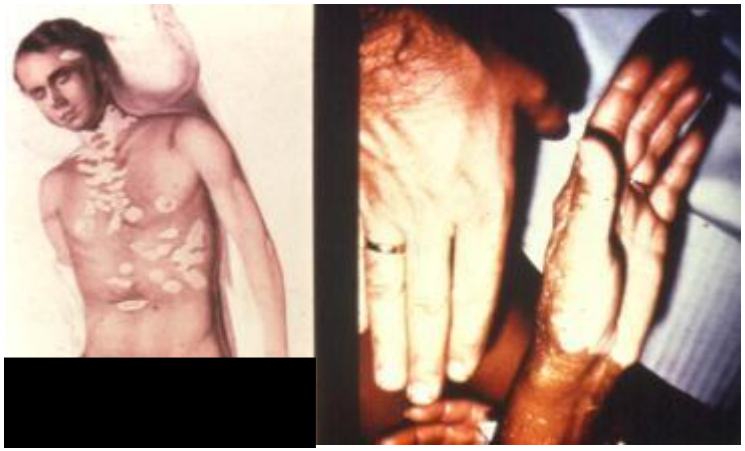
Beta Cell Mass may be a Key Risk Factor in Time of Development of Symptomatic T1D – A Current Hypothesis



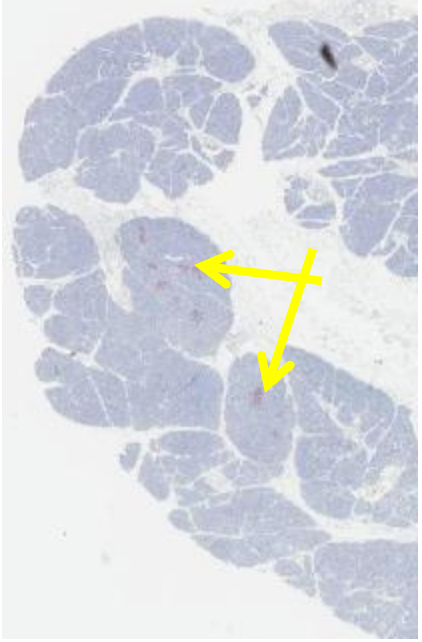
Battalia M. & Atkinson M. (submitted)

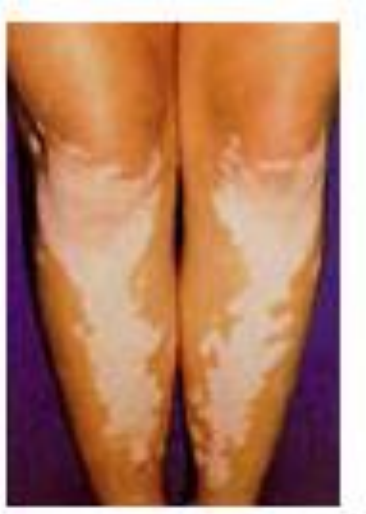
Are Early Stages of T1D Associated with a Relapsing/Remitting Pattern?

Type 1 Diabetes – Vitiligo of the Pancreas?



Insulin and Ki67 Staining

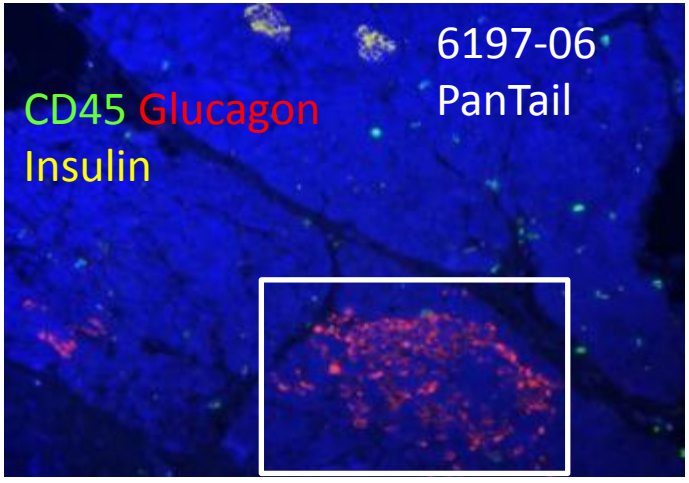




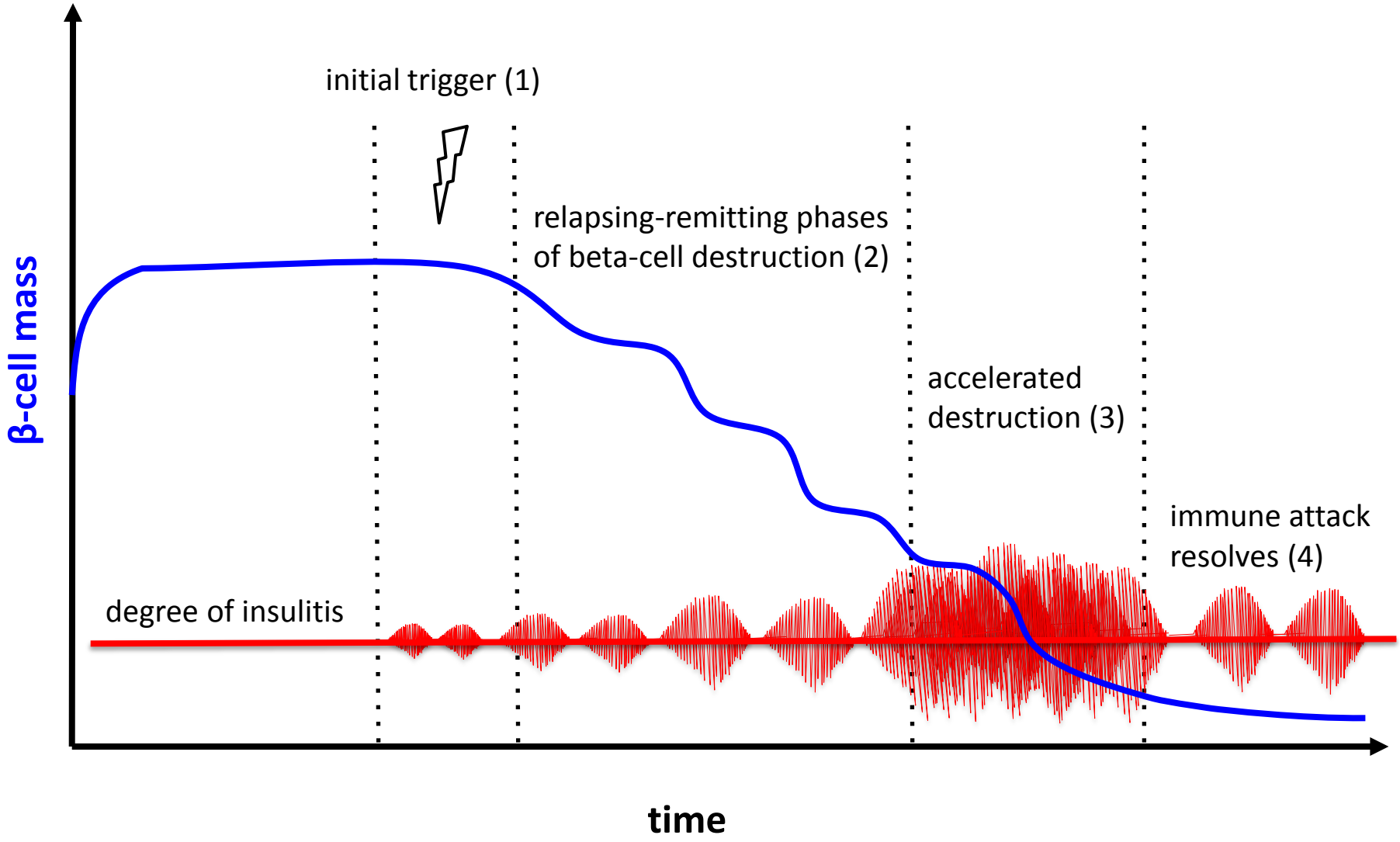
Eisenbarth, Diabetes 2010; Atkinson, nPOD Unpub.

Pancreatic pathology suggests:

- **Sporadic islet destruction (lobular)**
- **Perhaps a disease of relapse/remission ?**

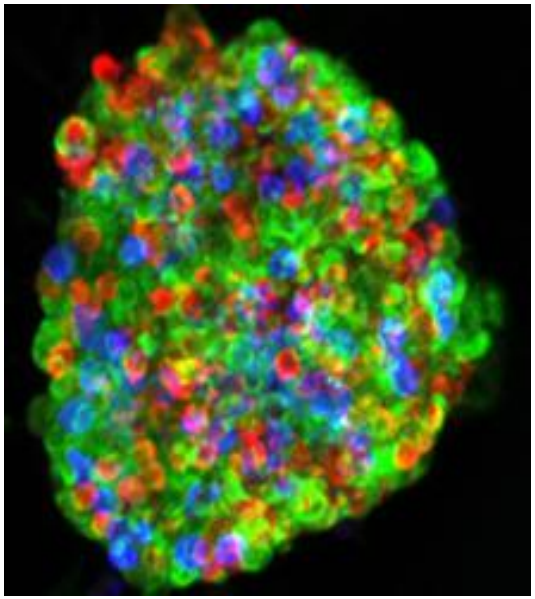


Are Early Stages of T1D Associated with a Relapsing/Remitting Pattern?



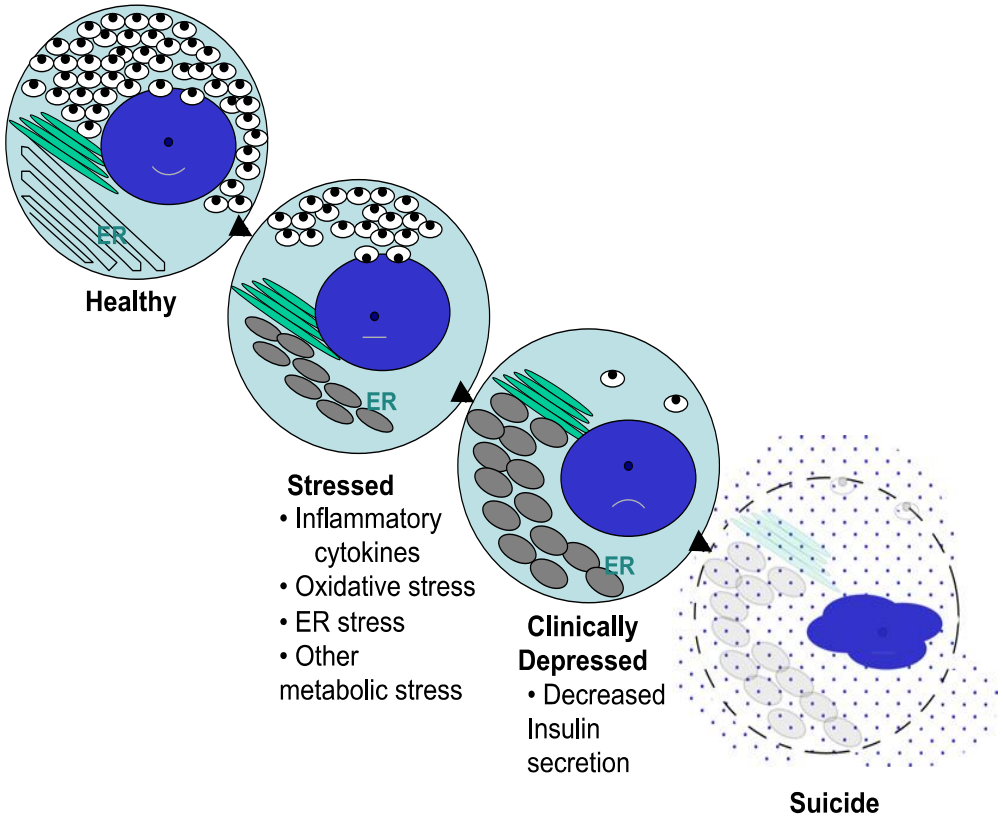
Von Herrath, 2014, Diabetologia

Beta Cell Destruction may be Homicide, Suicide, or Failed Mechanisms of Self-Protection



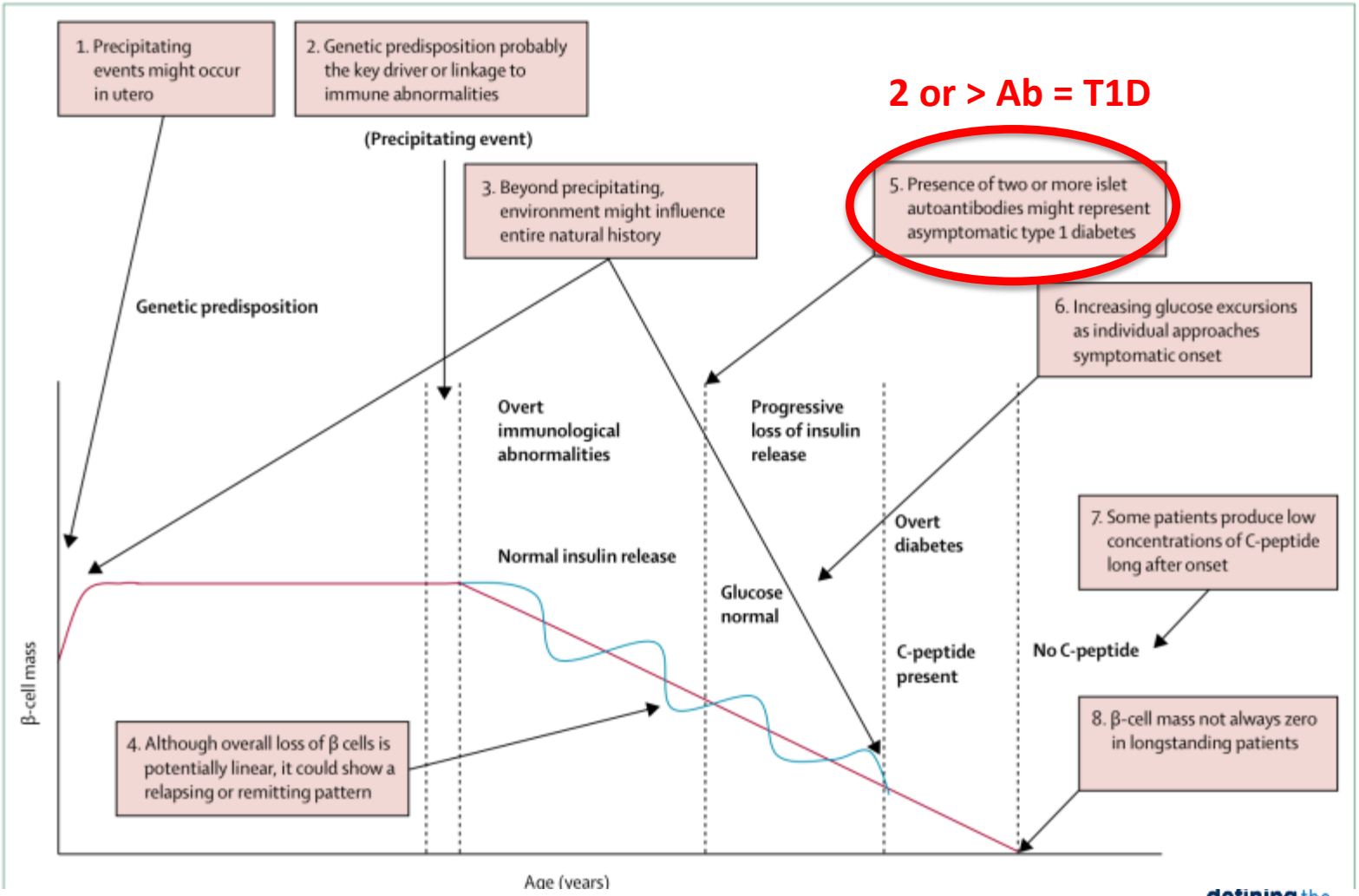
- *Glut 2 Receptor*
- *Empty Beta cells*
- *mRNA abberancies*
- *ER Stress*
- *UPR*

Disease Progression →



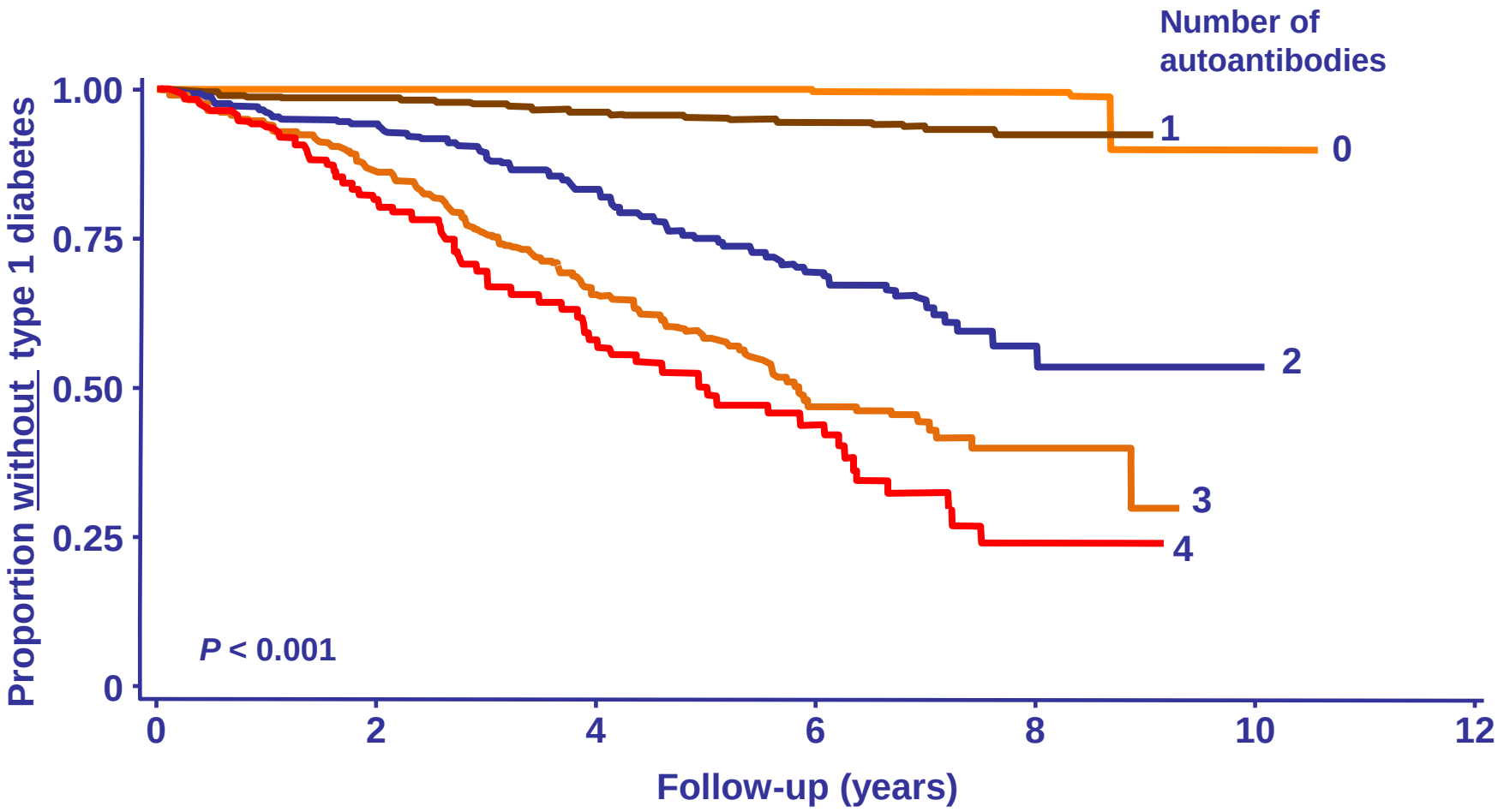
Courtesy, Al Powers: Atkinson, M. et al Diabetes, 2012 – Brehm Coalition

Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes



Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

Multiple Autoantibodies are Associated with Faster Progression to Symptomatic T1D in T1D Relatives



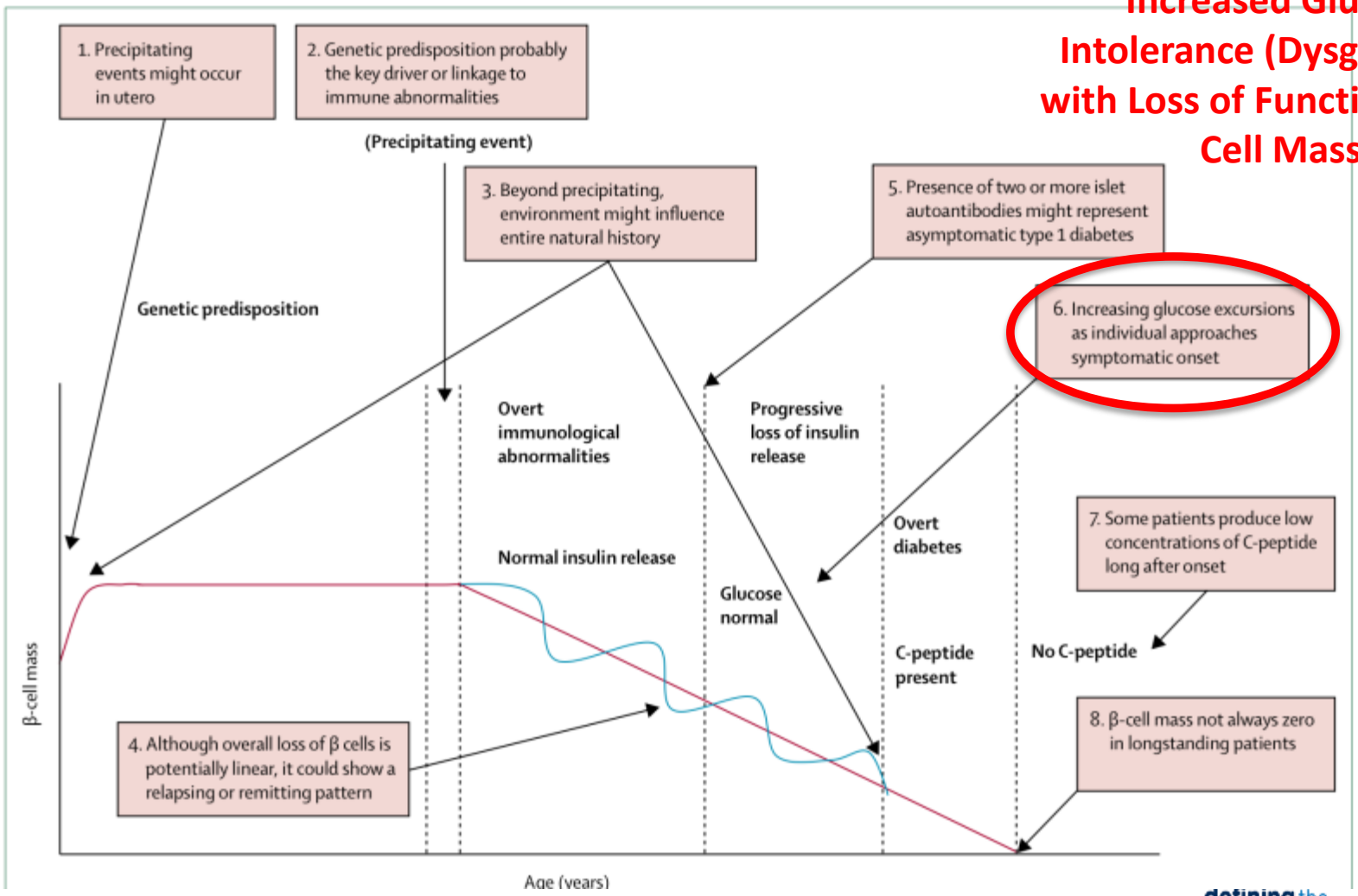
Numbers 1– 4 are number of autoantibodies at screening.

Curves indicate occurrence of type 1 diabetes over follow-up (n = 29,035). DPT-1 = Diabetes Prevention Trial–Type 1

Diabetes Care 2009;32:2269–2274.

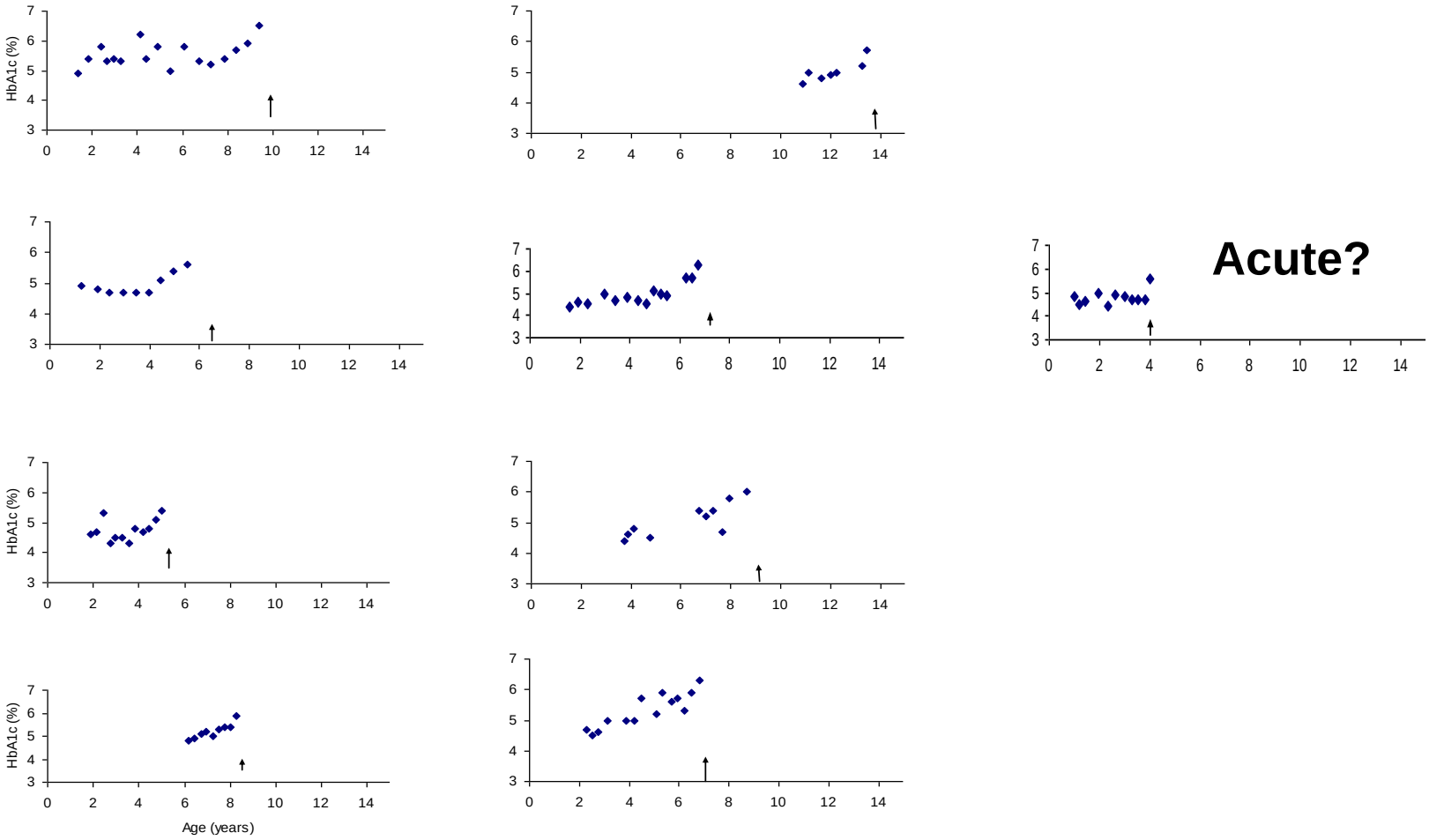
Potential "Future" Biomarkers Derived from Current Model for the Pathogenesis and Natural History of Type 1 Diabetes

Increased Glucose Intolerance (Dysglycmeia) with Loss of Functional Beta Cell Mass



Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

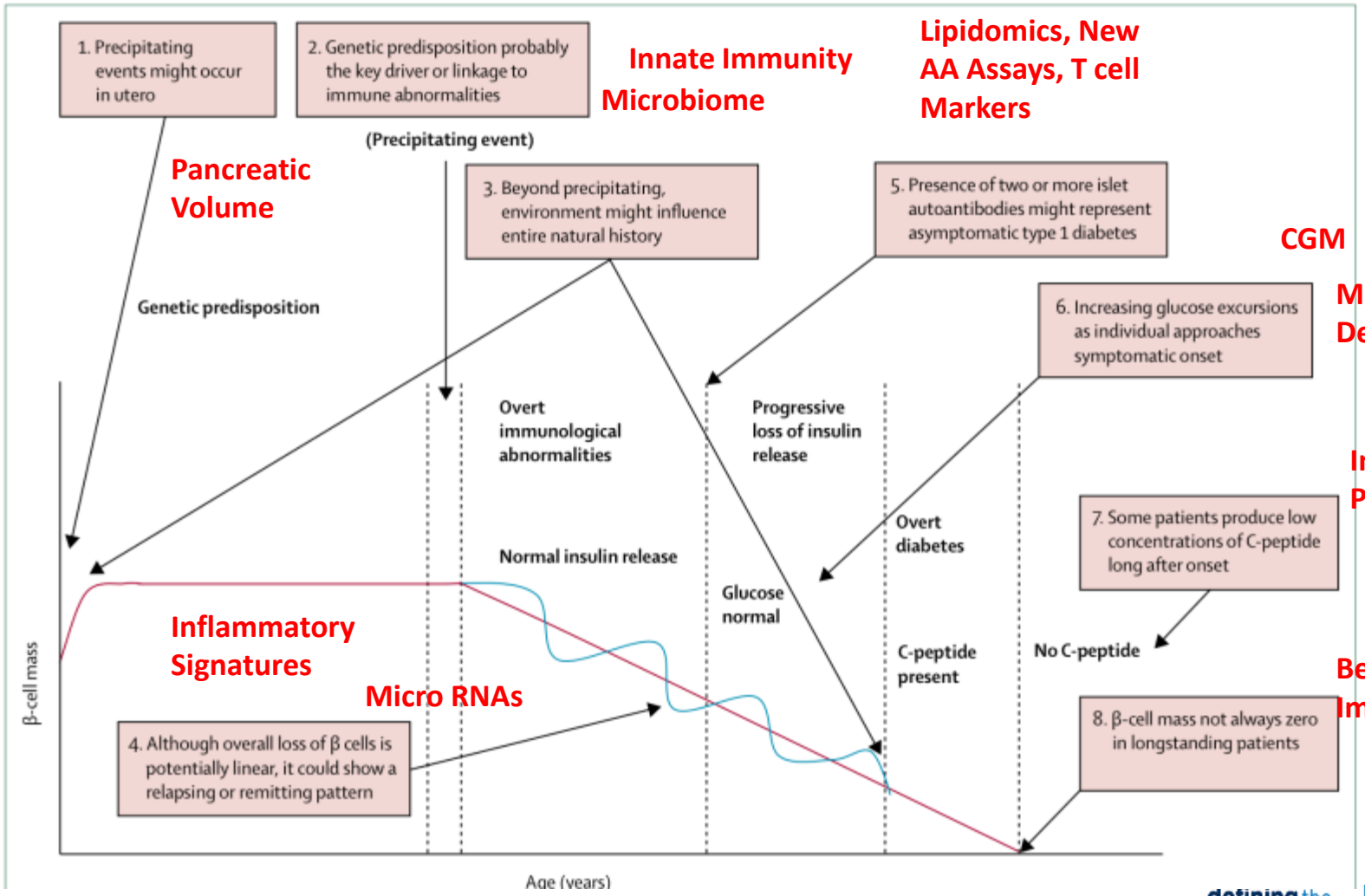
Rising HbA1c Can Precede Symptomatic T1D



Stene et al DAISY. Pediatr Diab 2006

Potential "Future" Biomarkers Derived from Current Model for Improved Staging of Type 1 Diabetes

Maternal Factors **Epigenetics** **Genotype/Phenotype**



Innate Immunity Microbiome

Lipidomics, New AA Assays, T cell Markers

Pancreatic Volume

CGM

Markers of B Cell Death

Improved C-Peptide Assays

Inflammatory Signatures

Micro RNAs

Beta Cell Imaging

Atkinson, M; Eisenbarth, G.S.; Michels, A. Lancet, 2014

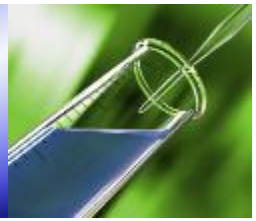
defining the early stages of type 1 diabetes

T1D

Overview of Natural History of Type 1 Diabetes: Lessons for Staging

Thank You





nPOD
Network for Pancreatic Organ Donors with Diabetes


defining the early stages of type 1 diabetes

Assessment of T1D Risk in Newborns

Marian Rewers, MD, PhD

Barbara Davis Center for Childhood Diabetes

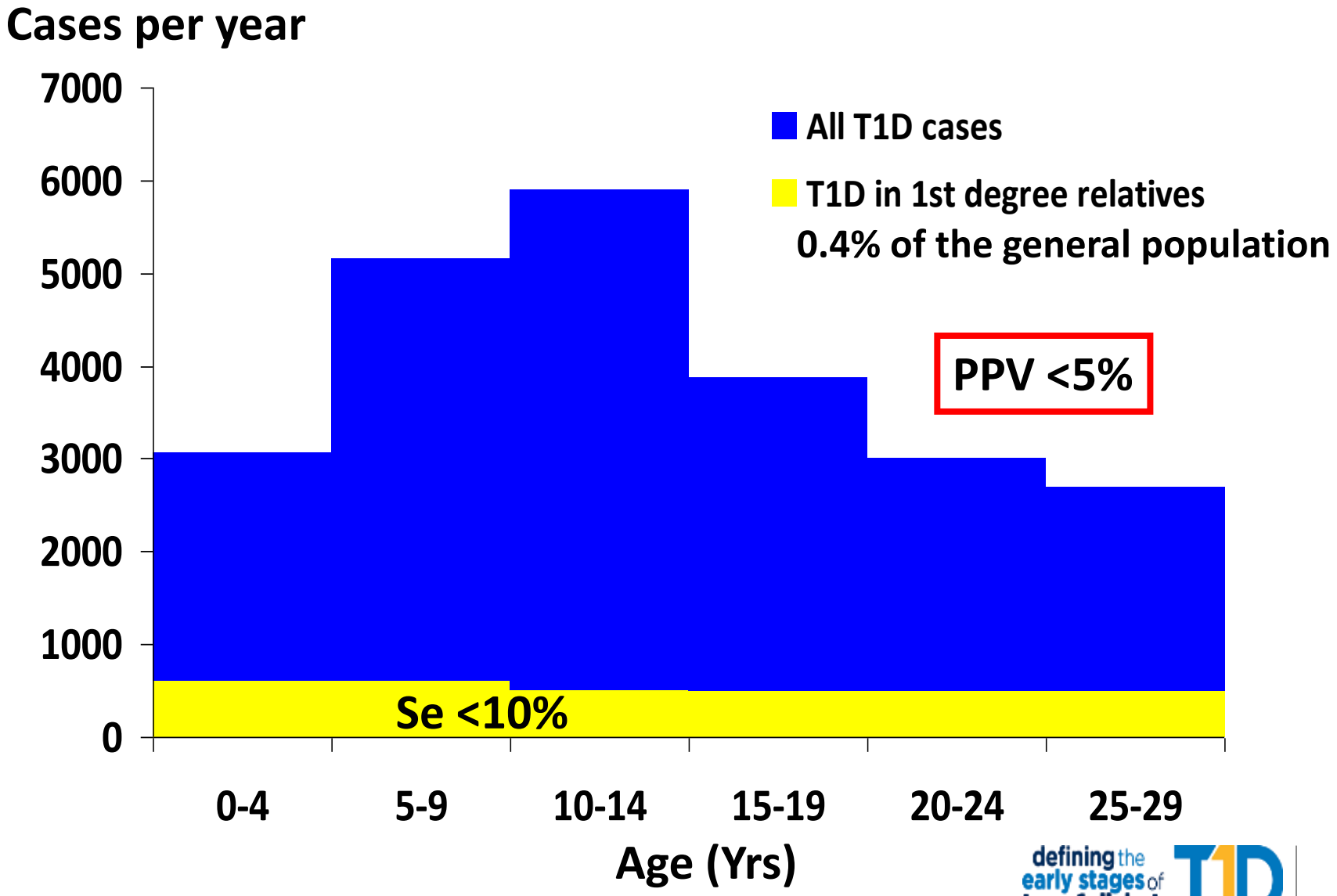
University of Colorado

Risk of Type 1 Diabetes by Age 20 Years

	T1 DM risk by age 20 yr
General Population	1:250
Offspring of women with T1D	1:50
Offspring of men with T1D Siblings	1:15 1:15
Monozygotic twins	1:3
No family history of T1D HLA-DR3/4,DQB1*0302 genotype	1:15

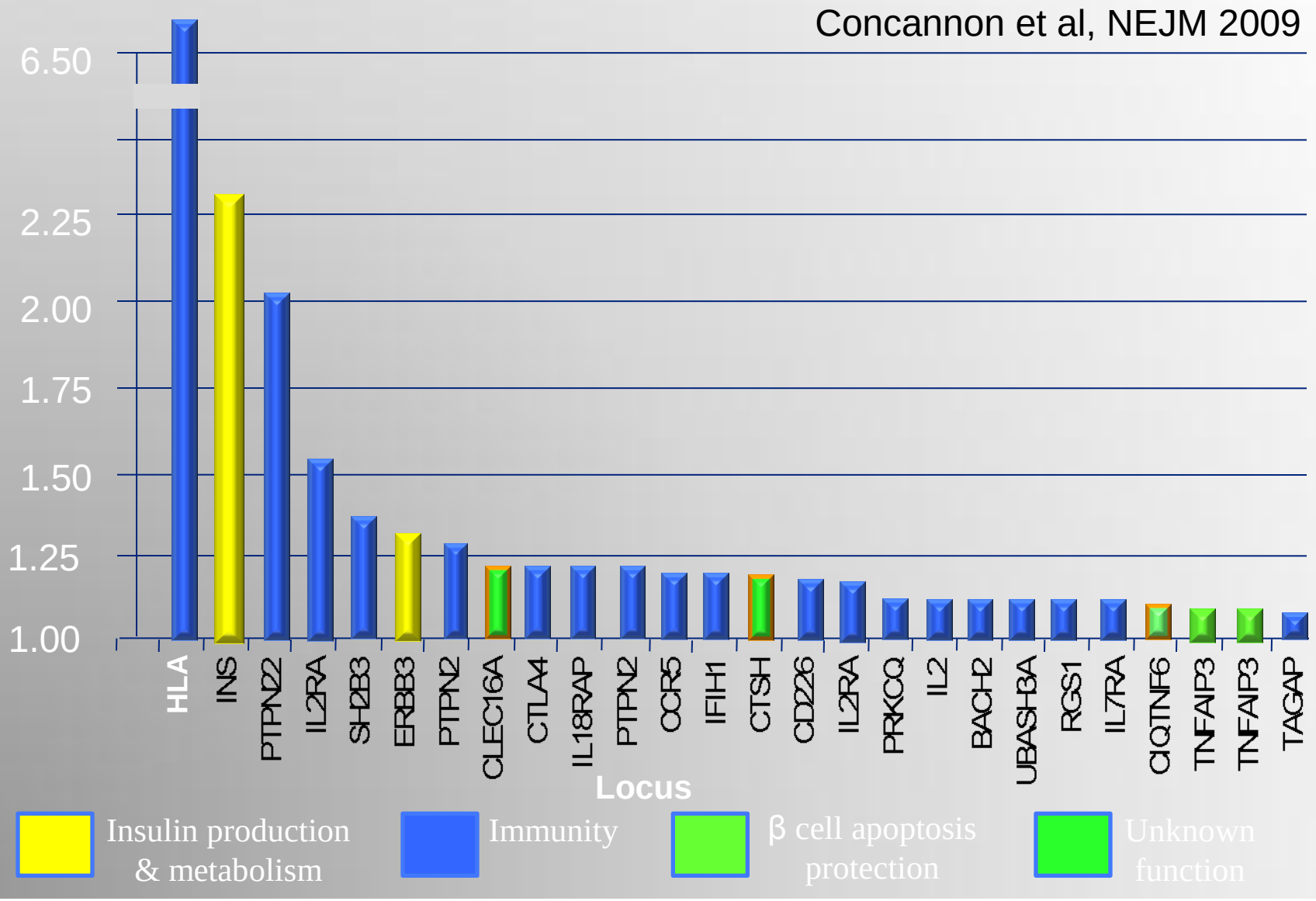
defining the early stages of type 1 diabetes T1D

Prediction of T1D under age 30 years in the U.S. (n= 25,000/yr)



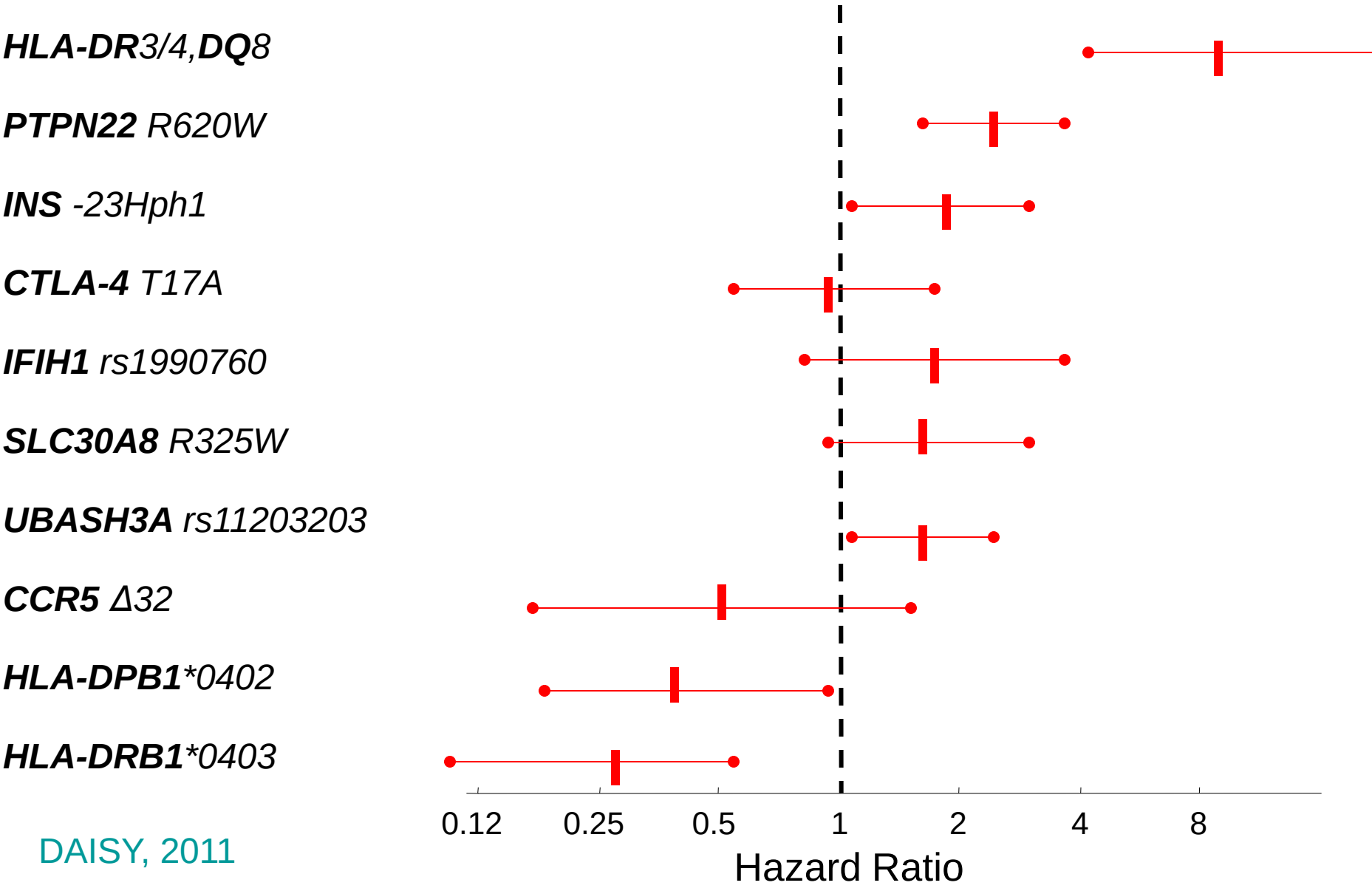
defining the early stages of type 1 diabetes T1D

Genome-wide Associations in T1D



Genetic markers and the Risk of T1D

Adjusting for sex, ethnicity, family history of T1D



DAISY, 2011

DAISY Strip (18 BSA-SSO probes) for DRB1 and DQB1

Epitopes:	WLF	WPR	YSTS	VH	YSTG	GYK	KDF	EEV	KGR	R-E	ERHFH	VDNYC	VDTYC	G	V	LGPPA	EGTRA	DQB1ALL

DR Type	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	X												X	+/-	+/-			X
2 (0602)		X											X	+/-	+/-		X	X
2#		X											X	+/-	+/-			X
3			X						X			X		+/-	+/-			X
4 (0302)				X									X	+/-	+/-	X		X
4*				X									X	+/-	+/-			X
0403/06/11				X						X			X		X	+/-		X
0407				X						X			X	X		+/-		X
11/13/14			X							+/-			X	+/-	+/-	+/-	+/-	X
12					X						X		X		+/-			X
7						X								X				X
8/1404/1411					X								X	+/-	+/-	+/-		X
9							X							X				X
10								X					X	X				X

M Rewers et al. Newborn screening for HLA markers associated with IDDM Diabetes Autoimmunity Study in the Young (DAISY). *Diabetologia 1996;39:807-812*

HLA-Defined T1 DM Risk Groups

DAISY, Denver Population, n=31,000

IDDM risk by age 20	HLA-DR	DQB1	Frequency %
High 1:15	3/4	0201/0302	2.4
Moderate 1:60-1:200	4/x	0302/	12.7
	4/4	0302/	3.0
	3/3	0201/0201	1.4
Average 1:300	3/x	0201/	12.5
	3/4	0201/not 0302	1.0
Lower than 1:300	4/x, 4/4	/not 0302	6.6
	2/x	0602	60.4
	others		

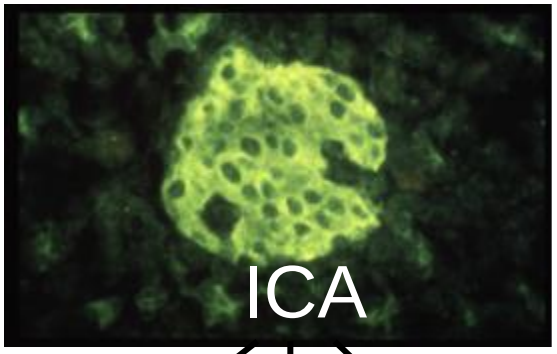
DAISY Newborn HLA Screening for Genetically High-risk Children

~10% of children with the highest T1D risk

DR-DQA1-DQB1 / DR-DQA1-DQB1	*Genotype frequency* General Population	T1D <15 yrs of age
4- 301-302 / 3- 501-201	2.3%	32.7%
4- 301-302 / 4- 301-*	3.0%	10.4%
4- 301-302 / 8- 401-402	1.5%	7.0%
4- 301-302 / 1- 101-501	2.3%	2.5%
4- 301-302 / 9- 301-303	0.3%	1.1%
3- 501-201 / 3- 501-201	1.3%	7.5%
Total	**10.7%**	**61.2%**

Islet Autoantibodies

1st generation assays



Insulin autoantibodies

2st generation RIA, ELISA

ZnT8A | **IA-2A** | **GADA** | **mIAA**

3rd generation ECL ElectroChemiLuminescent

ECL-IA-2A **ECL-GADA** **ECL-IAA**

Clinical Centers

- ★ Colorado
- ★ Finland
- ★ Georgia/Florida
- ★ Germany
- ★ Sweden
- ★ Washington

★ Data Coordinating Center, Tampa, FL

TEDDY

The Environmental Determinants of Diabetes in the Young

NIDDK
NIAID
NICHD
NIEHS
CDC
JDRF

TEDDY Newborn HLA Screening for Genetically High-risk Children

2004-2010

General Population
n= 418,709

DRB1-DQA1-DQB1/DRB1-DQA1-DQB1

4-301-302 / 3-501-201
4-301-302 / 4-301-302
4-301-302 / 8-401-402
3-501-201 / 3-501-201

5% of the population
50% of T1D cases

First-Degree Relatives
n= 6,417

DRB1-DQA1-DQB1/DRB1-DQA1-DQB1

4-301-302 / 3-501-201
4-301-302 / 4-301-302
4-301-302 / 4-301-201
4-301-302 / 8-401-402
4-301-302 / 1-101-501
4-301-302 / 13-102-604
4-301-302 / 4-301-304
4-301-302 / 9-301-303
3-501-201 / 3-501-201
3-501-201 / 9-301-303

22% of the FDRs
70% of T1D cases

TEDDY

Development of islet autoimmunity and T1D among TEDDY participants

1st Primary endpoint | **2nd Primary endpoint**

Genetic susceptibility

→

Confirmed persistent islet autoimmunity:

IAA, GADA, IA-2A or ZnT8A
at least twice 3 months apart & confirmed in the second laboratory

→

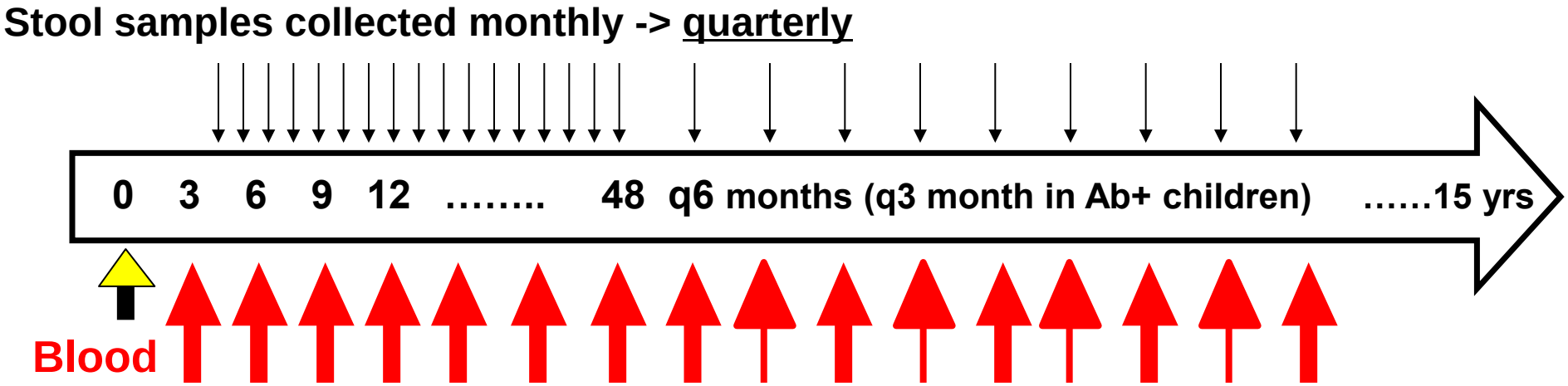
Clinical diabetes

ADA / WHO

N=8677		
August 2014	***n=603***	***n=191***
Expected by age 15 y:	**n~800**	**n~400**

TEDDY

TEDDY protocol



Clinic visits every 3 months (including ab+ children older than 4):

Blood for: GADA, IAA, IA-2A, ZnT8; DNA, mRNA, infectious agents, HbA1c, PBMC, erythrocytes, storage plasma/serum;

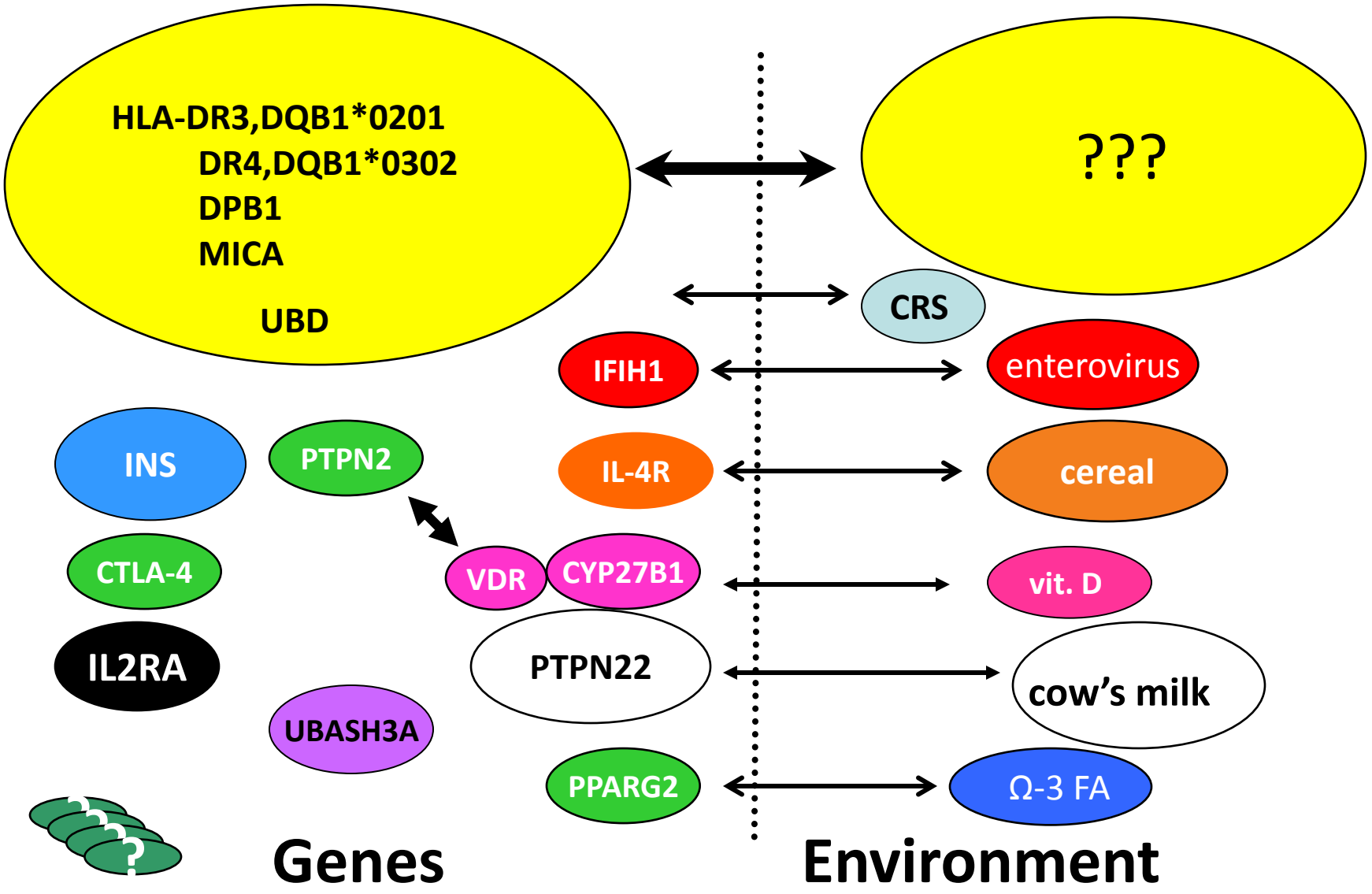
Nasal swabs, tap water, toenail clippings, and **salivary** cortisol.
urine samples; DNA from FDRs

Interviews: medications, immunizations, infections, family history;
Diet: maternal pregnancy diet; child's 24 hr recall, 3 day FFQ;
Physical activity quest., accelerometer;
Negative life events, parental anxiety, depression.

Summary:

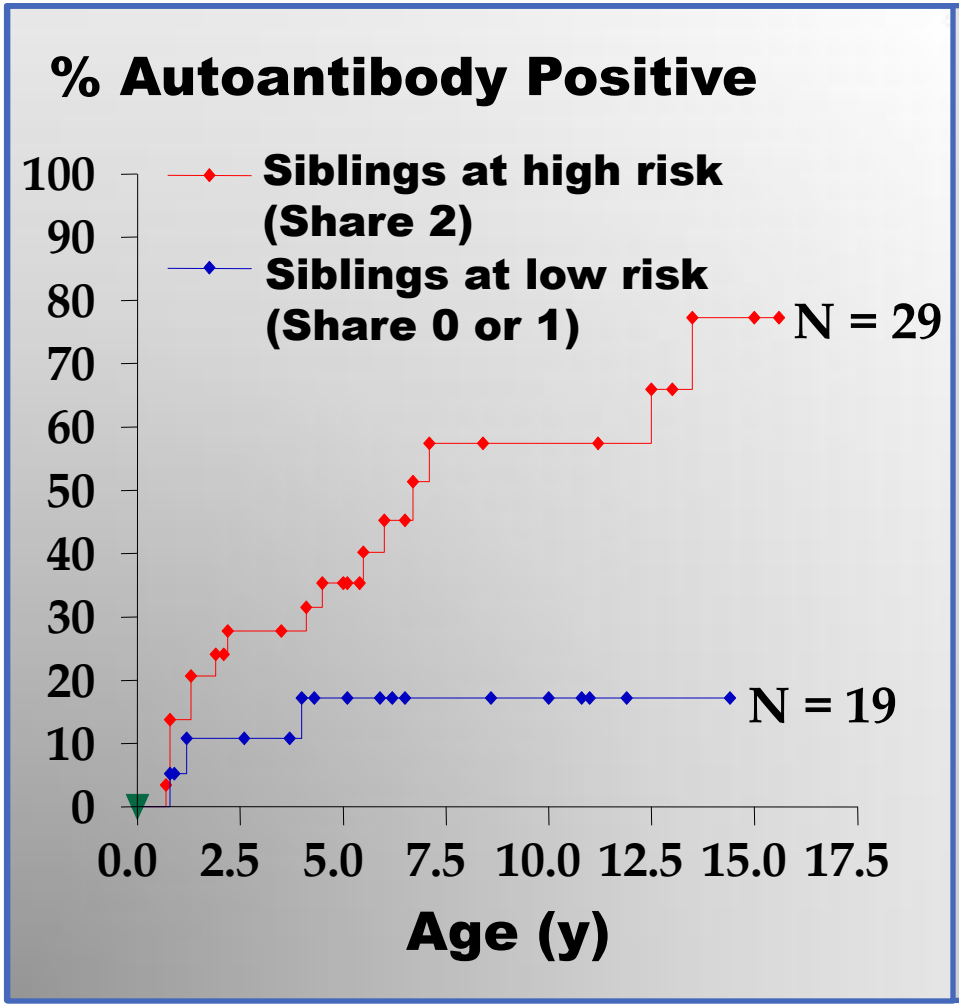
- **No simple 'genetic screening' for T1D**
  - **Polygenic disease**
  - **HLA region explains >50% of familiar clustering**
  - **HLA-DR,DQ-based newborn screening is 50-65% sensitive, but positive predictive value only 2-3%**
  - **Non-HLA markers may slightly improve prediction**
  - **Ethnic differences in HLA markers of T1D risk**
- **Islet autoantibody screening in combination with HLA pre-screening:**
  - **Sensitivity: ~60%**
  - **Specificity: ~35% (x2); up to ~50% (x3-4 tests)**

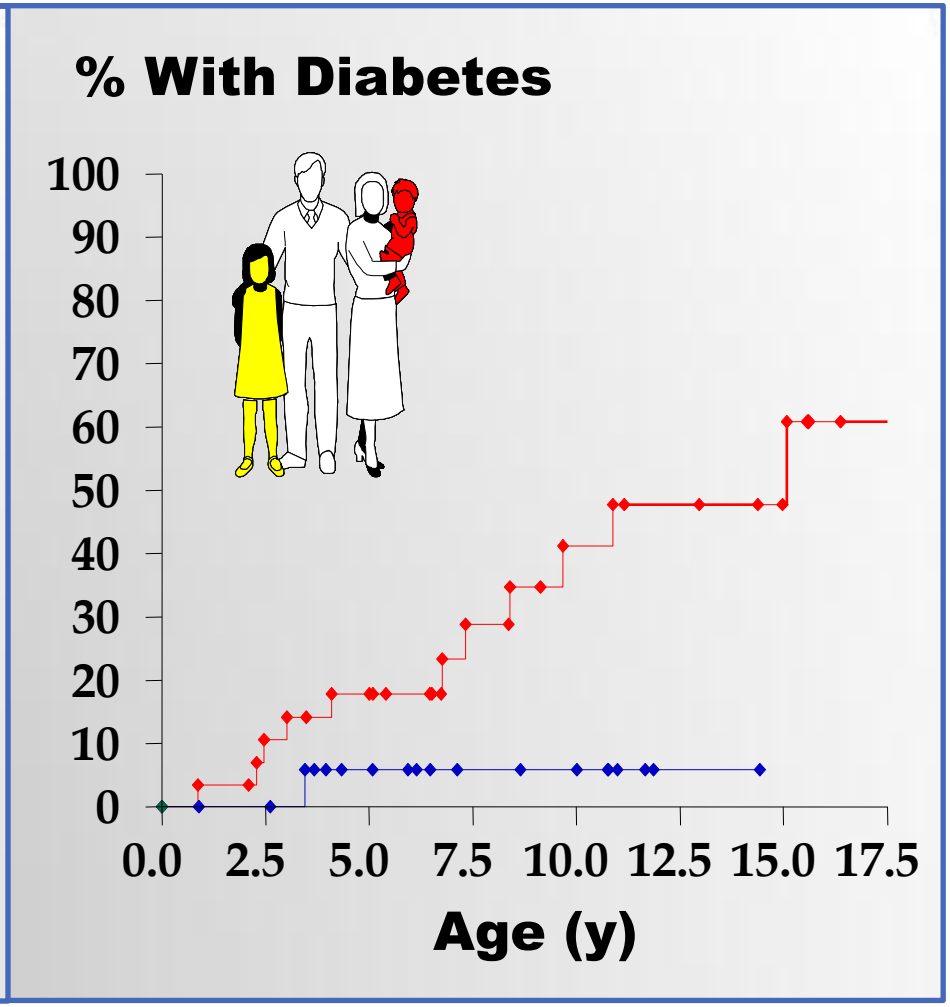
Should gene-environment interactions be accounted in T1D risk prediction?



M Rewers 2013

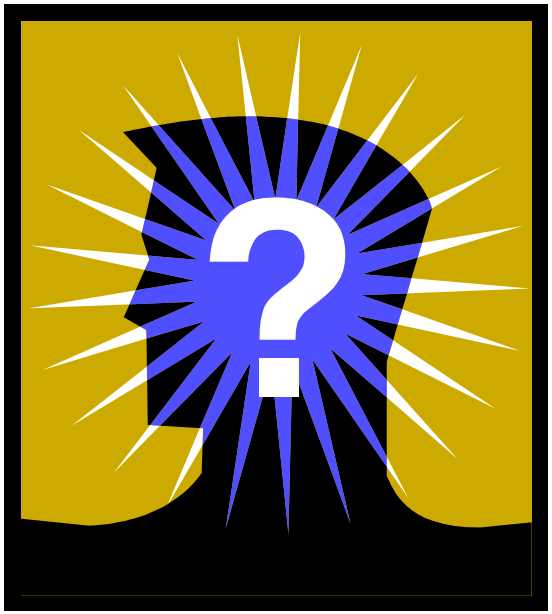
Extreme Risk for Diabetic Autoimmunity in DR3/4 Siblings

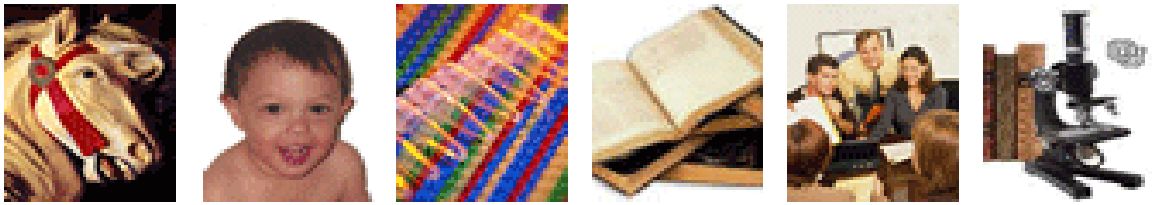




Aly et al, PNAS 2006

Questions?





Barbara Davis Center for Childhood Diabetes
www.barbaradaviscenter.org

marian.rewers@ucdenver.edu

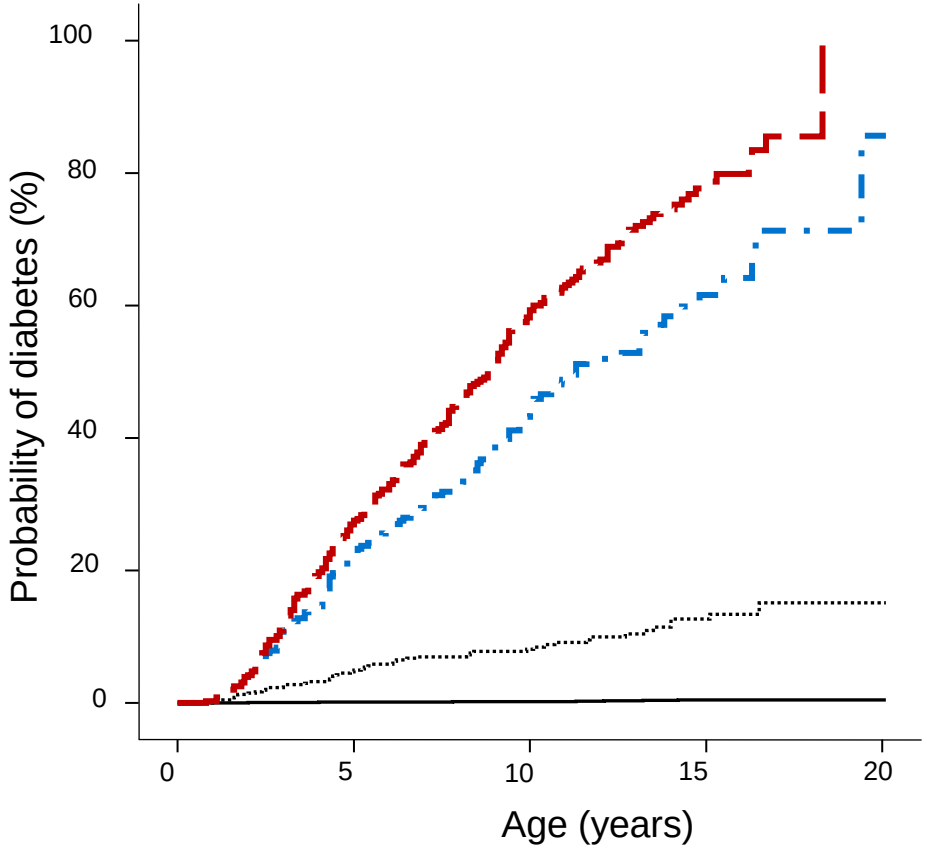
defining the early stages of type 1 diabetes

T1D

Public Health Screening for Early Type 1 Diabetes

Anette-Gabriele Ziegler
Helmholtz Zentrum München
Klinikum rechts der Isar
Technische Universität München

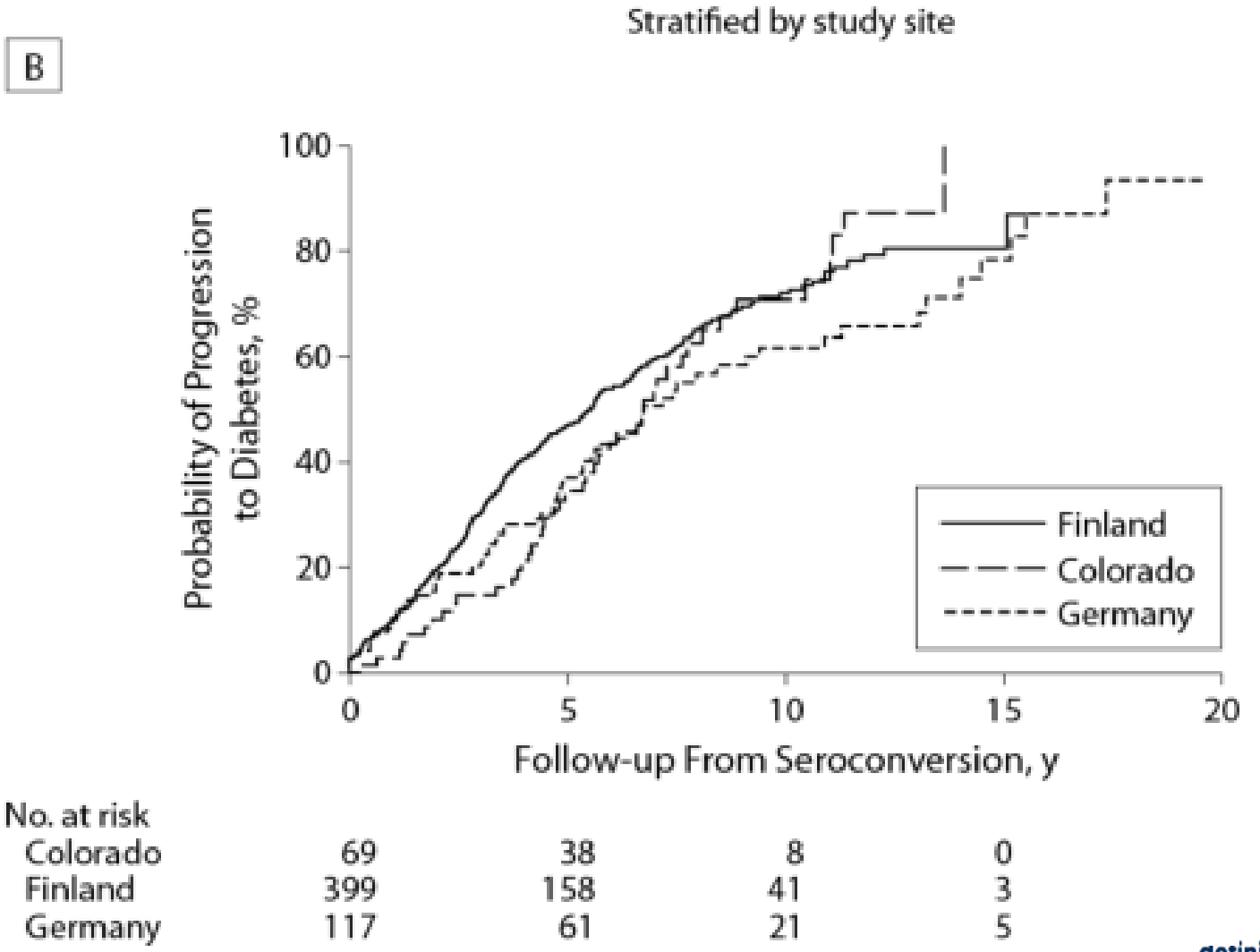
Children with Multiple Islet Autoantibodies Progress to Symptomatic Diabetes



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

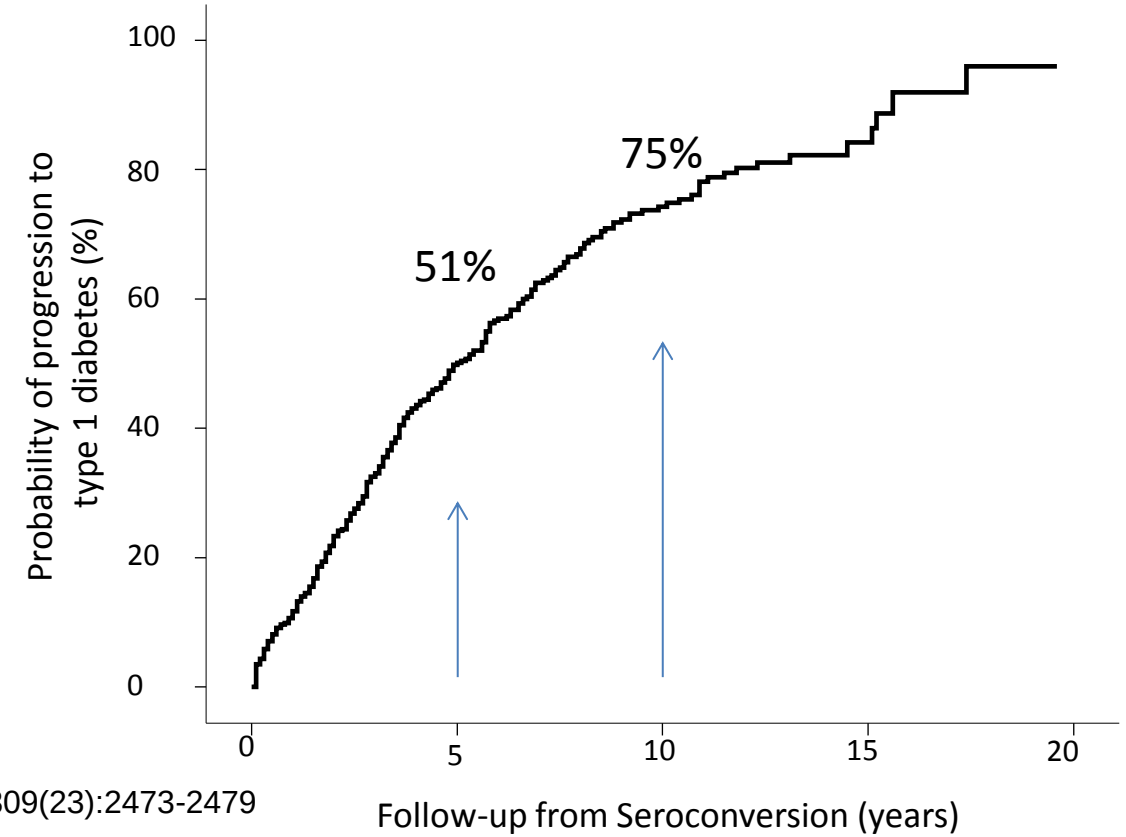
defining the early stages of type 1 diabetes T1D

Also in General Population Children



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

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**

Is Early Staging of T1D on a Public Health Level Feasible?

When ?

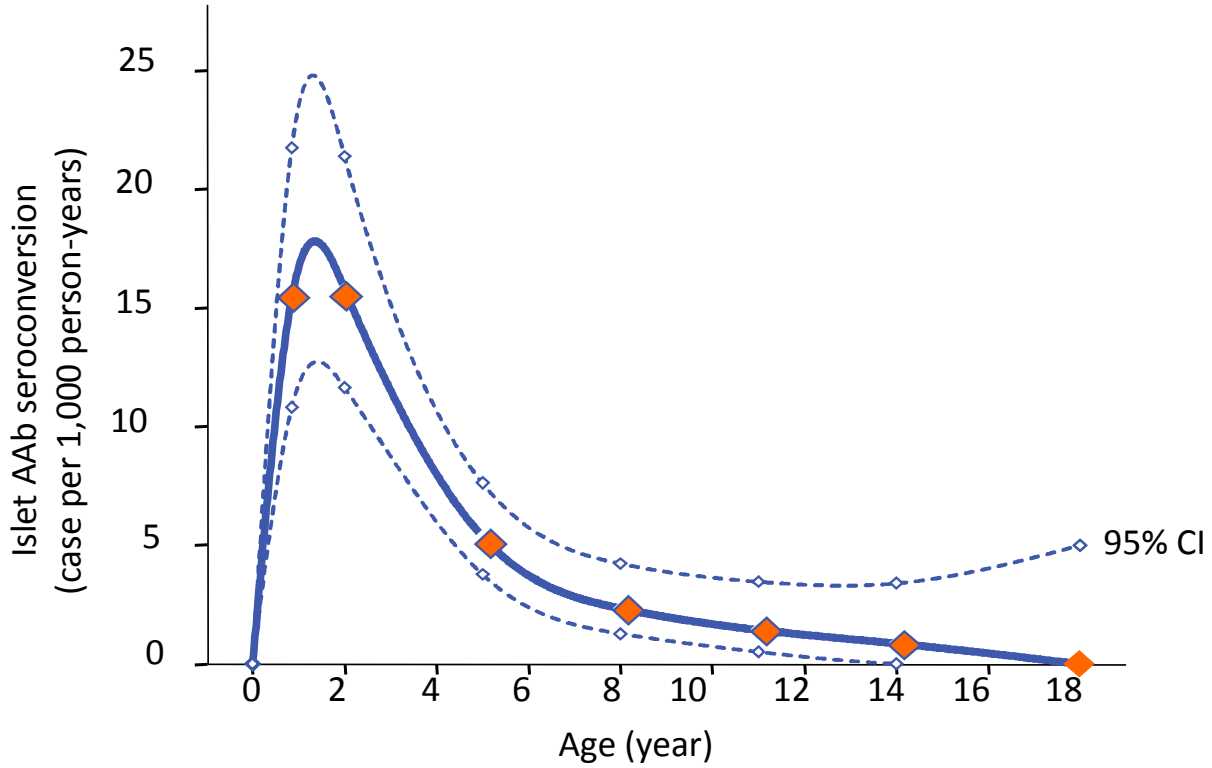
What test ?

Expected prevalence ?

Expected sensitivity ?

Multiple Islet Autoantibodies Are Detected Early in Life

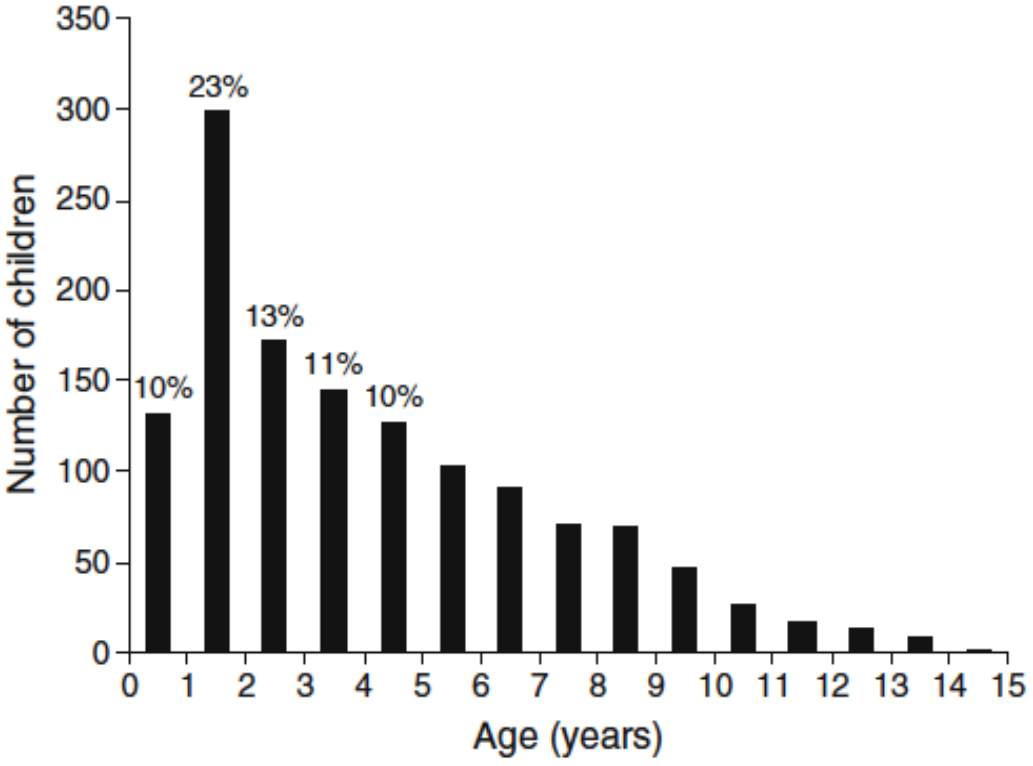
Incidence of islet autoantibodies in cases that become multiple Abs amongst unselected FDRs



Ziegler, Bonifacio, Diabetologia 2012

Also In The General Population

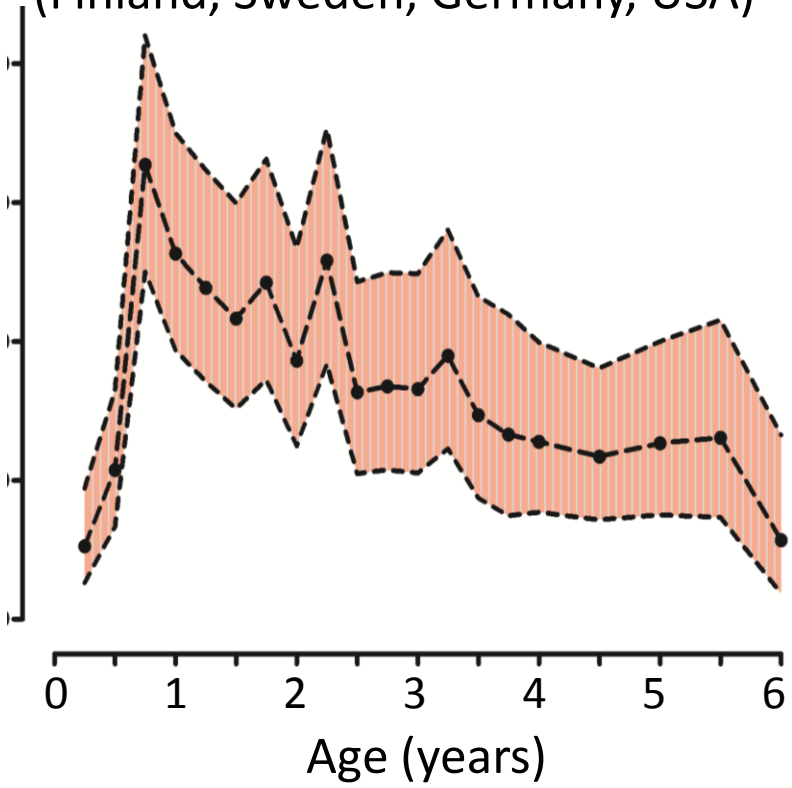
Finland



Parikka et al, 2012

TEDDY

(Finland, Sweden, Germany, USA)

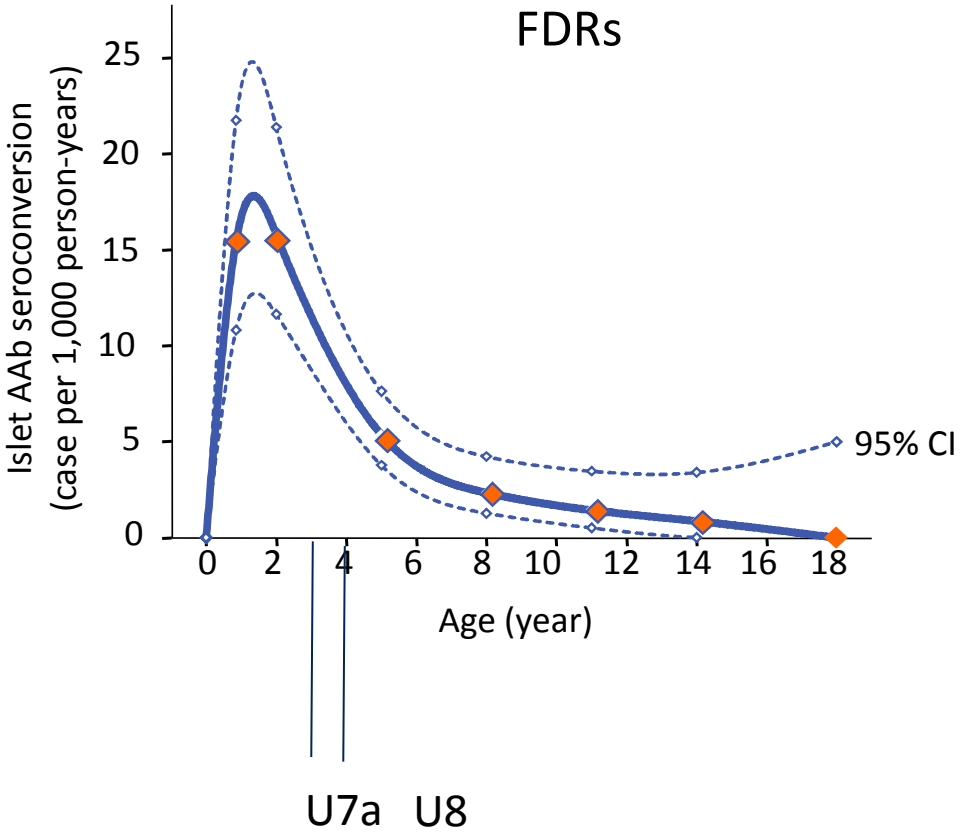


TEDDY study, IDS, 2013

defining the early stages of type 1 diabetes T1D

Age 3 and 4 years may be an optimal age for early staging

Incidence of islet autoantibodies in cases that become 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

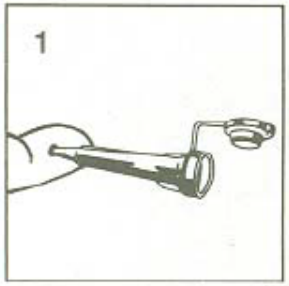
2/3 of multiples islet autoantibodies occur before age 4 years (JAMA).

11 % of youth T1D is before age 3 years

Ziegler, Diabetologia 2012

Validated Assay for Early Staging
(screening for multiple islet autoantibodies)

Capillary blood (200 µl) for combined measurement ELISA (RSR Ltd.):



- GAD65 antibody
- IA-2 antibody
- ZnT8 antibody

Negative
(99% - threshold set to 99th centile)

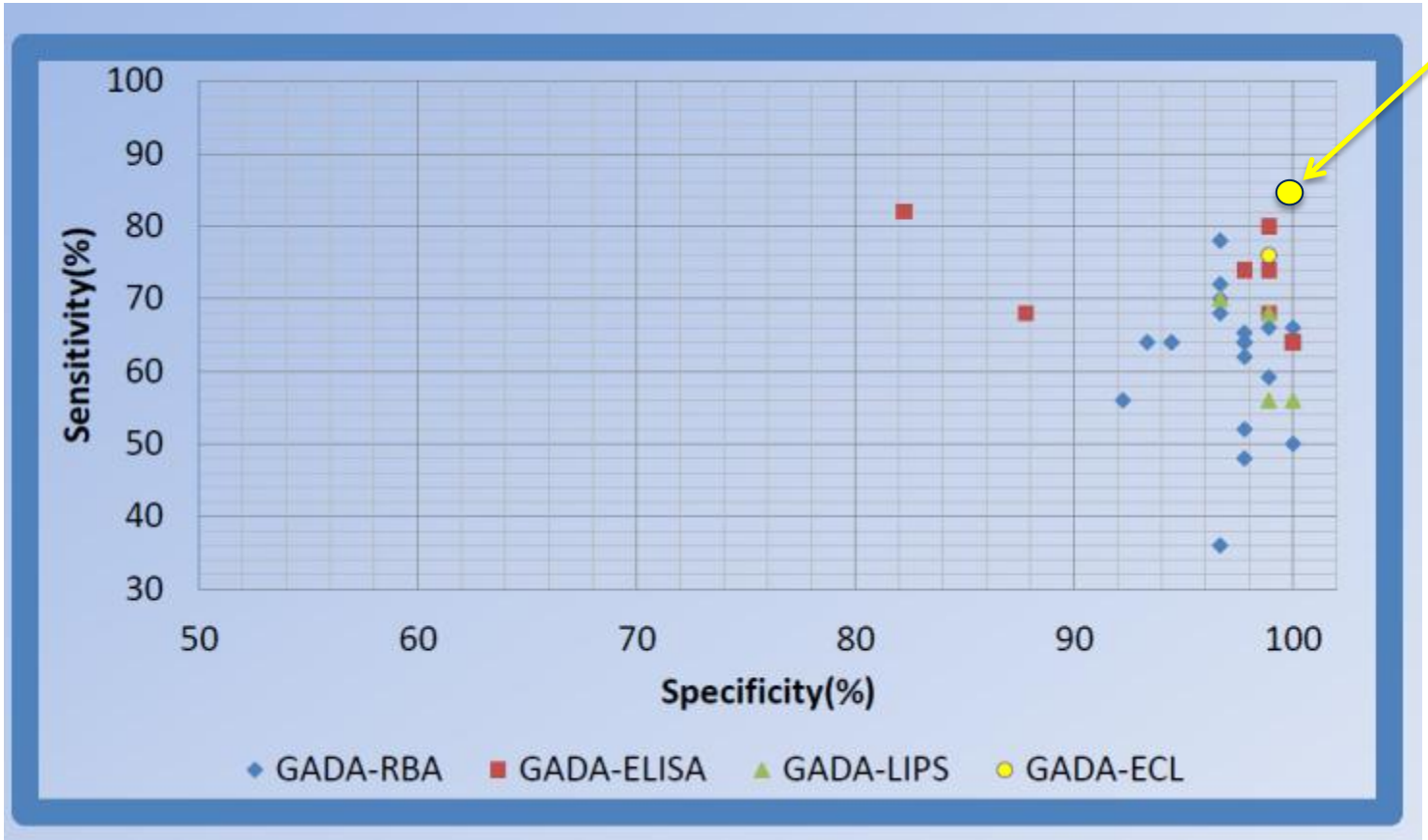
POSITIVE (1%)

Test IAA, GADA, IA-2A, ZnT8A in single assays*

**(Bonifacio et al., J Clin Endocrinol Metab 2010; Achenbach et al., Diabetologia 2009; Ziegler et al., Diabetes 1999).*

defining the early stages of type 1 diabetes T1D

Assay Performance of ELISA (RSR Ltd) for Combined Detection of GADA and IA2A (DASP/IASP workshops 2012)



GAD/IA2-ELISA (RSR)

defining the early stages of type 1 diabetes T1D

Estimated Prevalence of Multiple Islet Autoantibodies in General Population

Estimated prevalence at age 3-4 years:

0.3% or **300** children from 100,000 screened

Basis for estimate:

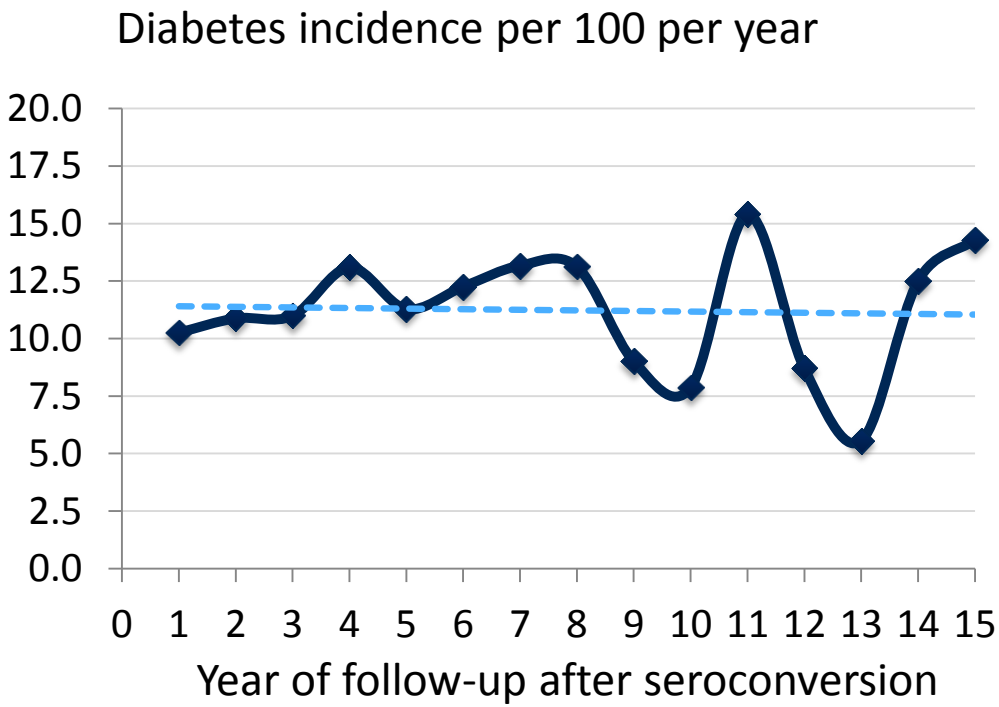
0.45% of children with diabetes between 3 and 20 years

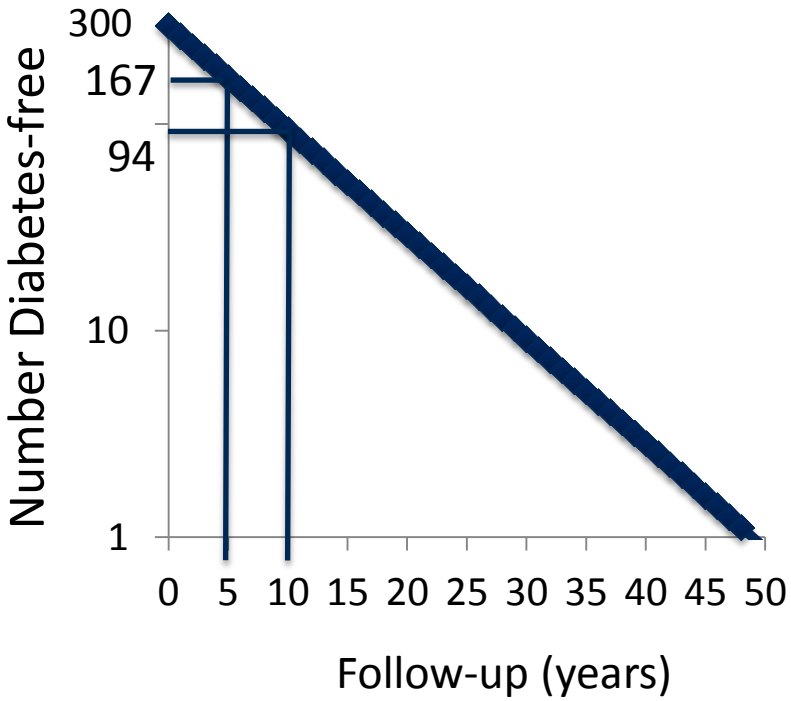
2/3 are positive for multiple islet autoantibodies by age 3-4

0.0045*100,000*0.667 = 300

Estimated Progression to Symptomatic T1D

Risk is persistently around 11% per year





defining the early stages of type 1 diabetes T1D

Design of Model Project Diabetes 2015

Fr1da
Typ 1 Diabetes: Früh erkennen – Früh gut behandeln

Information for pediatricians and parents:
Flyer, Public announcements, Bavarian Pediatric Convention

Screening: offered to all children in Bavaria at their U7a (age 3 years) und U8 (age 4 years) check-ups
Offered to 200,000 children in total (100,000 at U7a and 100,000 at U8)

Inclusion criteria:
- **Children living in Bavaria**
- **Written informed consent of one parent**
- **Capillary blood 200 µl**
- **Questionnaire (1 page)**

Estimated participation rate: 50% at U7a; 50% at U8
100,000 children (50,000 at U7a; 50,000 at U8)
Microvette and questionnaire
Shipment to IDF, HMGU
Islet autoantibody testing

Islet autoantibody negative: Ca 99,000 children

Positive in screening ELISA: Ca. 1,000 children

Separate measurement of IAA, GADA, IA2A, and ZnT8 by RBA in remaining serum

Negative or positive for only one antibody

Multiple islet autoantibodies: Ca 330

No written report will be sent

Confirmation sample requested (contact with pediatrician)

Separate measurement of IAA, GADA, IA2A, and ZnT8 by RBA

Ca 300: OGTT, HbA1c, Education and teaching, stress assessment, Check-up plan, comprehension test

Offer participation in Natural history and Prevention studies

Impact of Early Staging of T1D on a Public Health Level

- **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.

Summary:
Population Based Screening for Multiple Islet Autoantibodies at Age 3 or 4 years

100,000 children screened ⇨ 500 with T1D by age 20 years

⇩

300 detected positive

⇩

133 (44%) would develop T1D prior to age 8 – 9 years
(5 years of follow-up)
206 (69%) would develop T1D prior to age 13 – 14 years
(10 years of follow-up)
255 (85%) would develop T1D prior to age 20 years
(= 50% of all cases developing T1D before age 20 years)

defining the early stages of type 1 diabetes T1D

Dimelli and DPV Diabetes Register in Bavaria

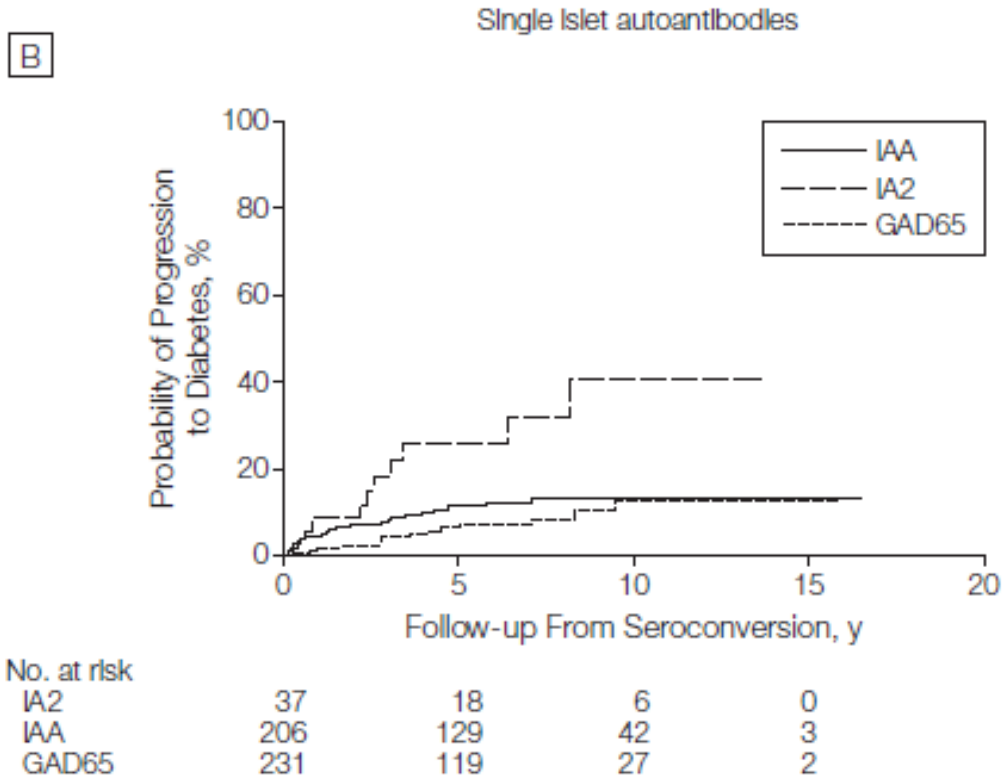
>95% of all diabetes cases before age 20 years in Bavaria are captured by Dimelli or DPV registers

Allows:

- validation of estimates
- Comparisons between screened and followed vs non-screened and non followed diabetes cases

What about children with single islet autoantibodies?

Certain single Ab positives have a risk



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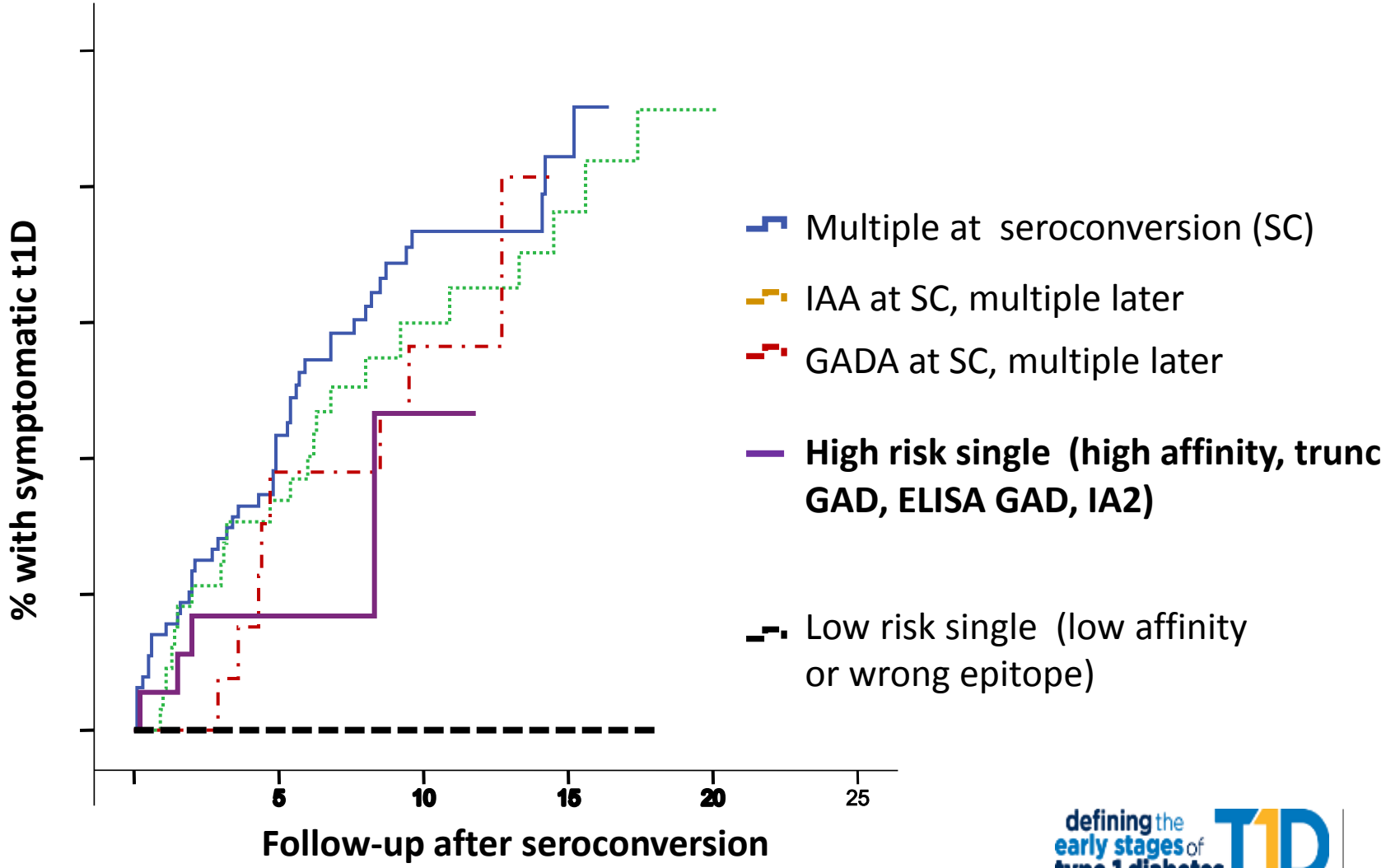
defining the early stages of type 1 diabetes T1D

What about children with single islet autoantibodies?

Certain single Ab positives have a risk



defining the early stages of type 1 diabetes T1D

Pre-selection by genetic testing ?
Feature Ranking of Type 1 Diabetes Susceptibility Genes For Improved Risk Prediction

HLA + 40 non-HLA SNPs → multivariable logistic regression and Bayesian feature selection

T1DGC cohort (training cohort)	
Patients n=4574	**Controls** n=1207

→ **Training** cohort

→ **Validation** cohort

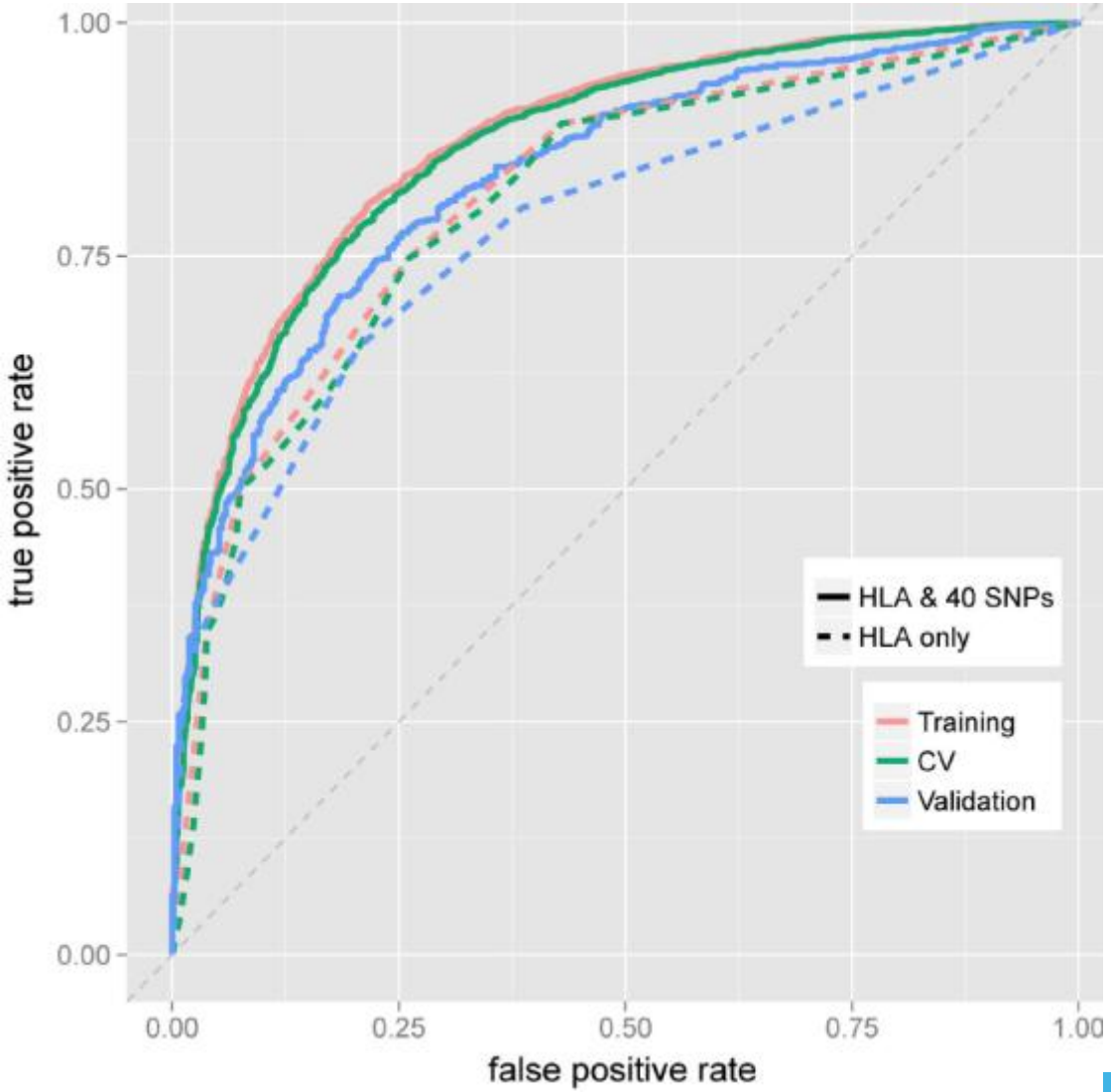
German validation cohort	
Patients n=765	**Controls** n=423

Winkler, Krumsiek, Diabetologia 2014

defining the early stages of type 1 diabetes T1D

Prediction of type 1 diabetes using HLA class II genotypes and 40 minor susceptibility genes

Higher discrimination when SNP genotyping of the 40 minor susceptibility genes was added to the HLA risk model (p value of increase: 2.6×10^{-11})

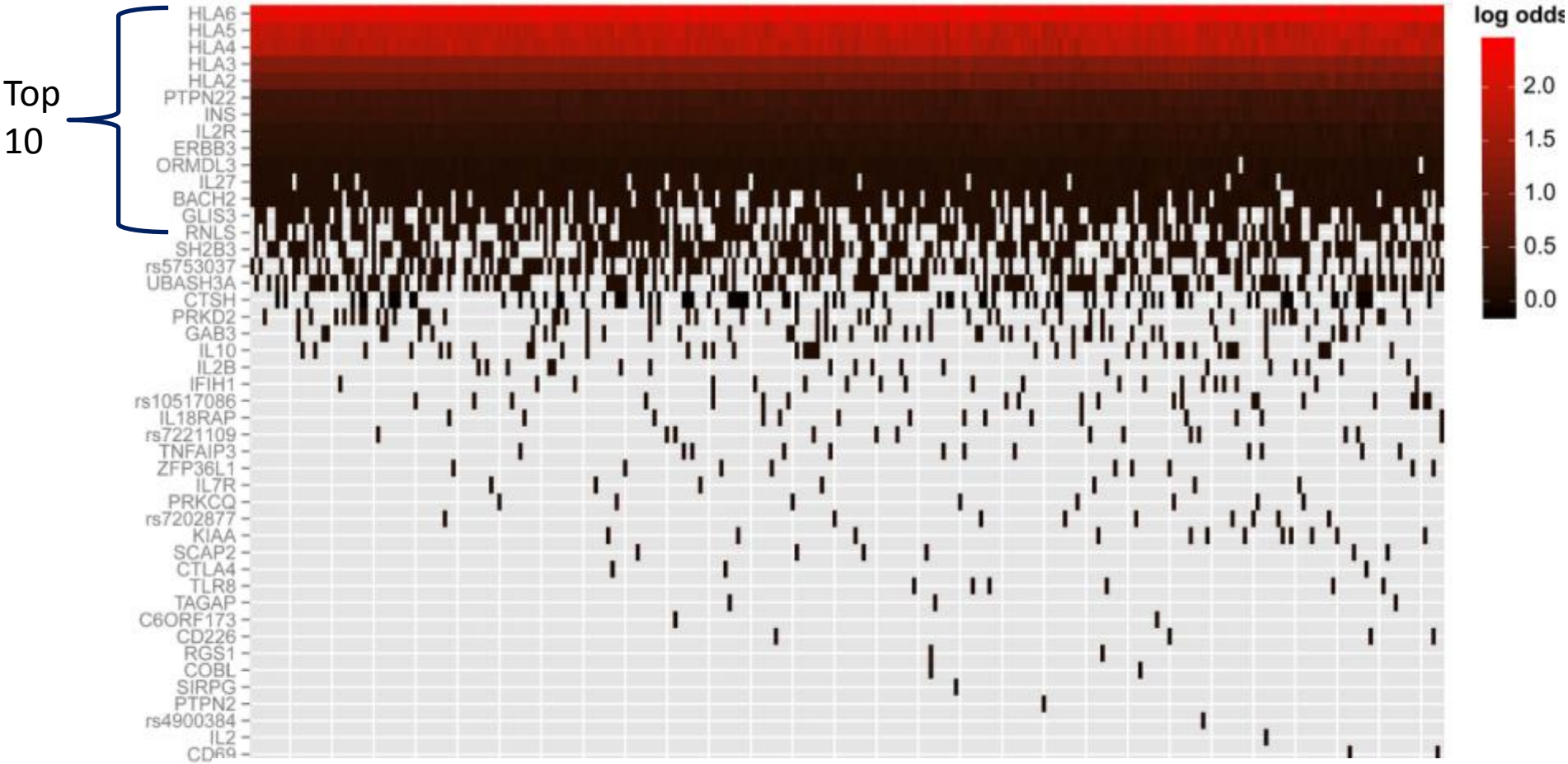


AUC

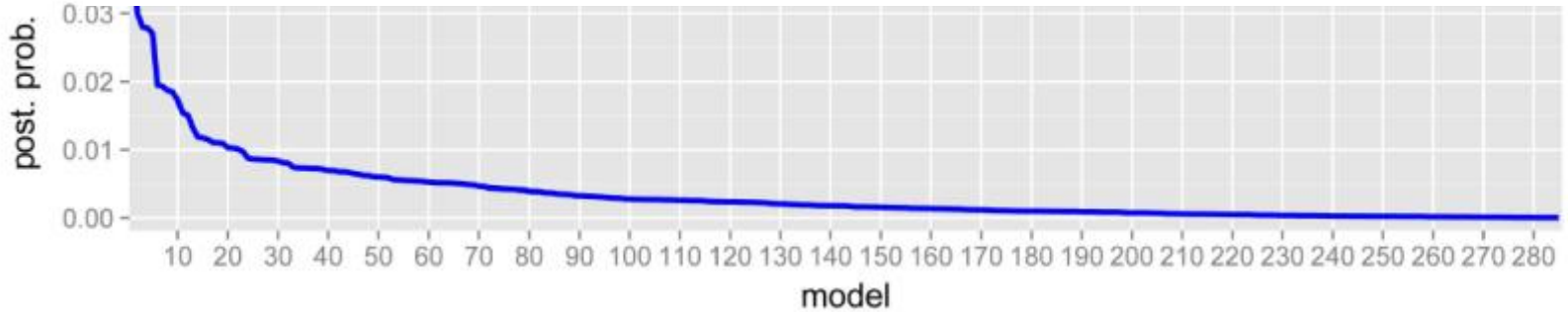
Model	**T1DGC cohort (Training)**	**10-fold cross-validation**	**Validation cohort**
HLA	0.82	0.81	0.78
HLA + 40 SNPs	0.87	0.87	0.84

defining the early stages of type 1 diabetes T1D

Selection of a reduced set of SNPs with comparable prediction quality
Feature ranking



top 10 model: *HLA, PTPN22, INS, IL2R, ERBB3, ORMDL3, BACH2, IL27, GLIS3, RNLS*



Population Based Screening
Application of the Top 10 Model

10 SNP set: *HLA*, *PTPN22*, *INS*, *IL2R*, *ERBB3*, *ORMDL3*, *BACH2*, *IL27*, *GLIS3*, *RNLS*

Screening with the top 10 model

100,000 children screened
(99,500 no diabetes, 500 develop diabetes)

At threshold selecting 0.5% of controls (risk score of >0.97)
618 selected

120 (19.5%) would develop T1D prior to age 20 years

24% of all cases

72 will develop islet antibodies by age 3 years

Population Based Screening
Application of the Top 10 Model

10 SNP set: *HLA*, *PTPN22*, *INS*, *IL2R*, *ERBB3*, *ORMDL3*, *BACH2*, *IL27*, *GLIS3*, *RNLS*

Screening with the top 10 model

100,000 children screened
(99,500 no diabetes, 500 develop diabetes)

At threshold selecting 2.5% of controls (risk score of >0.95)
2654 selected

167 (6.3%) would develop T1D prior to age 20 years

33% of all cases

100 will develop islet antibodies by age 3 years

defining the early stages of type 1 diabetes T1D

Helmholtz Zentrum Munich /Forschergruppe Diabetes eV

Peter Achenbach
Christiane Winkler
Andreas Beyerlein
Florian Haupt
Ramona Puff
Jan Krumsiek
Fabian Theis

Center for Regenerative Therapies Dresden

Ezio Bonifacio
Anne Eugster

Collaborators

Marian Rewers and DAISY team
Olli Simell and DIPP team
John Todd

defining the early stages of type 1 diabetes

Screening for Risk of T1D: Relatives of Individuals with T1D

Carla Greenbaum

Diabetes TrialNet and Benaroya Research Institute

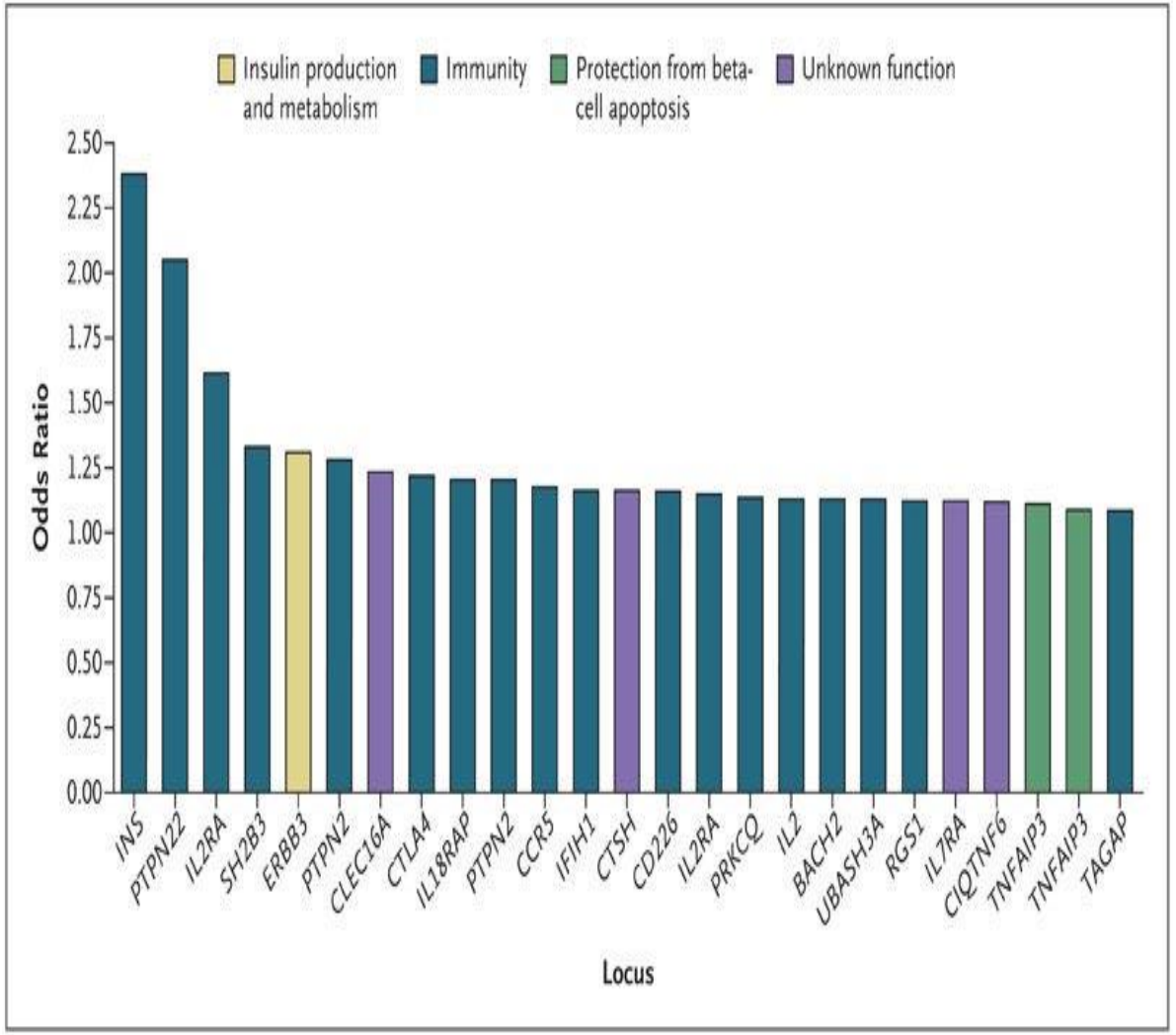
Agenda

- Rational for testing relatives
- Historical perspective: Diabetes Prevention Trial
  - Primary results
  - Key information about Natural History of Disease
- Current screening for risk: Diabetes TrialNet
  - Scope of screening effort
  - Algorithm to determine risk
  - Clinical Trial Enrollment

Why Test Relatives?

- Comprehensive “genetic” screening
  - Assumption that T1D genes are enriched in families, both those we know and don’t know
- Knowledge and experience about living with T1D
  - Assumption that family members are most committed to finding a cure and prevention strategy
- Several decades of robust data about the pre-clinical natural history of disease
- Relative risk of disease ~15X higher than risk in general population

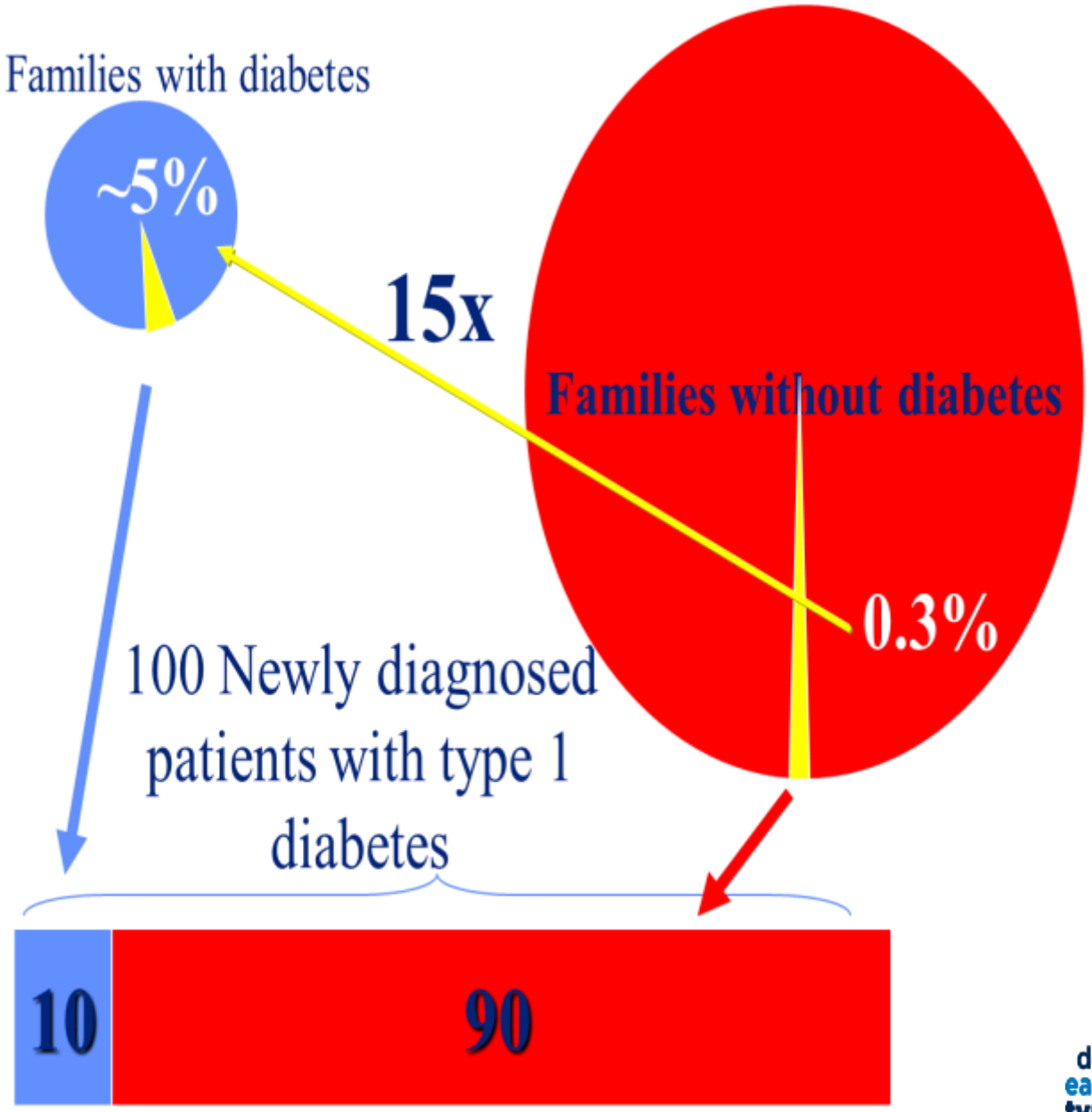
T1D non-HLA Genetic Associations



Why NOT test relatives?

- ~85-90% of those who will get T1D do NOT have a relative with T1D

RATIONALE FOR TESTING RELATIVES



Diabetes Prevention Trial (DPT-1)

- AIM: Identify relatives at risk for T1D to enroll in one of two randomized clinical trials testing:
- Can parenteral insulin delay or present the onset of T1D in those at high risk of disease?
- Can oral insulin delay or prevent the onset of T1D in those at intermediate risk of disease?

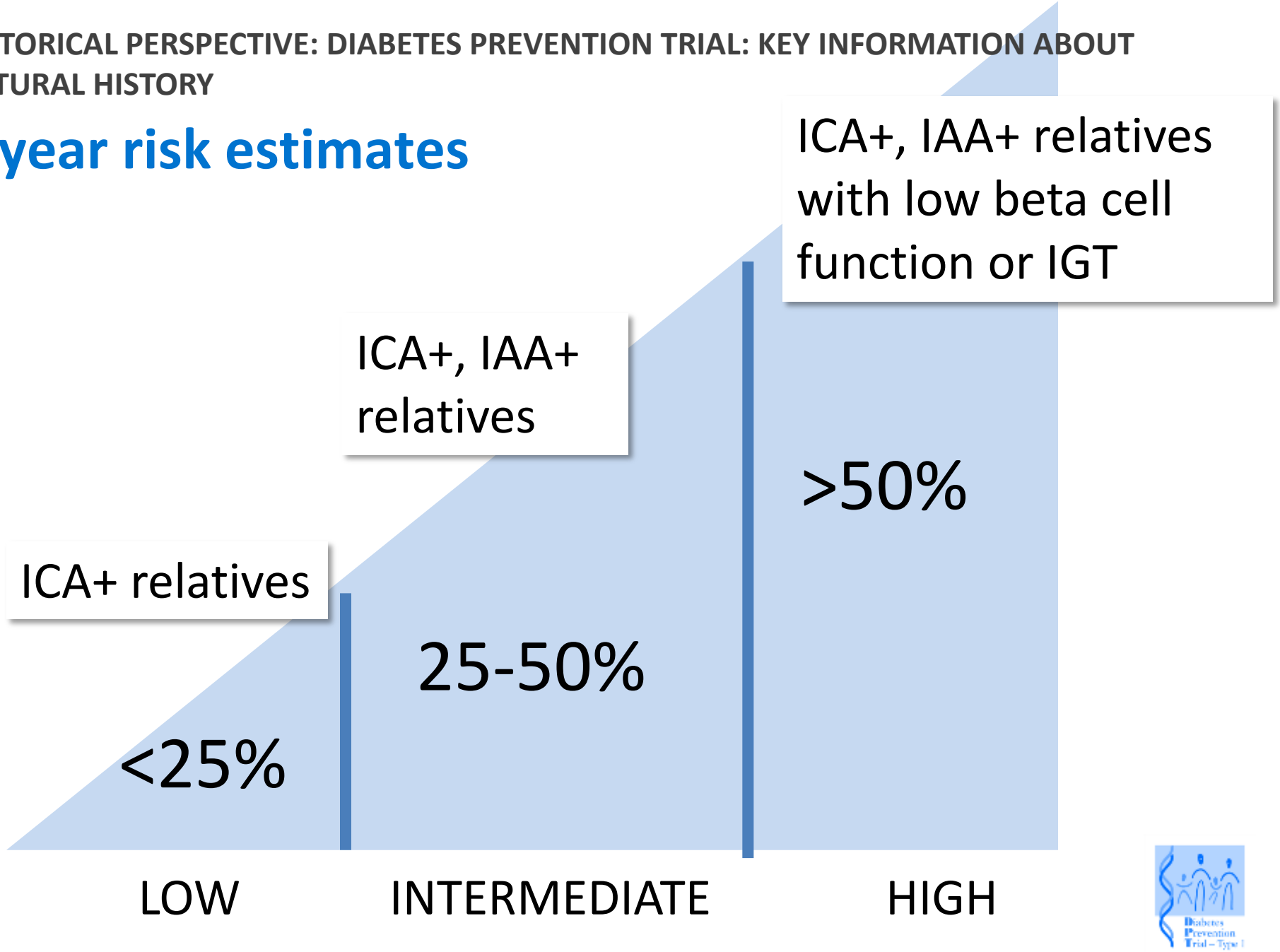
Diabetes Prevention Trial (DPT-1)

- Begun in early 1990's using "state of the art" antibody testing
  - Islet cell antibodies (ICA)
  - Insulin autoantibodies (IAA)
- Tested 103,391 relatives over 8 years for presence of ICA and IAA → Antibody positive: 3,483
- N= 339 (high 5 year risk >50%) randomized in Parenteral Insulin Trial and N=372 (intermediate 5 year risk 25-50%) randomized in Oral Insulin Trial
- Primary Results: Neither Parenteral or Oral Insulin delayed or prevented onset of disease

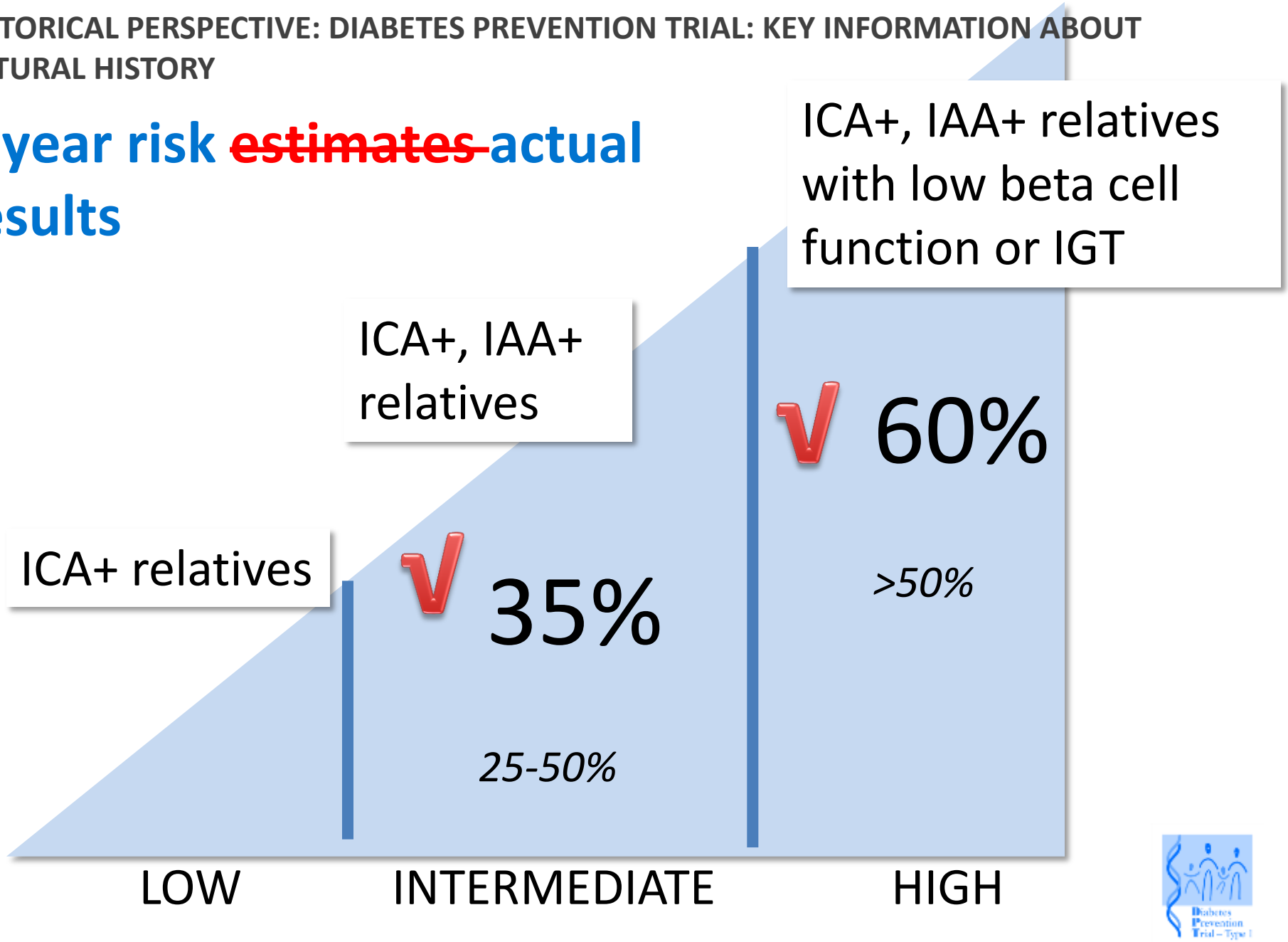
Diabetes Prevention Trial (DPT-1)

- Increased knowledge despite negative trials: Laying the groundwork for future studies

5-year risk estimates



5-year risk ~~estimates~~ actual results



TYPE 1 DIABETES TRIALNET

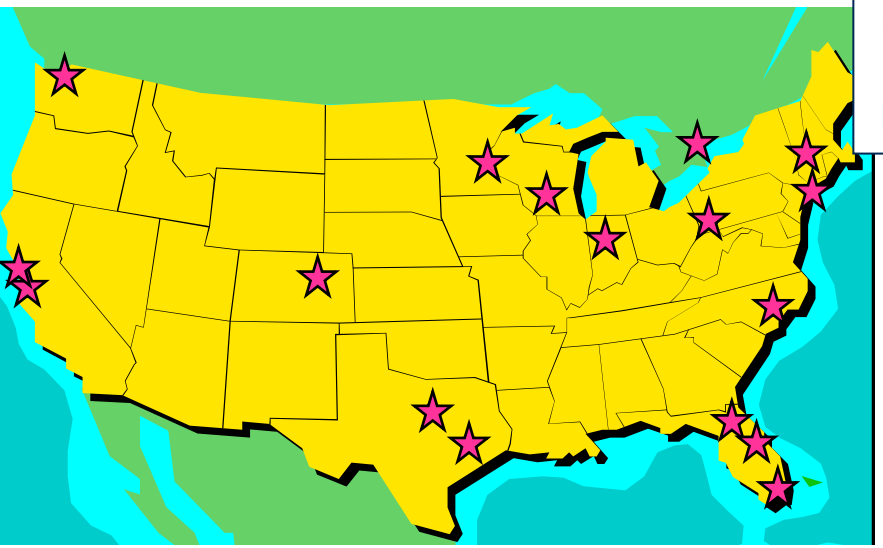
TrialNet Goals

- Delay, prevent, or modify the course of T1D
  - Explore new therapies in:
    - Secondary prevention – antibody-positive relatives “at risk” of T1D
    - Primary prevention – high genetic risk infants
    - New-onset T1D
- Further define epidemiology, natural history, and risk factors of T1D
- Advance translational science to lay groundwork for future generations of trials and future clinical use

CURRENT SCREENING FOR RISK: DIABETES TRIALNET: SCOPE OF SCREENING EFFORT

Type 1 Diabetes TrialNet

NORTH AMERICA



AUSTRALIA

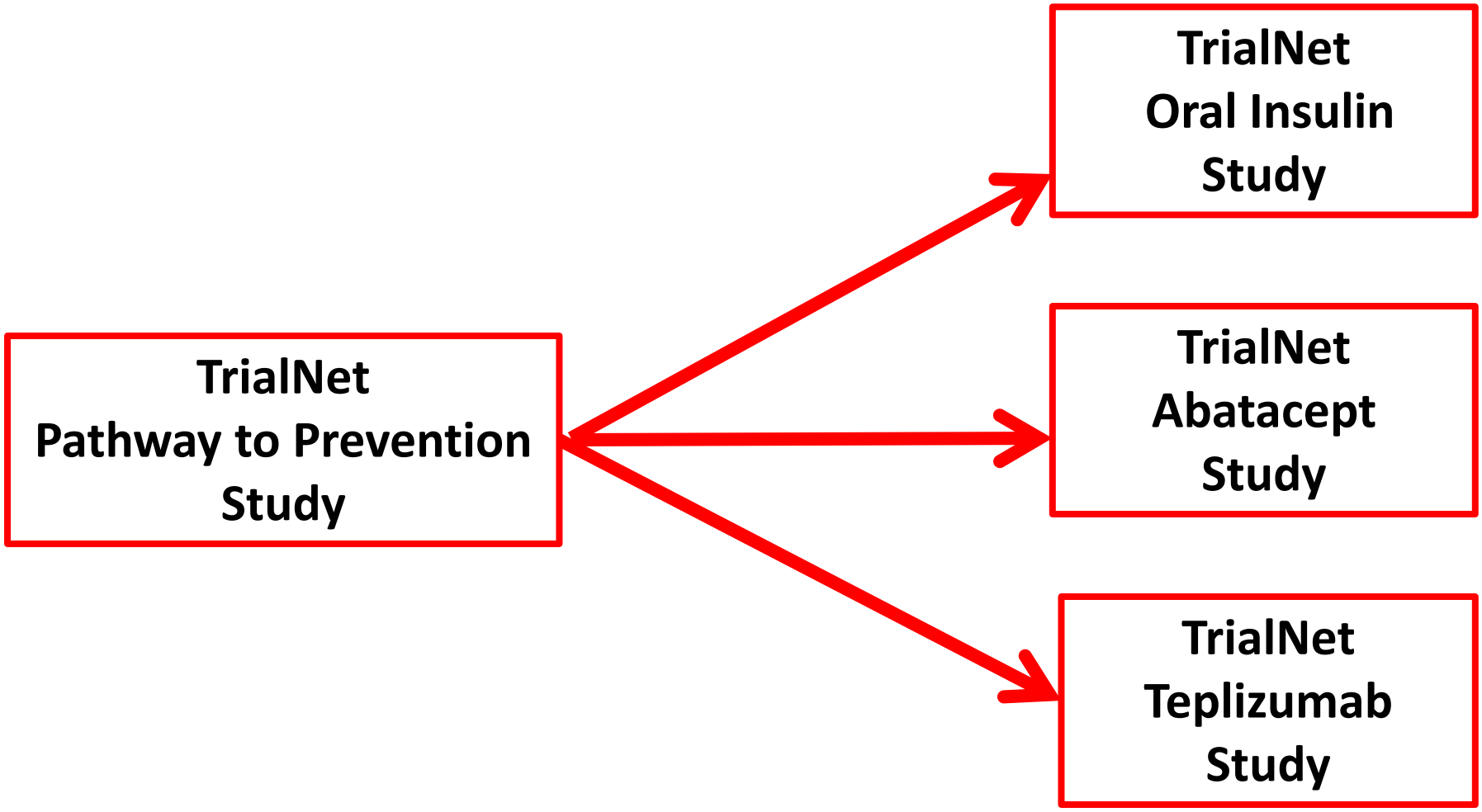
FINLAND + Sweden

UNITED KINGDOM

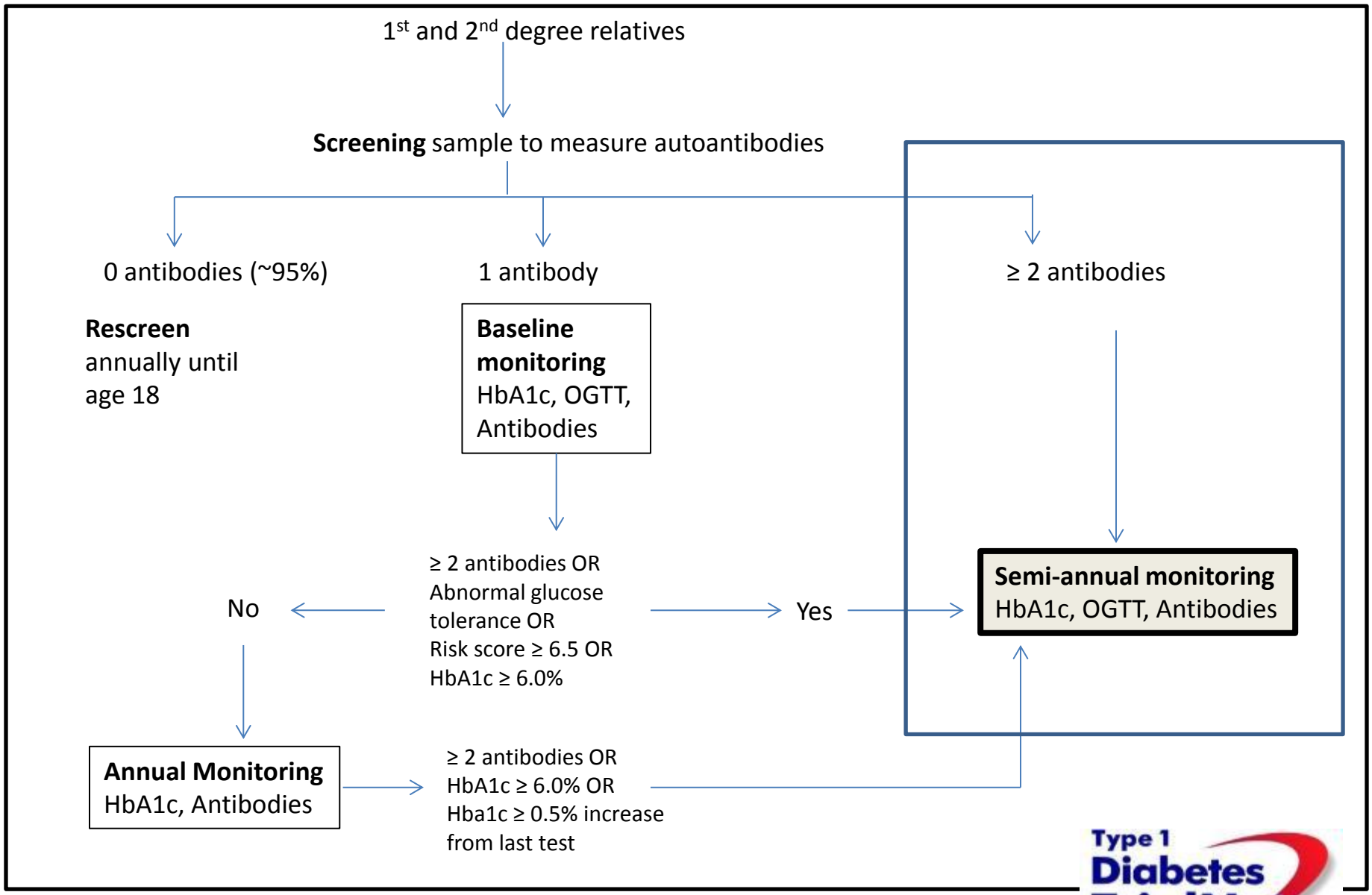
ITALY + Germany

PREVENTION

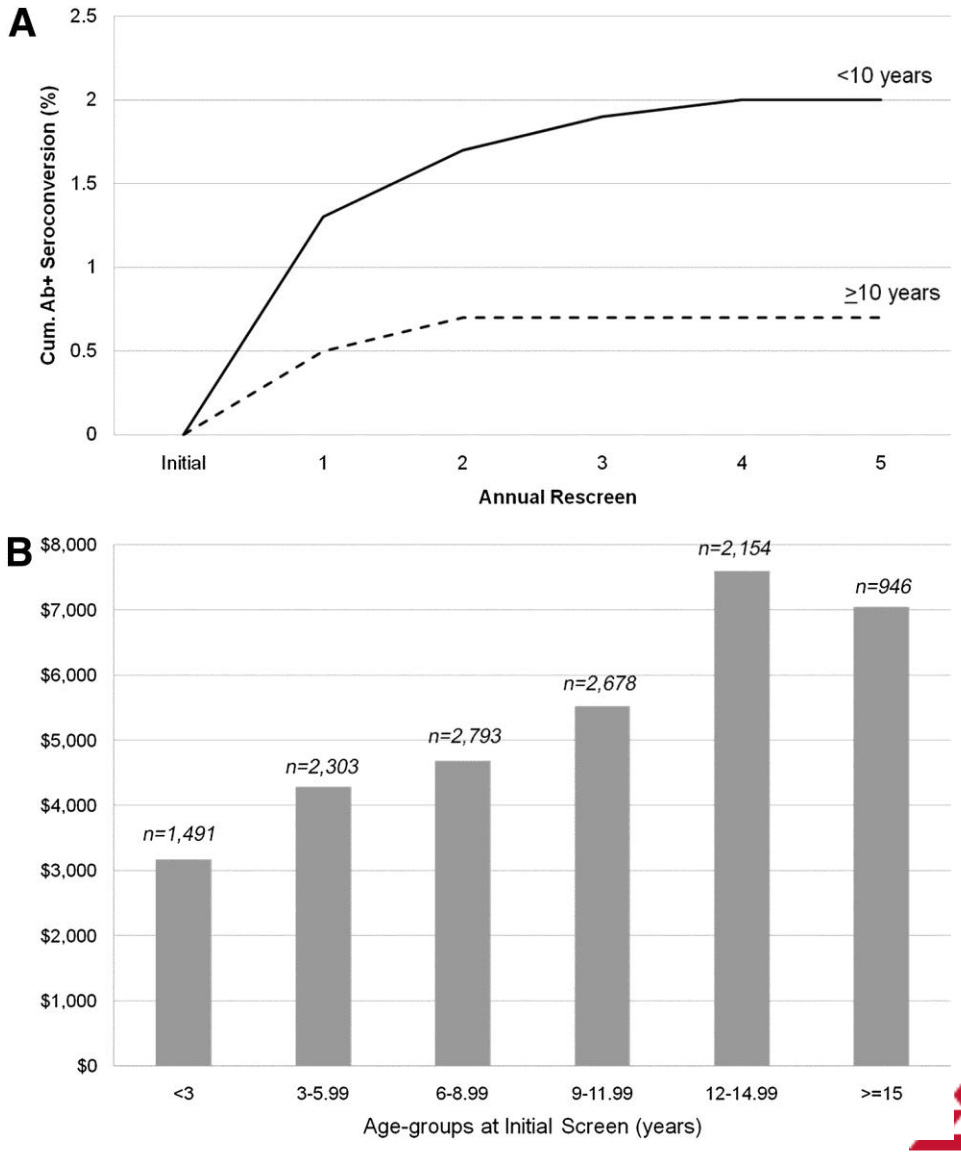
TrialNet Prevention Studies



CURRENT SCREENING FOR RISK: DIABETES TRIALNET: ALGORITHM TO DETERMINE RISK



TNNHS: Cumulative Ab seroconversion by annual rescreen number by age (A) and cost of rescreening by age at initial screen (B).



American Diabetes Association.

Vehik K et al. Dia Care 2011;34:1897-1901

American Diabetes Association.

Consensus Conference

Exploring the Drug Development Pathway for Type 1 Diabetes in the Pediatric Population

Co-Chairs: Carla Greenbaum, MD and Diane Wherrett, MD, FRCPC

WHEN:
January 14, 2015
8:30 am - 4 pm EST

LOCATION:
Hilton Mark Center
5000 Seminary Road
Alexandria, VA 22311

OPEN REGISTRATION:
To register, please contact Sonya Pendleton at spendleton@diabetes.org or 703.549.1500 ext. 2311 by **December 1, 2014**

STATEMENT OF NEED

Despite medical advances, type 1 diabetes (T1D) remains a significant burden on individuals with T1D and their families; thus there is need for disease modifying therapy. While autoimmune diabetes occurs in all age groups, emerging data highlights important differences in pathophysiology and clinical course according to age at diagnosis. Consequently, the effectiveness of disease modifying treatments is expected to be different between children and adults. Understanding the development and regulatory pathways for T1D disease modifying therapies according to age will enable industry, academia, funders, advocacy organizations, and regulators to collectively translate new science to clinical care.

OBJECTIVES

The objectives for this Consensus Conference are to characterize the fundamental differences in T1D between children and adults and to propose a thoughtful approach for developing disease modifying therapeutics in children before or after the onset of clinical T1D; encompassing a development and regulatory pathway considering both safety and efficacy. It is the intent that the Consensus Conference Report will be published in Diabetes Care and notable pediatric journals.

SPONSORED BY

American Diabetes Association. · JDRF · T1D Exchange · Benaroya Research Institute at Virginia Mason

IN COLLABORATION WITH

Type 1 Diabetes TrialNet · Immune Tolerance Network

TrialNet Pathway to Prevention

Group	Five-year risk of T1D
0 ab+	< 1%
1 ab+, NGT	3%
≥ 2ab+, NGT	35%
≥ 2ab+, AGT (dysglycemia)	75-80%

Type 1 Diabetes TrialNet

TrialNet Pathway to Prevention

Group	Five-year risk of T1D	Prevention Trial
0 ab+	< 1%	Not currently eligible; rescreen until age 18
1 ab+, NGT	3%	Not currently eligible; annual monitoring

Type 1 Diabetes TrialNet

TrialNet Pathway to Prevention

Group	Five-year risk of T1D	Prevention Trial
≥ 2ab+, NGT	35%	Oral Insulin (if mIAA+) Abatacept
≥ 2ab+, AGT (dysglycemia)	75-80%	Teplizumab

Type 1 Diabetes TrialNet

defining the early stages of type 1 diabetes

Screening for Risk of T1D: Relatives of Individuals with T1D

Thank You

defining the early stages of type 1 diabetes

T1D

Predicting Rate of Progression to Type 1 Diabetes

Jeffrey Krischer

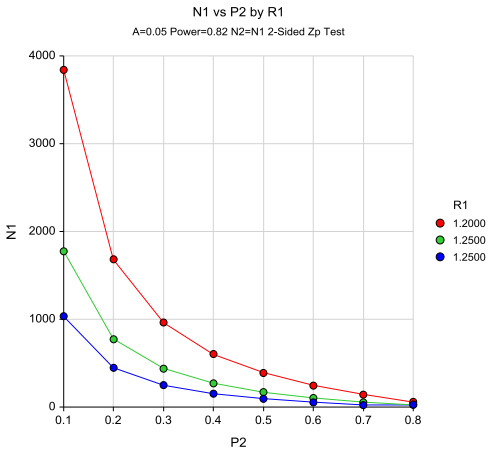
University of South Florida

Why predict rates of progression?

- Identifying a population with elevated rate of progression allows the test of interventions to alter disease progression.

  Need to identify high risk population to justify high risk interventions.

- It is easier to measure the effect of an intervention in a higher risk population.



But we already know how to predict who is susceptible to get T1D

- Genetics — Human leukocyte antigen (HLA) class II genes
- Age — 4-7 and 10-14 years
- Family History
- Geography

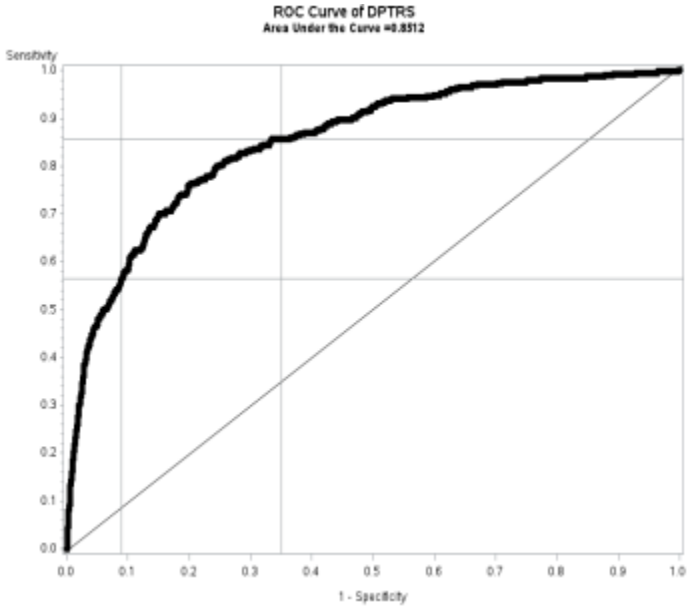
Biomarkers

- Immunologic — ICA, GAD, IA2, IA, ZnT8
- Metabolic — Insulin, glucose, C-peptide, HbA1c

The appearance of these markers, either singly or in combination predicts the risk and the rate of T1D development.

The problems of sensitivity and specificity

- Markers that are more specific, P(D|M), are generally less sensitive: P(M|D) is low.
- Is this a generalizability problem?



The problem of sensitivity and specificity

- Markers that are more specific, P(D|M), are often less frequent: P(M) is low.

$$P(D|M) = P(M|D)\,P(D)/\,P(M)$$

as $P(D|M) \rightarrow 1$,
then $P(M) \rightarrow P(D)$

- This is a cost problem requiring screening large numbers.

An Example from TEDDY

Human leukocyte antigen eligibility for First Degree Relatives (FDR) and General Population (GP) newborns:

Haplotype genotypes	Abbreviation	FDR	GP
*DR4-DQA1*030X-DQB1*0302/DR3-DQA1*0501-DQB1*0201*	*DR3/4*	Y	Y
*DR4-DQA1*030X-DQB1*0302/DR4-DQA1*030X-DQB1*0302*	*DR4/4*	Y	Y
*DR4-DQA1*030X-DQB1*0302/DR8-DQA1*0401-DQB1*0402*	*DR4/8*	Y	Y
*DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201*	*DR3/3*	Y	Y
*DR4-DQA1*030X-DQB1*0302/DR4- DQA1*030X-DQB1*020X*	*DR4/4b*	Y	N
*DR4-DQA1*030X-DQB1*0302/DR1- DQA1*0101-DQB1*0501*	*DR4/1*	Y	N

An Example from TEDDY

	Specificity	Sensitivity
DR 3/4 or DR 4/4	97%	39%
9 TEDDY Genotypes (FDR)	90%	69%
4 TEDDY Genotypes (GP)	94%	50%

An Example from TEDDY

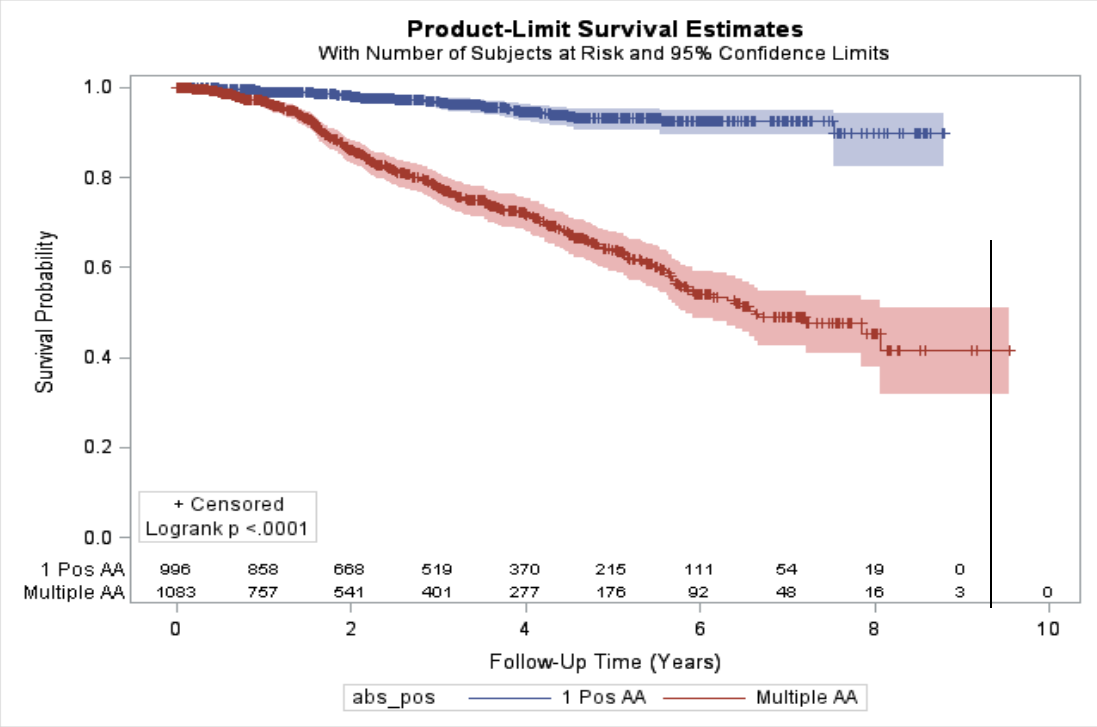
	Specificity	Sensitivity	P(M)
DR 3/4 or DR 4/4	97%	39%	2.9%
9 TEDDY Genotypes (FDR)	90%	69%	22%
4 TEDDY Genotypes (GP)	94%	50%	4.8%

Markers of Diabetes Risk

Family history	Risk	Prevalence
None	0.3%	85%
Some	3-5%	15%
1st degree		
• Multiple affected	20-50%	
• Sib	8%	
• Identical Twin	30-70%	
• Offspring	3-5%	

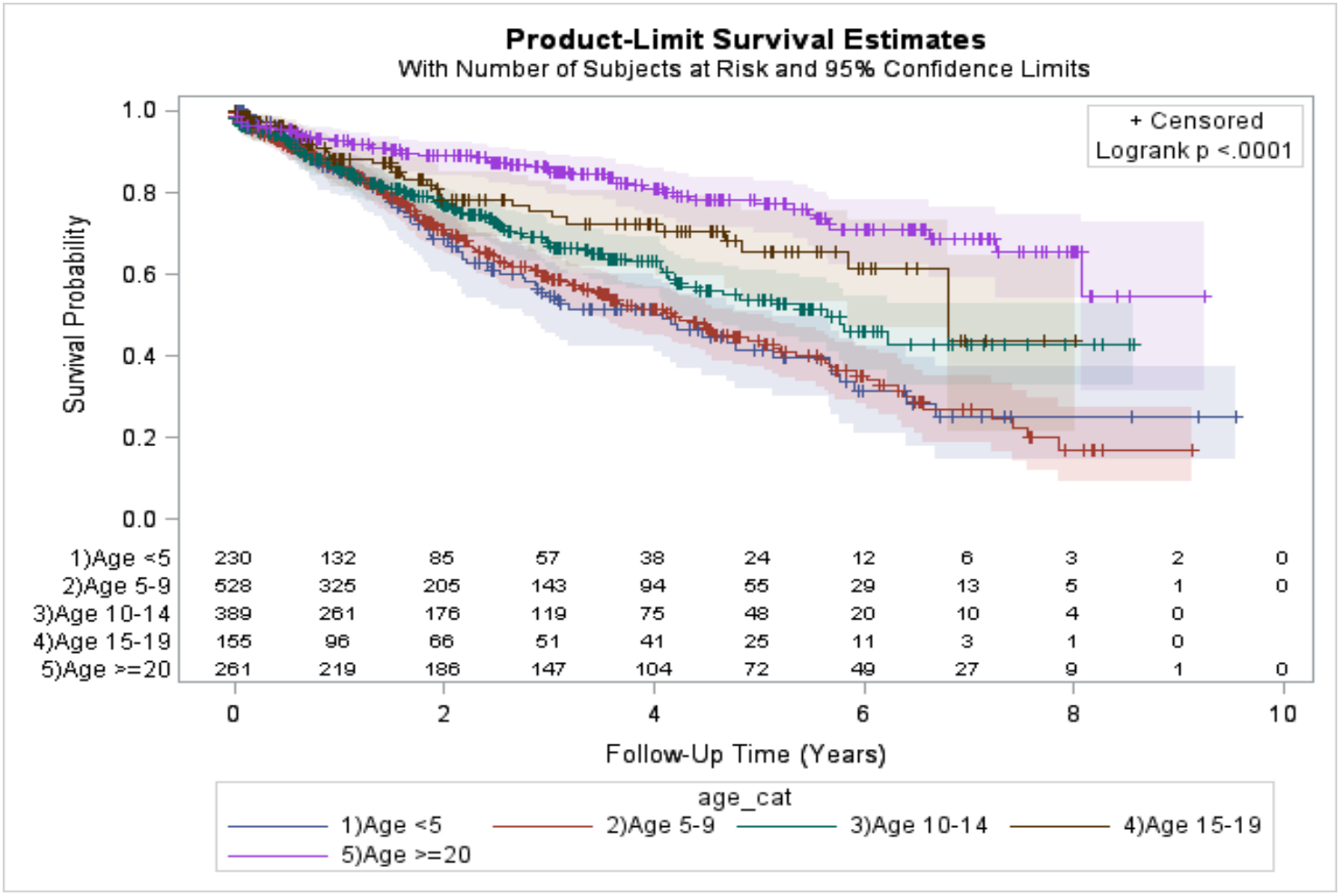
Immune Markers of Symptomatic Diabetes Risk in First Degree Relatives

	5-Year Risk	Prevalence
▪ Single antibody	<10%	3.1%
▪ Multiple antibodies	30-50%	2.2%



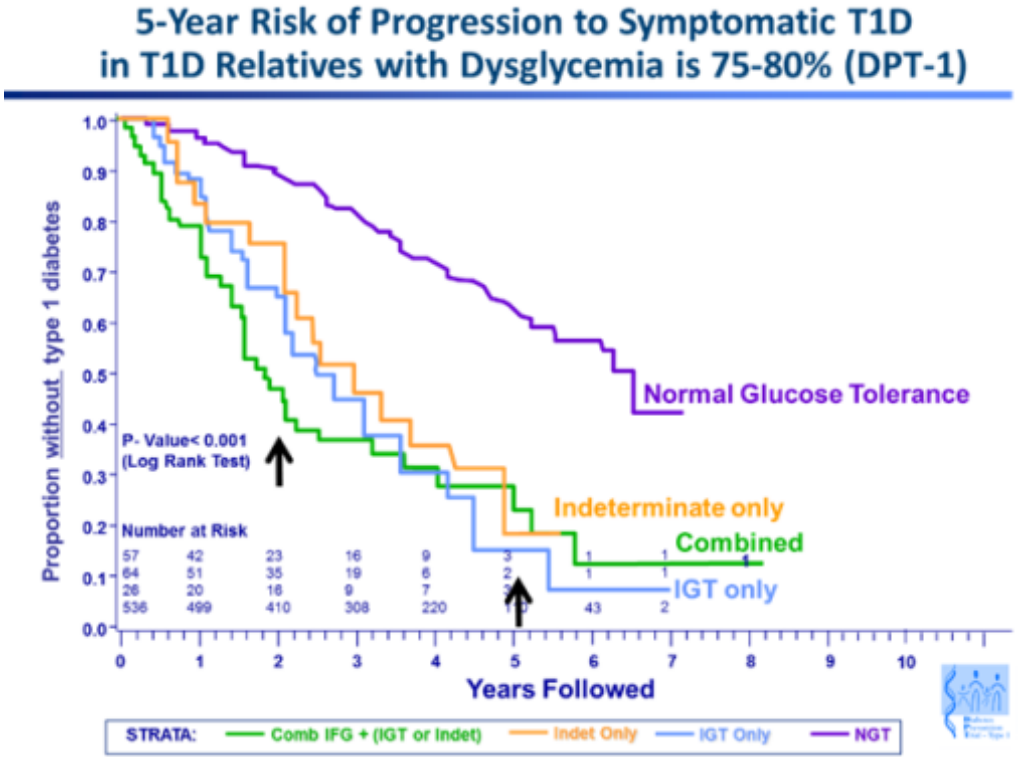
Even in the presence of other risk markers, age is important.

T1D-free curves by age categories among first degree relatives with multiple autoantibodies.

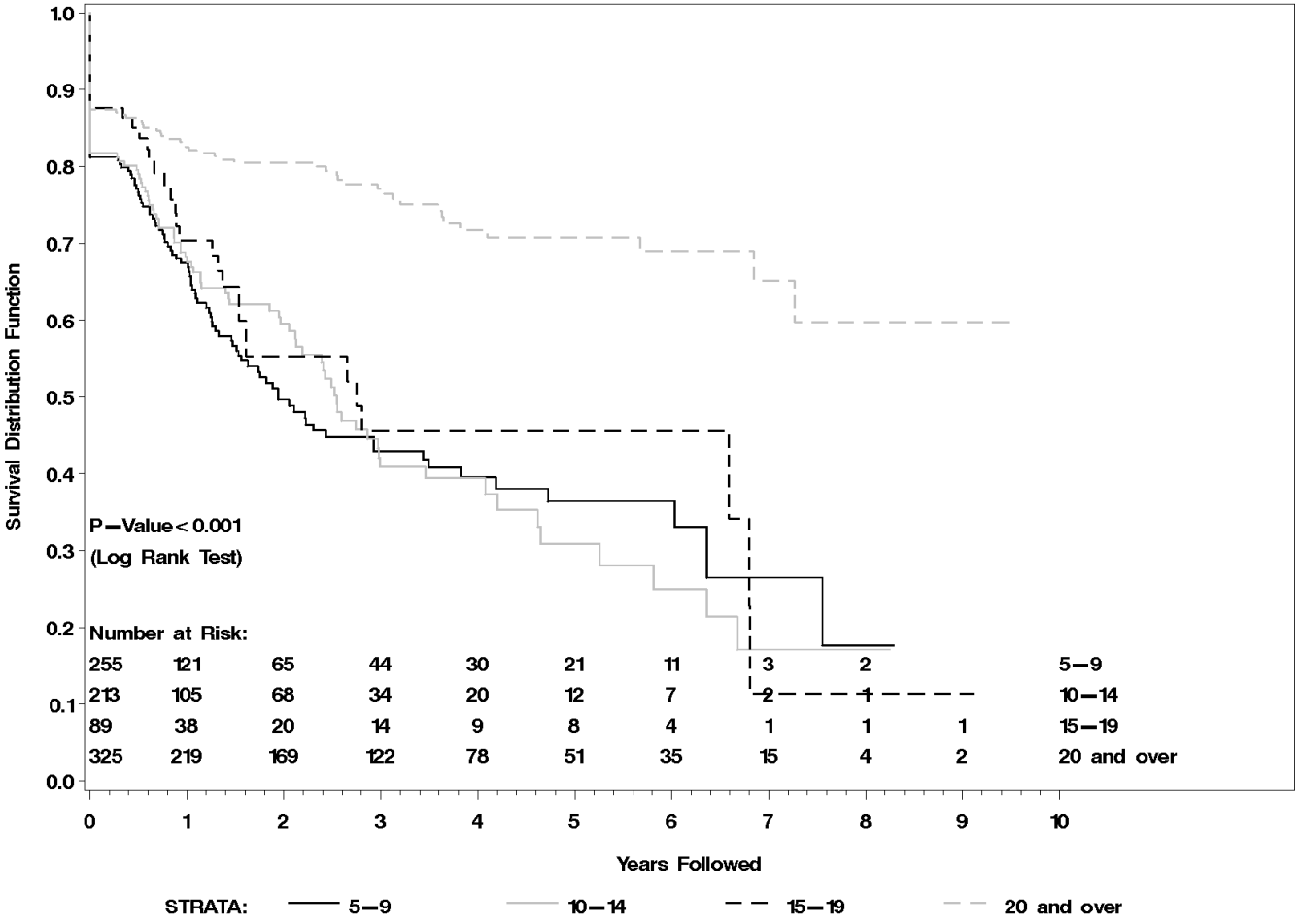


Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

	5-Year Risk	Prevalence
▪ Abnormal Oral Glucose Tolerance Test	75-80%	0.7%



Again, age is a modifying factor.



HbA1c vs. T1D

Is HbA1c 6.5% a good threshold?

N=587

	T1D+ by OGTT	T1D- by OGTT	
HbA1c >=6.5	32	11	43
HbA1c <6.5	103	441	544
	135	452	587

N=554 with multiple pairs from same patient

Sensitivity = 23.7%
Specificity = 97.6%
PPV = 0.74

N=734

	T1D+ by OGTT	T1D- by OGTT	
HbA1c >=6.5	18	2	20
HbA1c <6.5	50	664	714
	68	666	734

N=676 with multiple pairs from same patient

Sensitivity = 26.4%
Specificity = 99.7%
PPV = 0.90

N=426*

	T1D+ by OGTT **or Physician**	T1D- by OGTT	
HbA1c >=6.5	5	0	5
HbA1c <6.5	8	413	421
	13	413	426

N=10 with multiple pairs from same patient

Sensitivity = 38.5%
Specificity = 100.0%
PPV = 1.0

* Control arm only

HbA1c vs. T1D

Is HbA1c 5.7% a good threshold?

N=587

	T1D+ by OGTT	T1D- by OGTT	
HbA1c >=5.7	99	209	308
HbA1c <5.7	36	243	279
	135	452	587

N=554 with multiple pairs from same patient

Sensitivity = 73.3%
Specificity = 53.8%
PPV = 0.32

Type 1 Diabetes TrialNet

N=734

	T1D+ by OGTT	T1D- by OGTT	
HbA1c >=5.7	44	63	107
HbA1c <5.7	24	603	627
	68	666	734

N=676 with multiple pairs from same patient

Sensitivity = 64.7%
Specificity = 90.5%
PPV = 0.41

TRIGR

N=426*

	T1D+ by OGTT **or Physician**	T1D- by OGTT	
HbA1c >=5.7	6	46	52
HbA1c <5.7	7	367	374
	13	413	426

N=10 with multiple pairs from same patient

Sensitivity = 46.2%
Specificity = 88.9%
PPV = 0.12

* Control arm only

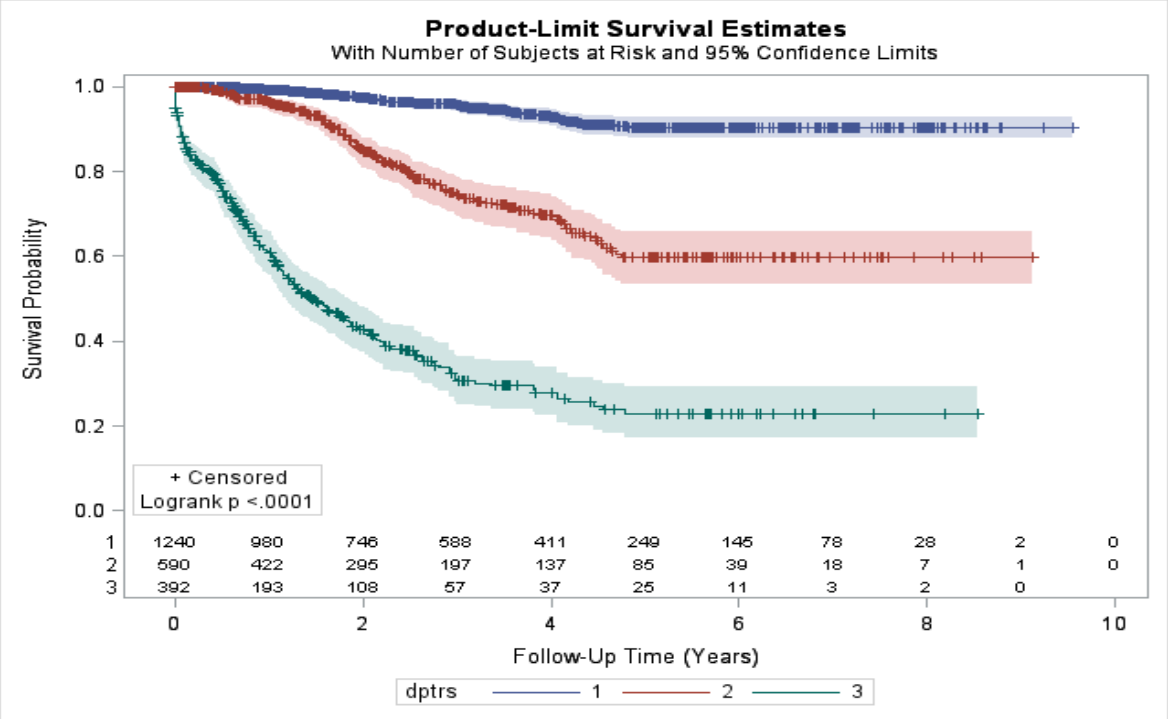
A confession…..

- Much of the data available on risk markers has been obtained from studies of first degree relatives.
- Much of that data is available only on antibody positive individuals.
- Much of that data is from cross-sectional studies.
- So it is natural to ask, what about combinations of markers?

DPTRS risk score derived from DPT-1 by Sosenko et al.

DPTRS=1.569*log(bmi)
-0.056*age
+0.00813*sumglu^
+0.476*log(fastcpep)
-0.0848*total c-peptide^

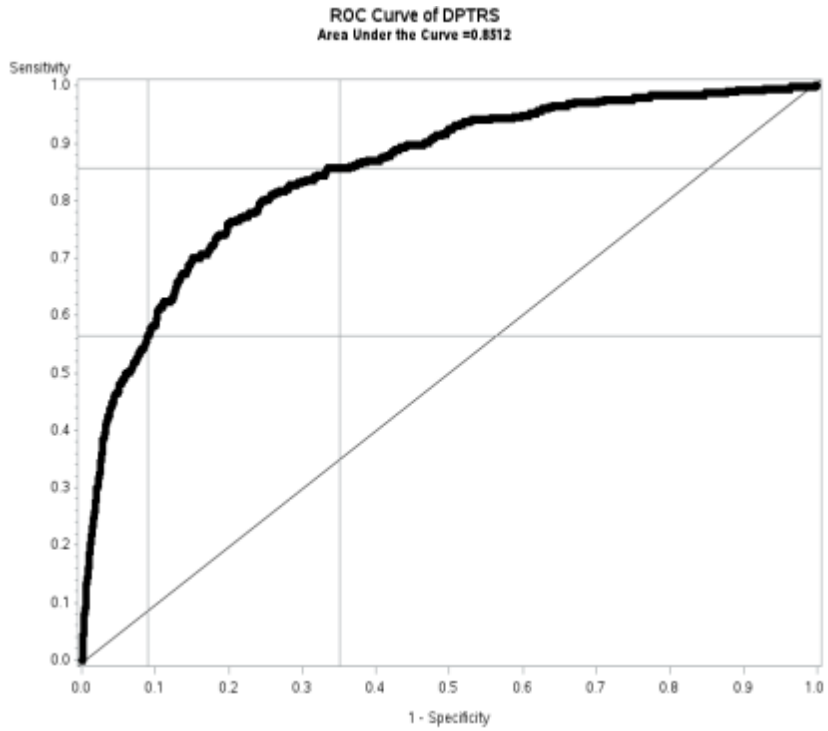
^ sum from 30 to 120 minutes/100 from an OGTT



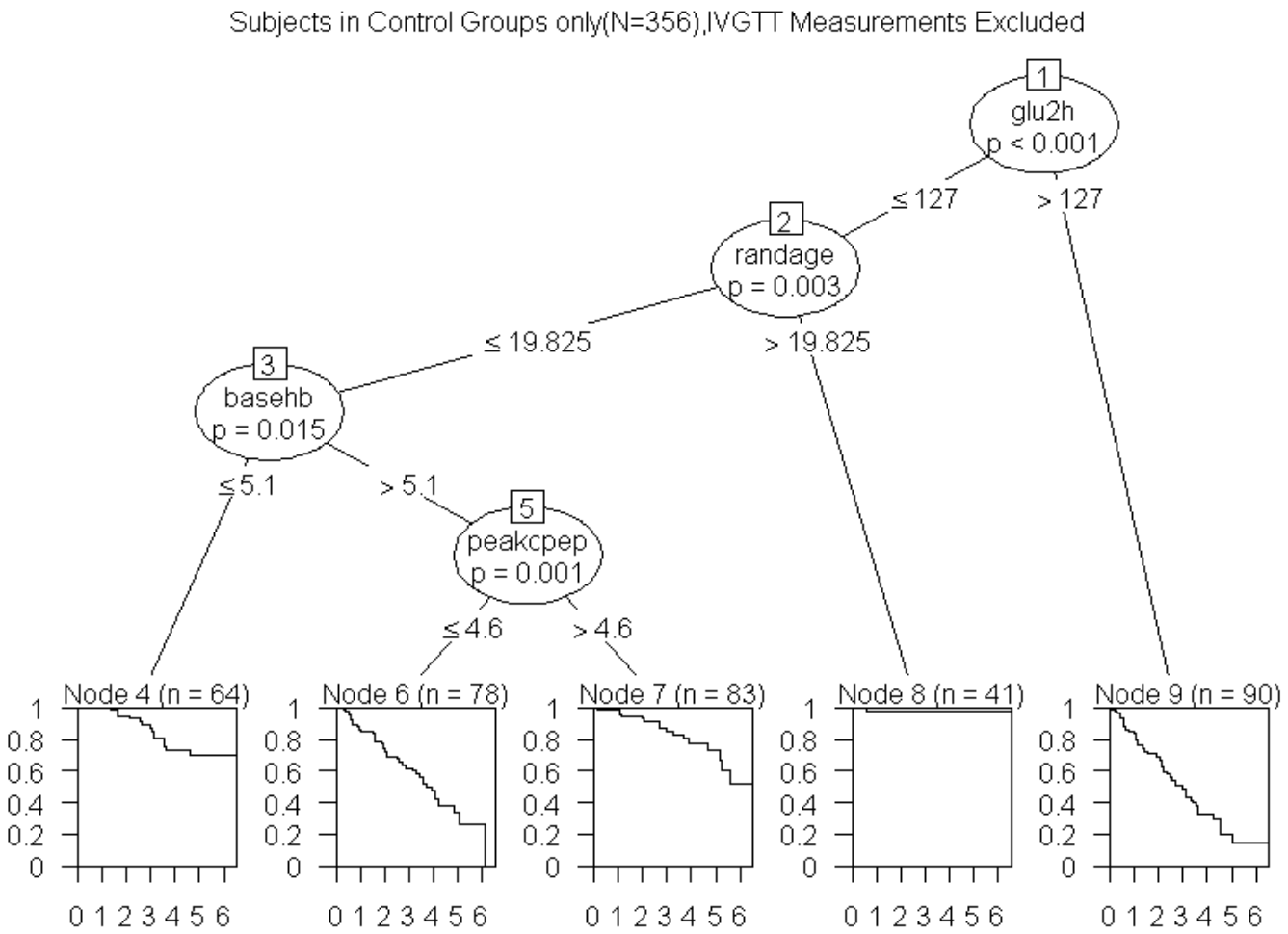
DPTRS	T1D Risk	Prevalence
< 6.50	0.09	56%
≥ 6.50 and ≤ 7.50	0.40	27%
> 7.50	0.77	18%

DPTRS risk score derived from DPT-1 by Sosenko et al.

The DPTRS is a continuous measure of risk and exhibits the same trade-off between sensitivity and specificity



Combinations of Diabetes Risk Markers: Recursive partitioning



Recursive Partitioning Risk Groups

Low risk: (Five-year risk=2.5%)

Two hour glucose <=127 mg/Dl and age >19.8 years

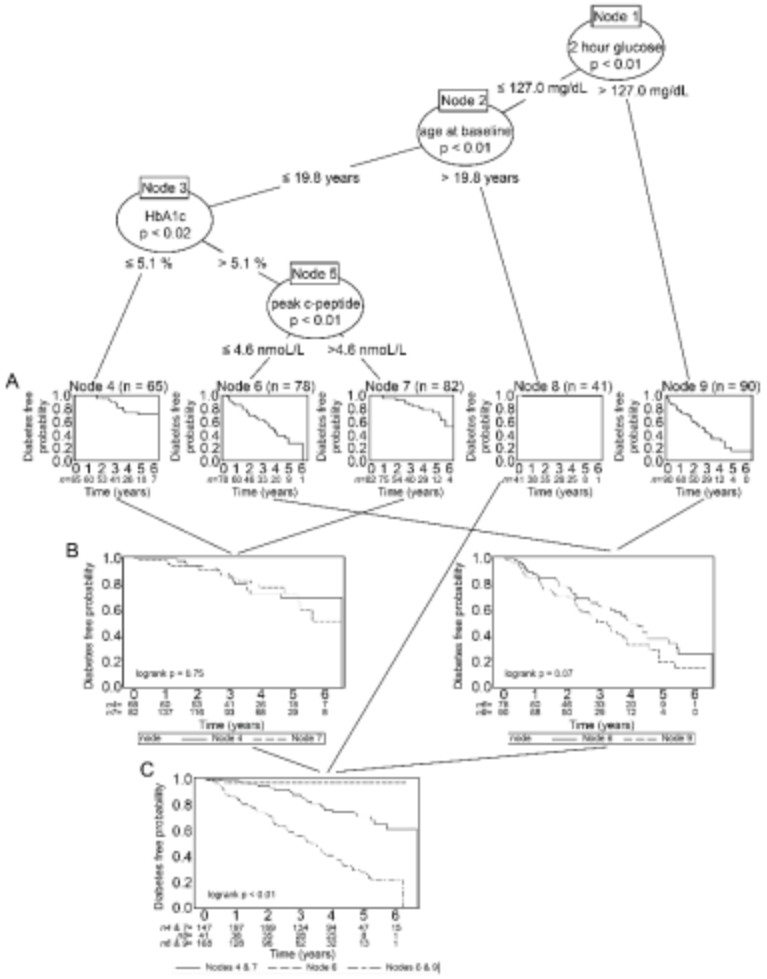
Moderate Risk: (Five-year risk= 29%)

Two hour glucose <=127 mg/Dl and age <19.8 years and either (HbA1c>5.1% and peak C-peptide>4.6 nmol/L) or HbA1c<=5.1%.

High risk: (Five-year risk: 74.8%)

Two hour glucose >127 mg/Dl or
(Two hour glucose <=127 mg/Dl and age <19.8 years and HbA1c>5.1% and peak C-peptide<=4.6 nmol/L)

RPA classification is based on 2-hour glucose (127 mg/DL), age at baseline (19.825 years), HbA1c (5.1%) and Peak C –peptide (4.6) derived from DPT-1



RPA classification	T1D Risk	Prevalence
Low Risk	0.03	12%
Medium Risk	0.29	41%
High Risk	0.75	47%

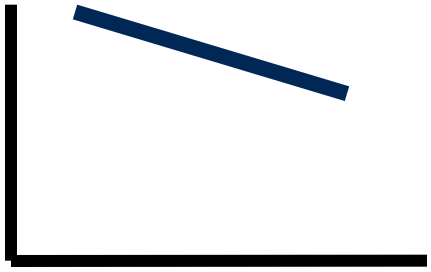
Relative Comparison of the DPTRS and RPA Analyses

DPTRS	T1D Risk	Prevalence
< 6.50	0.09	56%
≥ 6.50 and ≤ 7.50	0.40	27%
> 7.50	0.77	18%

RPA classification	T1D Risk	Prevalence
Low Risk	0.03	12%
Medium Risk	0.29	41%
High Risk	0.75	47%

The Effect of Time
Diabetes Risk Markers

- Risk based upon baseline or screening

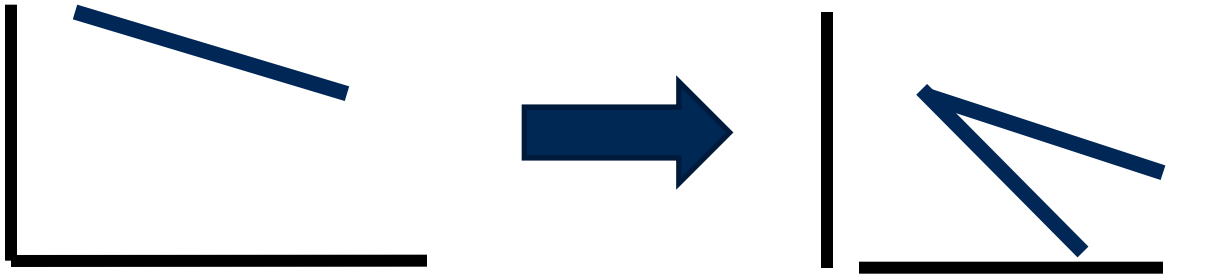


1 2 3 4 5

1 2 3 4 5

The Effect of Time
Diabetes Risk Markers

- Diabetes risk is not static

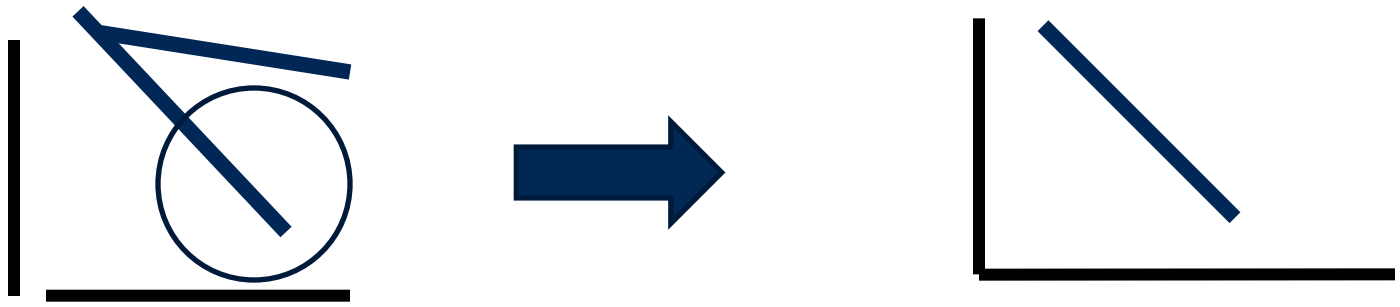


1 2 3 4 5

6 7 8 9 10

The Effect of Time
Diabetes Risk Markers

- What we observe is consequence of cross-sectional screening



6 7 8 9 10

1 2 3 4 5

Future Directions

- Identify markers with higher specificity and prevalence

  - Limited by underlying incidence of T1D

- Markers that are more homogeneous – p=.5 has highest s.d., moving to the extremes reduces sample size.

- Markers that are easier to screen for – e.g. HbA1c vs. IGT

Future Directions

- Expanding/testing generalizability to the larger cohort of individuals that will develop T1D
  - If an intervention works/doesn't work in a particular risk group what does this tell us about whether it will work in another risk group? E.g., anti-CD3 or antigen therapy going in either direction.

Where we are

- Use risk markers as eligibility criteria for prevention studies
  - 1 ab – none yet
  - 2 ab – oral insulin, abatacept
  - IGT – anti CD-3
- Now beginning to use risk markers as surrogate end points
  - abatacept

The end

Grateful acknowledgements:

The DPT-1 Study Group
The TrialNet Study Group

defining the early stages of type 1 diabetes

T1D

Use of risk detection and staging for design of prevention clinical trials

Carla Greenbaum

Diabetes TrialNet and Benaroya Research Institute

Type 1 Diabetes TrialNet

BENAROYA RESEARCH INSTITUTE Virginia Mason

Agenda

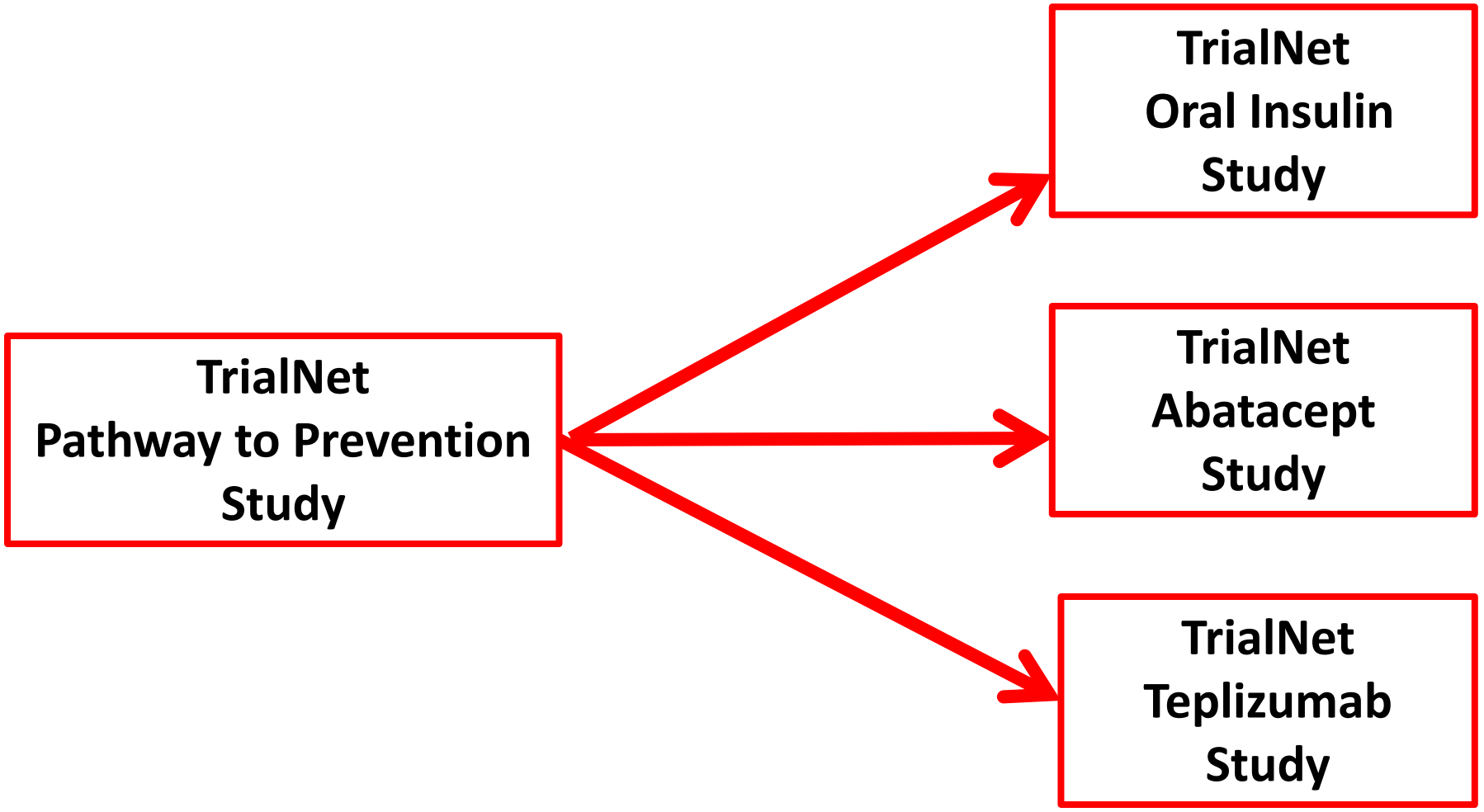
- Current Prevention Trials: Rationale, planning parameters
  - Oral Insulin
  - Abatacept
  - Teplizumab
- Additional Planned Prevention Trials: Rationale, planning parameters
  - Silent Diabetes
- Newer Considerations
  - Other intermediate risk parameters
  - Risk beyond 5 years
    - Islet autoimmunity as a disease
    - Islet autoimmunity prevention trial

TrialNet Pathway to Prevention

Group	Five-year risk of T1D
0 ab+	< 1%
1 ab+, NGT	3%
≥ 2ab+, NGT	35%
≥ 2ab+, AGT (dysglycemia)	75-80%

Type 1 Diabetes TrialNet

TrialNet Prevention Studies



Current TrialNet Prevention Protocol Considerations

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

ORAL INSULIN PREVENTION TRIAL

Oral Insulin Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 35%
- Relative with T1D
- mIAA+ and at least one other antibody
- Normal Glucose Tolerance

Type 1 Diabetes TrialNet

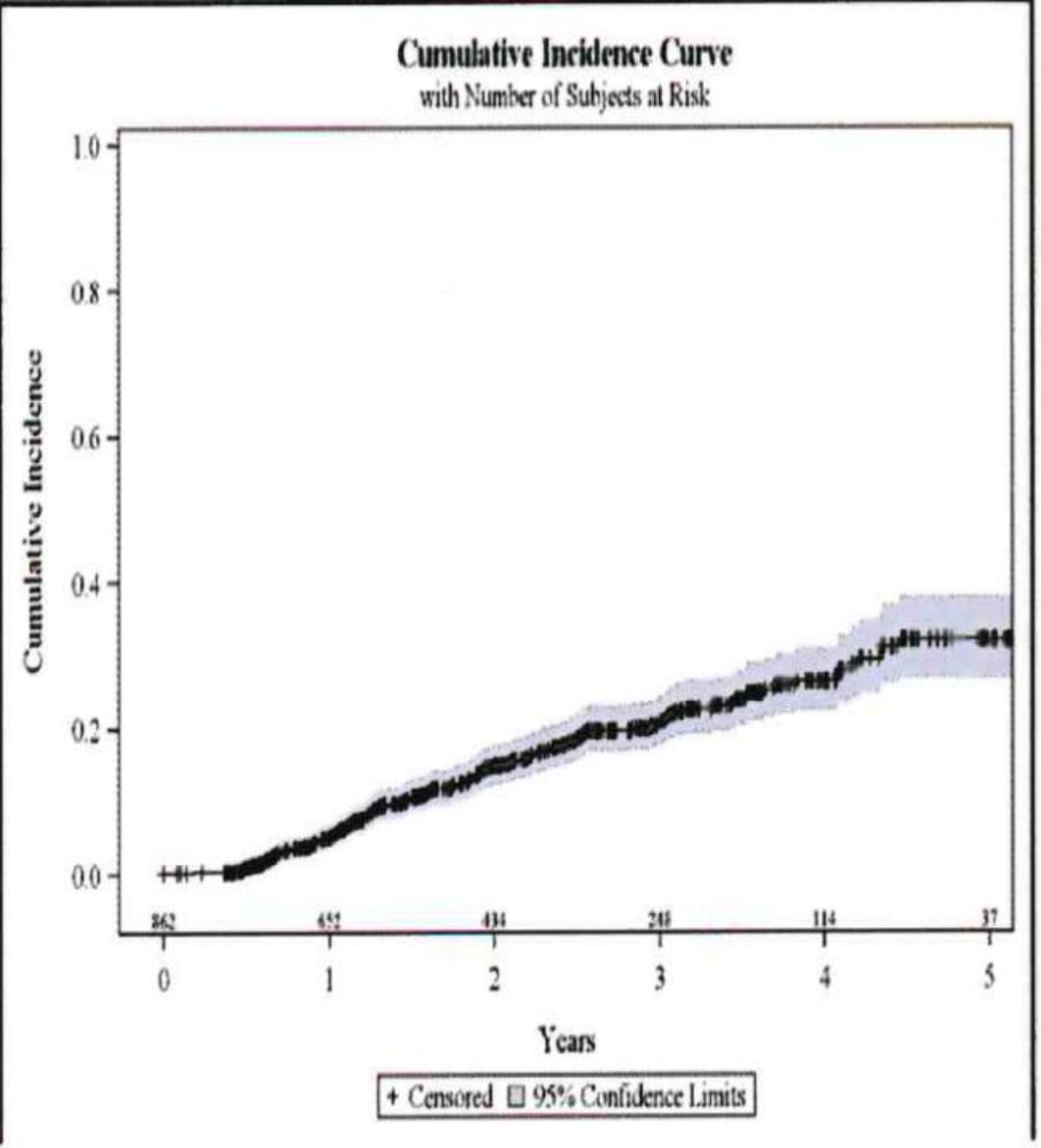
Oral Insulin Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Primary stratum
  - **mIAA+**, ICA+, NGT, nl insulin secretion*
  - **mIAA+,** ICA512ab+, GAD65ab+, NGT, nl FPIR
- Other stratum
  - Same antibodies, NGT, below threshold FPIR
  - mIAA+, ICA512ab+ OR GADab+; NGT, nl FPIR
  - mIAA+, ICA512ab+ OR GADab+; NGT, below threshold FPIR

*above threshold first phase insulin release (FPIR)

Type 1 Diabetes TrialNet



35% 5-year risk in those with 2 or more antibodies and normal glucose tolerance

Diabetes Prevention Trial – Type 1

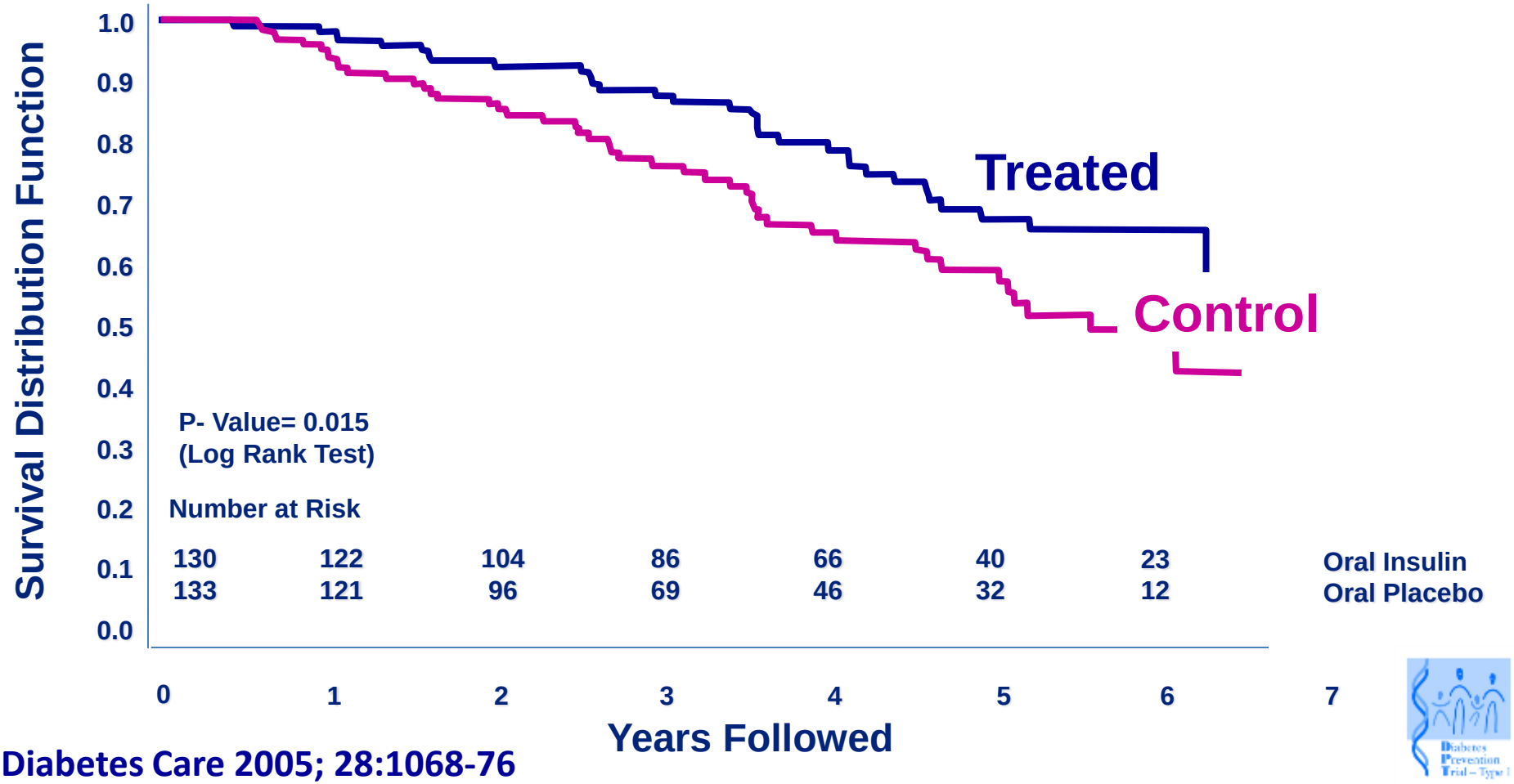
Oral Insulin Prevention Trial

- Why mIAA+?
  - Original insulin autoantibody assay (IAA) used in Diabetes Prevention Trial.
  - Post-hoc analysis of that trial identified that those with high levels of IAA had an apparent benefit of treatment: 4-year delay in diabetes
  - Next generation of insulin autoantibody assay (mIAA); only included those with post-hoc benefit

Type 1 Diabetes TrialNet

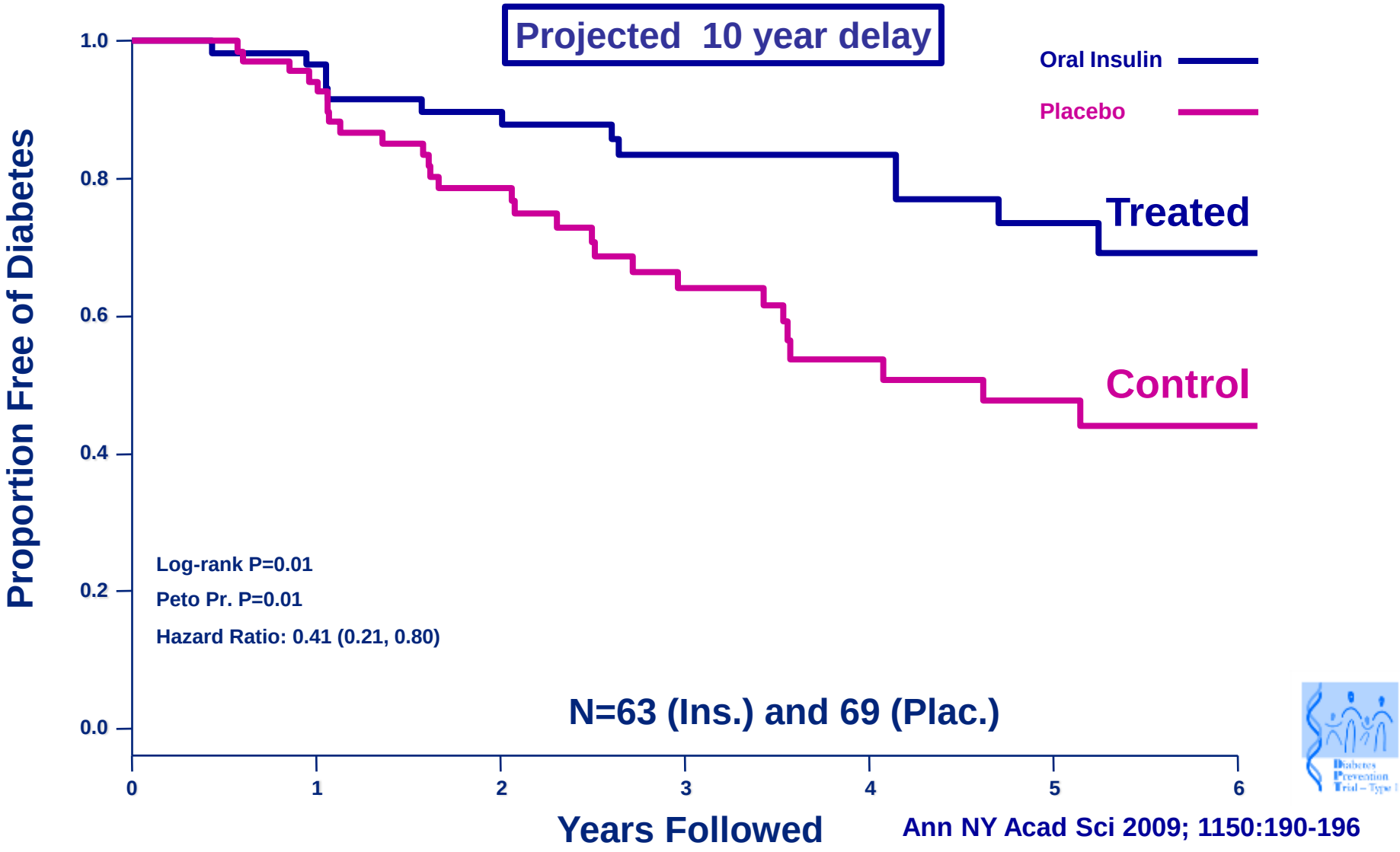
HISTORICAL PERSPECTIVE: DIABETES PREVENTION TRIAL: KEY INFORMATION ABOUT NATURAL HISTORY

A Subset with IAA Confirmed > 80 nU/ml
Suggested Potential 4.5-5-year Delay of T1D



Diabetes Care 2005; 28:1068-76

Delay in T1D was Most Evident in Subjects with Baseline IAA ≥ 300: Up to10 years



Ann NY Acad Sci 2009; 1150:190-196

Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Development of T1D (ADA criteria)
  Two of the following on separate days
  - OGTT on two separate days*
    - Fasting ≥ 126 mg/dl
    - 2 hour ≥ 200 mg/dl

  OR
  - Clear symptoms and random glucose ≥ 200 mg/dl

*~2/3 of those diagnosed with T1D was from two OGTTs

Type 1 Diabetes TrialNet

Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Maximum Information Trial: subjects are recruited and followed until the required amount of information is achieved.
  - If 50/year…duration of ~8 years
- Effect size: 40% risk reduction
- Power: 85%; one-sided test

Type 1 Diabetes TrialNet

Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Safety
  - Dose ranging test study in healthy humans – no effect on glycemia
  - Prior exposure DPT-1 oral insulin trial, same population and age range – no associated AE
- Efficacy
  - Animal models suggestive of efficacy
  - Primary endpoint DPT-1 negative, post hoc analysis of high IAA subgroup suggestive of significant effect (4 to 10 year delay in onset)

Type 1 Diabetes TrialNet

Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Study start 2007
- N=436 randomized;
  - 304 to primary stratum
- No therapy related AEs

Oral Insulin Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- High benefit if efficacy demonstrated
- Strong pre-clinical and clinical data with above average likelihood of efficacy
- Minimal risk to all age groups

Type 1 Diabetes TrialNet

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

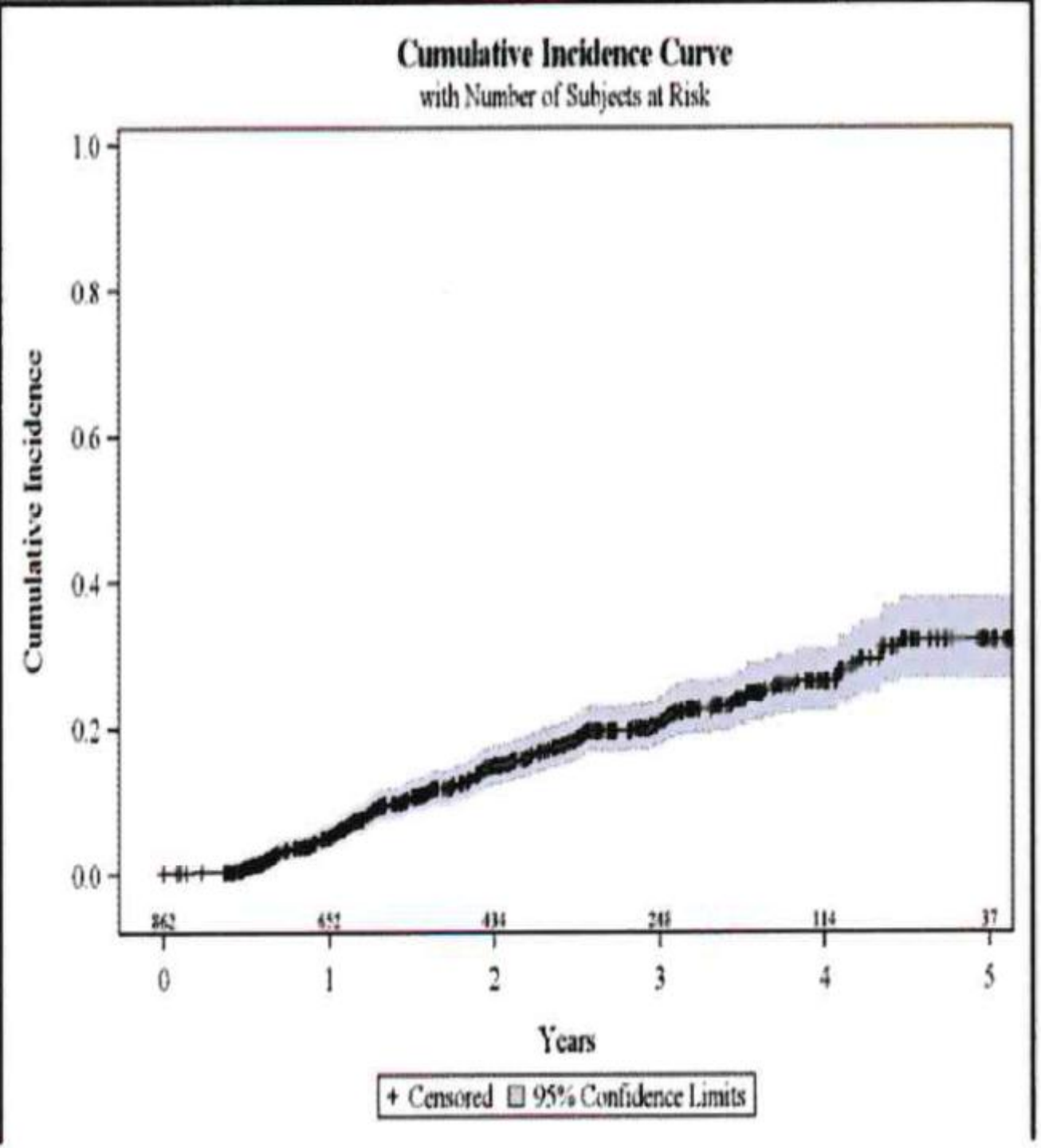
ABATACEPT PREVENTION TRIAL

Abatacept Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 35%
- Relative with T1D
- 2 or more ab+, not mIAA
- Normal Glucose Tolerance

Type 1 Diabetes TrialNet



35% 5-year risk in those with 2 or more antibodies and normal glucose tolerance

Diabetes Prevention Trial – Type 1

Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Development of Abnormal glucose tolerance or T1D

  Abnormal Glucose Tolerance

  – OGTT on two separate days*
    - Fasting ≥ 110 mg/dl and <126 mg/dl
    - 2 hour ≥ 140 mg/dl and <200 mg/dl
    - 30, 60, 90 min ≥ 200 mg/dl

  OR

  Diabetes

  – T1D by ADA criteria

*~2/3 of those diagnosed with T1D was from two OGTTs

Type 1 Diabetes TrialNet

Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Effect size: 40% risk reduction
- Power: 80%; two-sided test at 0.05
- N= 206; randomized 1:1
- Estimated enrollment 50/year; recruitment 4 years – outcome at 6 years

Type 1 Diabetes TrialNet

Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Safety
  - FDA approved in kids (age 6+) and adults for Adult RA, Juvenile RA; >60,000 total person/years of exposure
  - Prior exposure in 112 T1D new onset subjects ages 6-45; no significant treatment related AE
  - Expected AEs = infusion reactions; infections; not expected with limited duration of therapy (12 months)
- Efficacy
  - Animal models suggestive of efficacy
  - New onset trial with positive result

Type 1 Diabetes TrialNet

Abatacept (CTLA4-Ig)
(co-stimulation blockade)

Treatment period

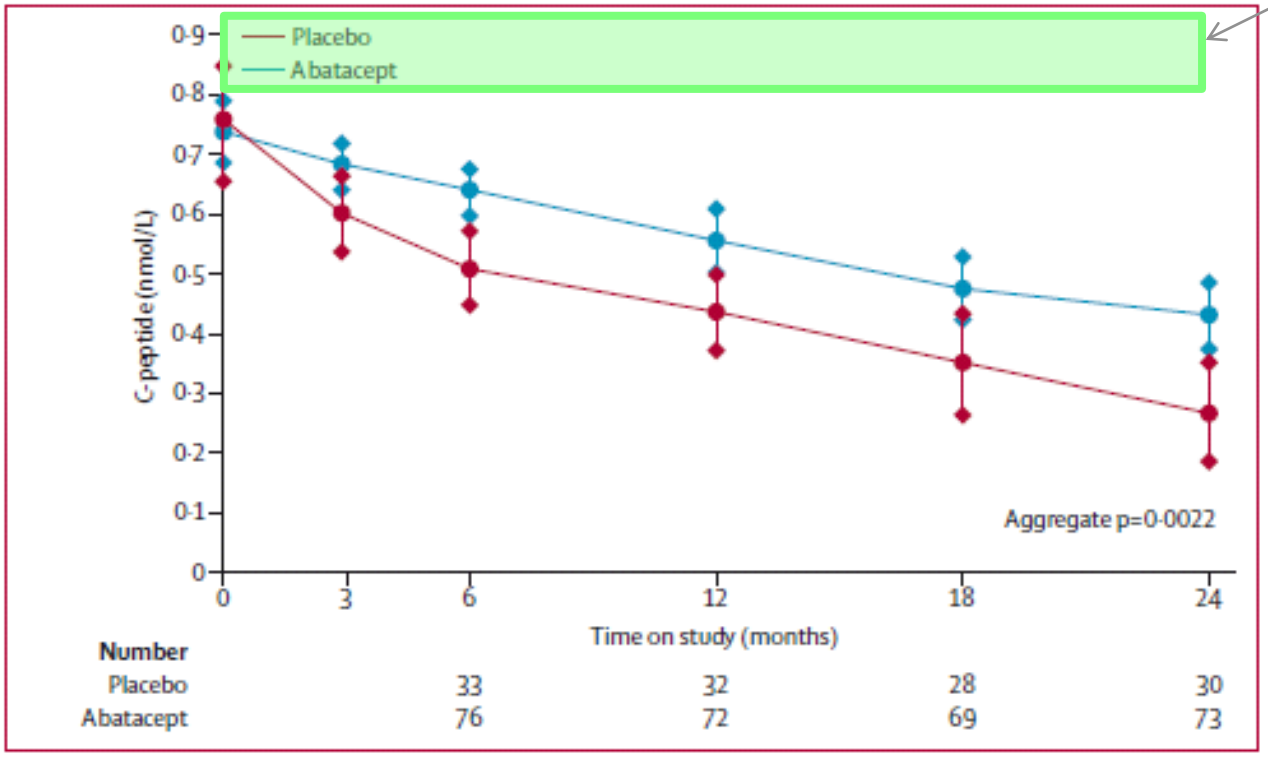


Figure 2: **Population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group**
The estimates are from the ANCOVA model adjusting for age, sex, baseline value of C-peptide, and treatment assignment. Y-axis is on a log(y + 1) scale. Error bars show 95% CIs. AUC=area under the curve.

Moran, Lancet 2012

Type 1 Diabetes TrialNet

Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Study start 2013
- N=65 randomized;
- No therapy related AEs

Abatacept Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- High benefit if efficacy demonstrated
- Strong clinical data in other diseases and initial data in T1D with above average likelihood of efficacy
- Slightly greater than minimal risk to all age groups

Type 1 Diabetes TrialNet

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

TEPLIZUMAB PREVENTION TRIAL

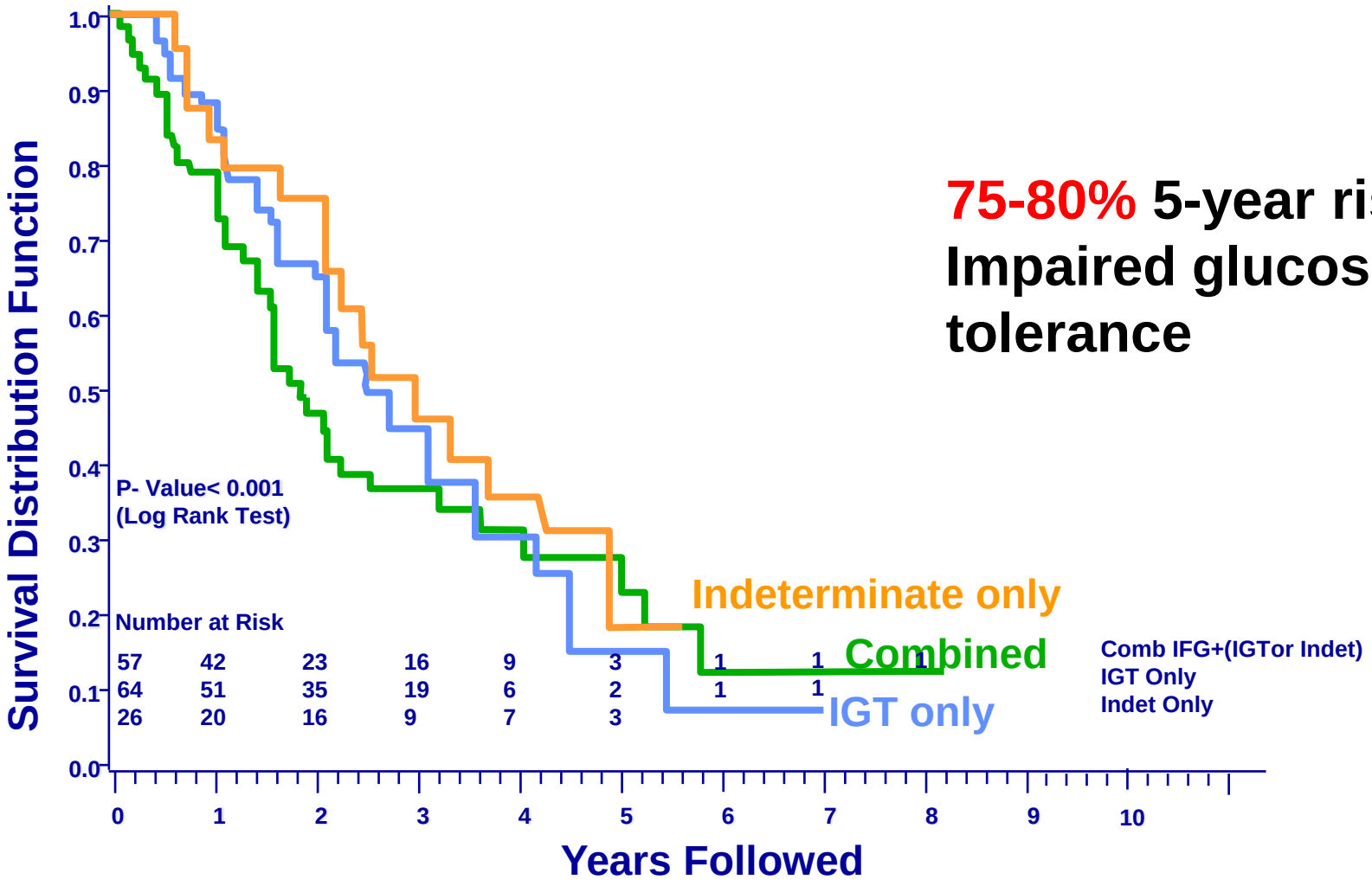
Teplizumab Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- 5-year risk of T1D: 78%;
  - Varies by age
- Relative with T1D
- 2 or more ab+,
- Abnormal glucose Tolerance

Type 1 Diabetes TrialNet

Risk of T1D in ab+ relatives with abnormal glucose tolerance



75-80% 5-year risk with Impaired glucose tolerance

Diabetes Prevention Trial – Type 1

Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Development of T1D (ADA criteria)
  Two of the following on separate days
  - OGTT on two separate days*
    - Fasting ≥ 126 mg/dl
    - 2 hour ≥ 200 mg/dl

  OR
  - Clear symptoms and random glucose ≥ 200 mg/dl

Type 1 Diabetes TrialNet

Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Effect size: 60% risk reduction
- Power: 80%; two-sided test at 0.05
- N= 71; randomized 1:1
- Complete recruitment within 3 more years and follow for an additional 4 years

Type 1 Diabetes TrialNet

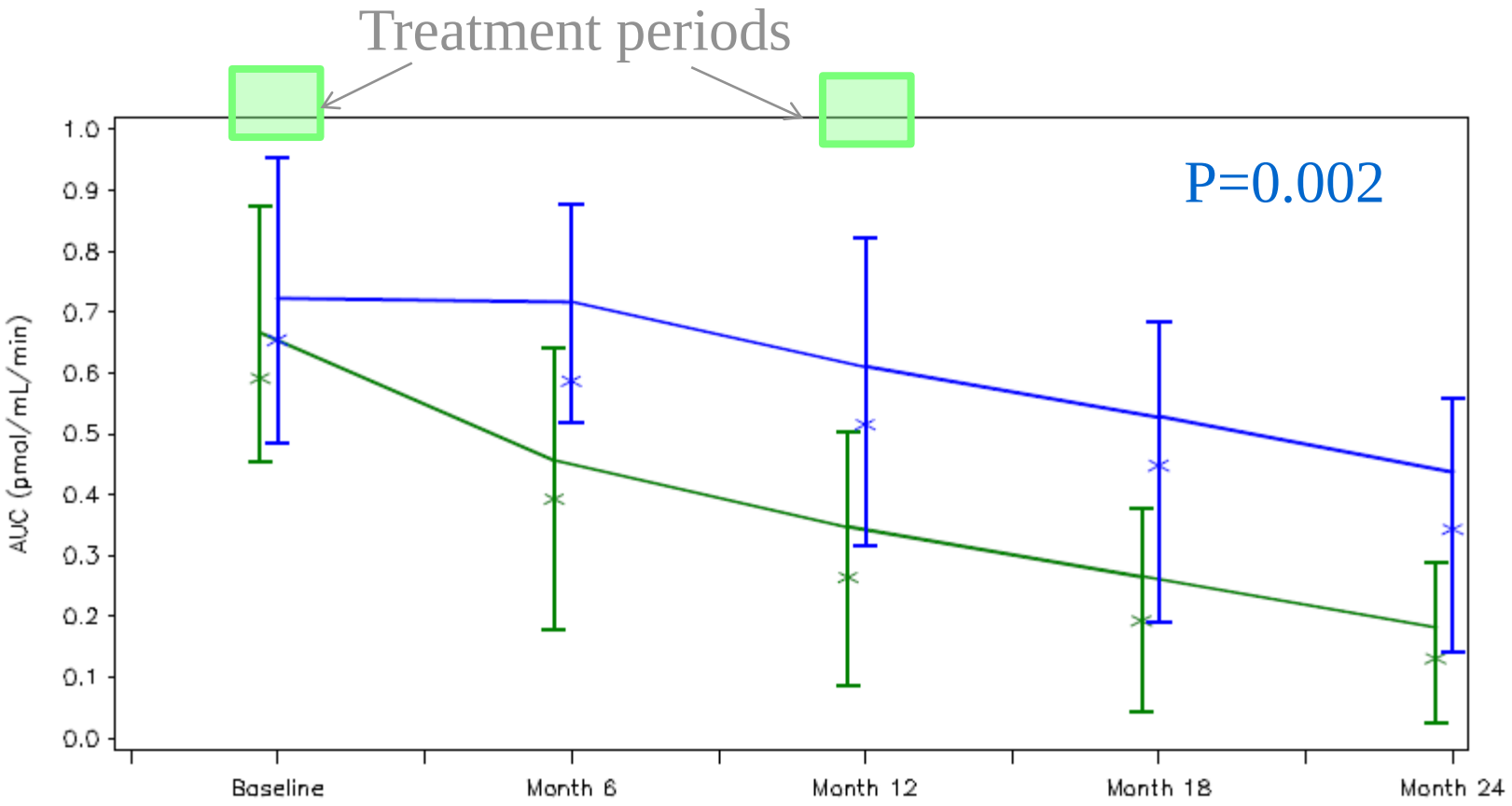
Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Safety
  - Prior exposure in >600 T1D subjects ages 8-45;
  - Expected AEs = transient lymphopenia, cytokine release syndrome, infections, rash
- Efficacy
  - Animal models suggestive of efficacy
  - New onset trials with positive result (and one with negative result overall)

Type 1 Diabetes TrialNet

Teplizumab (hOKT3γ1 (ala-ala): AbATE



Herold, Lancet Endo

Immune Tolerance Network

Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- Study start 2011
- N=41 randomized;

Teplizumab Prevention Trial

- Population to be included
- Primary outcome
- Planning parameters
- Choice of Intervention
- Current status
- Summary

- High benefit if efficacy demonstrated
- Clinical data in T1D suggestive of above average likelihood of efficacy
- Greater than minimal risk to all age groups

Type 1 Diabetes TrialNet

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Teplizumab Prevention Trial

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

PLANNING STAGES; NEW PREVENTION TRIAL

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

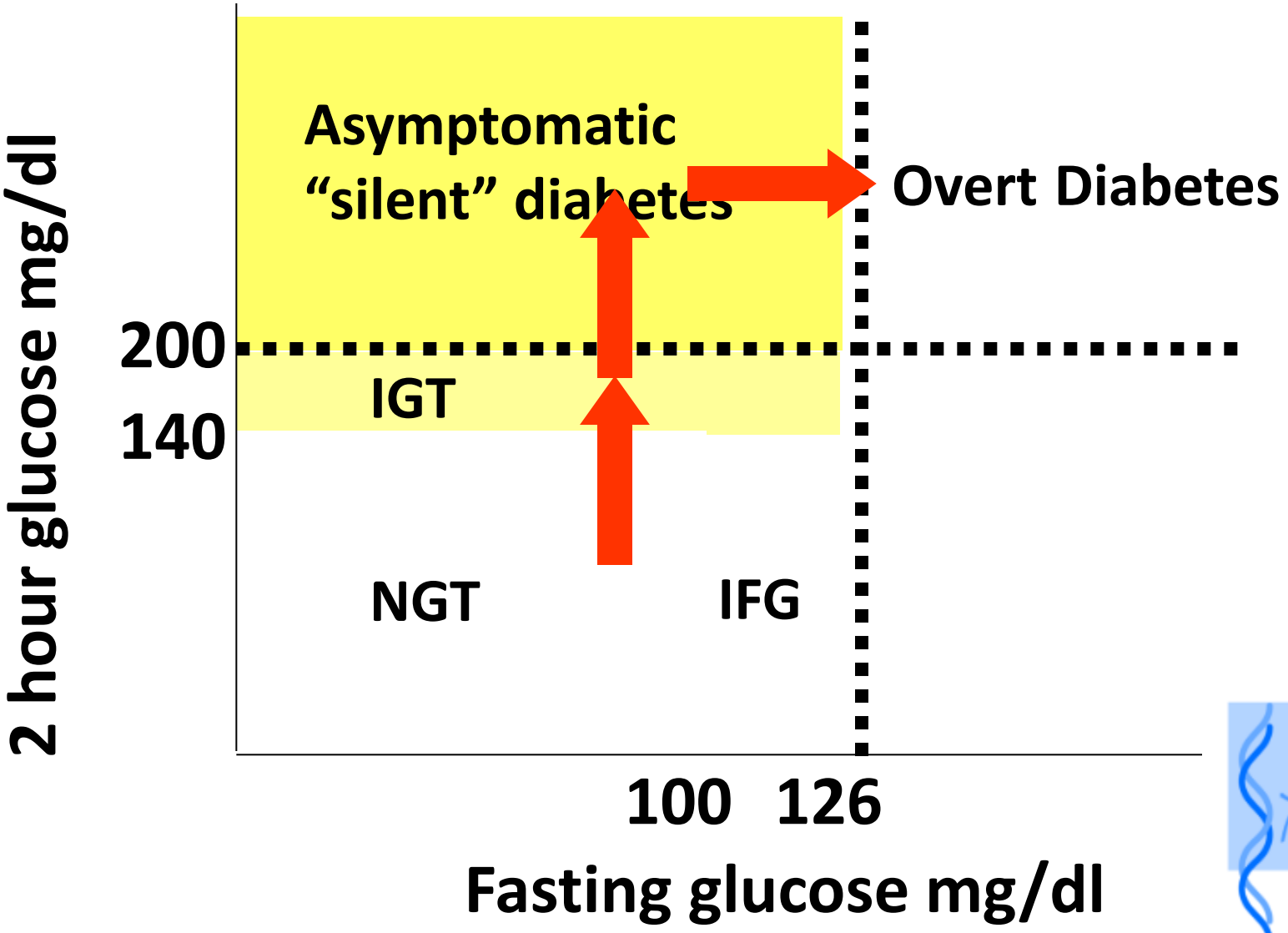
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Teplizumab Prevention Trial

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Progression to Type 1 diabetes: DPT-1



Diabetes Prevention Trial – Type 1

New therapy Prevention Trial

- Population to be included
  - Risk estimate
  - Entry criteria
- Primary outcome
- Planning parameters
- Choice of Intervention

- OGTT = Diabetes
- HbA1c <6.5%
- No insulin therapy

Kevan Herold, Jeff Krischer

Type 1 Diabetes TrialNet

New therapy Prevention Trial

- Population to be included
- Primary outcome

- Proportion of participants who **revert** to non-DM OGTT at 6 months

Kevan Herold, Jeff Krischer

Type 1 Diabetes TrialNet

PREVENT ISLET AUTOIMMUNITY

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

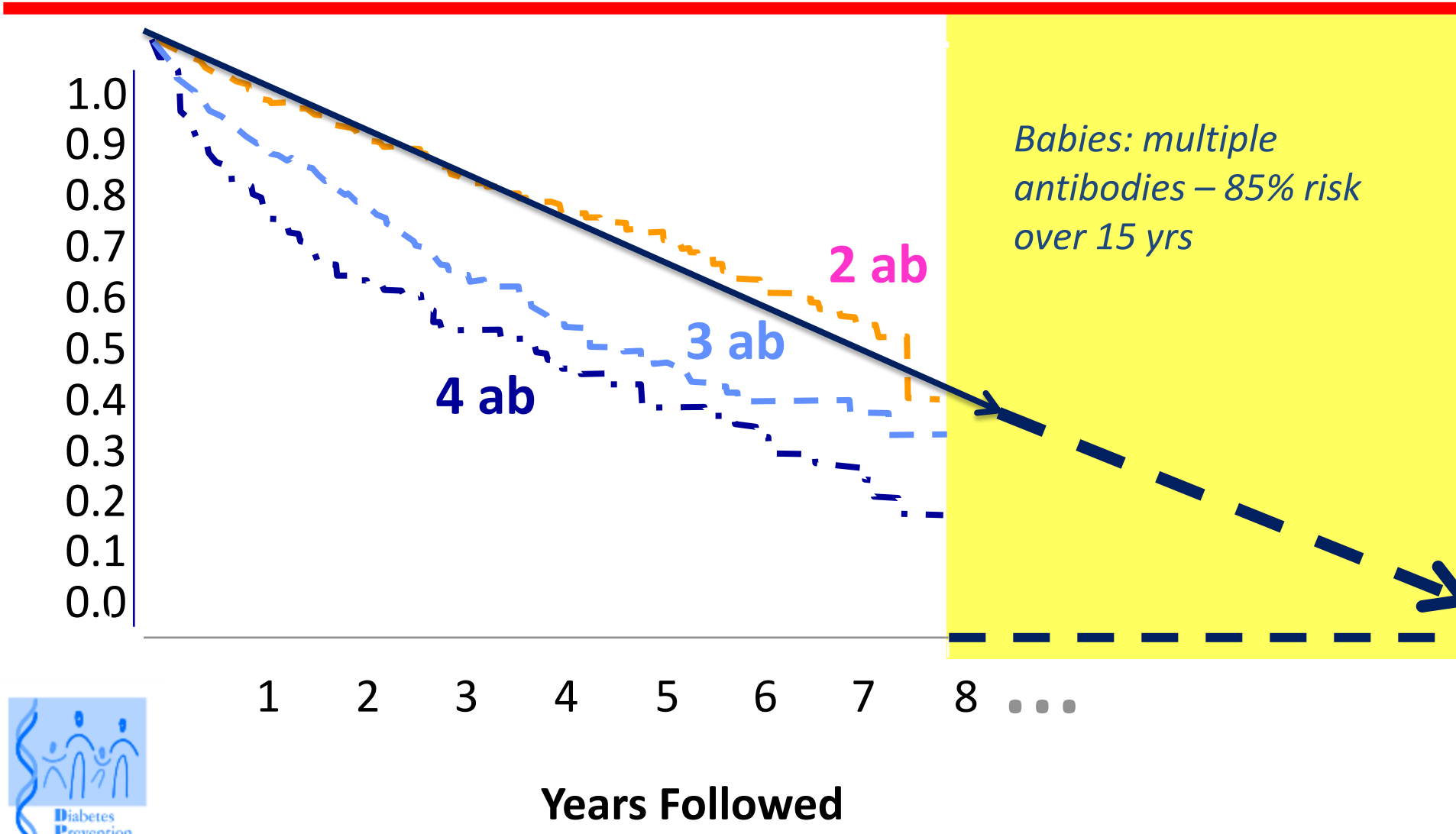
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Teplizumab Prevention Trial

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Risk of T1D with ≥ 2 antibodies does not appear to level off



Diabetes Prevention Trial – Type 1

Risk and Benefit Considerations

- Current evidence supports the concept that essentially ALL relatives with two or more antibodies will develop clinical diabetes at some time
- Thus, islet autoimmunity could be considered a disease like hypertension

Type 1 Diabetes TrialNet

What defines a disease to be treated?
First, give it a name

		Lab results	Clinical signs and symptoms	Later consequences	Treatment
1	Clinical presentation of hyperglycemia and symptoms	Abnormal HbA1c. Fasting and 2 hour elevated	YES	YES: complications	Insulin
2	"Silent" diabetes	Normal HbA1c Normal fasting 2 hour ≥ 200	NO	YES: Symptomatic DM	??? Insulin
3	Abnormal glucose tolerance	Normal HbA1c Normal fasting 2 hour 140-199	NO	YES: 85% with clinical T1D in 3-5 years	???

Islet Autoimmunity

Is islet immunity a disease that should be treated?

Disease	**Hypertension***
Consequence within 4-5 years	2.4/100 get coronary heart disease (CAD) and 1.9/100 have stroke
Relative risk reduction (effect size) of treatment	Treating HTN reduces CAD by 16% and stroke by 40% (relative risk)
Absolute benefit of treatment	Treating 100 HTN patients prevents 2 people from getting CAD or stroke

**Hebert PR, Moser M, Mayer J, et al. Arch Intern Med 1993; 153:578*

Proposed Stages of Type 1 Diabetes

Single T1D-associated islet autoantibody

Prevent Islet Autoimmunity

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Oral Insulin Prevention Trial

Abatacept Prevention Trial

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

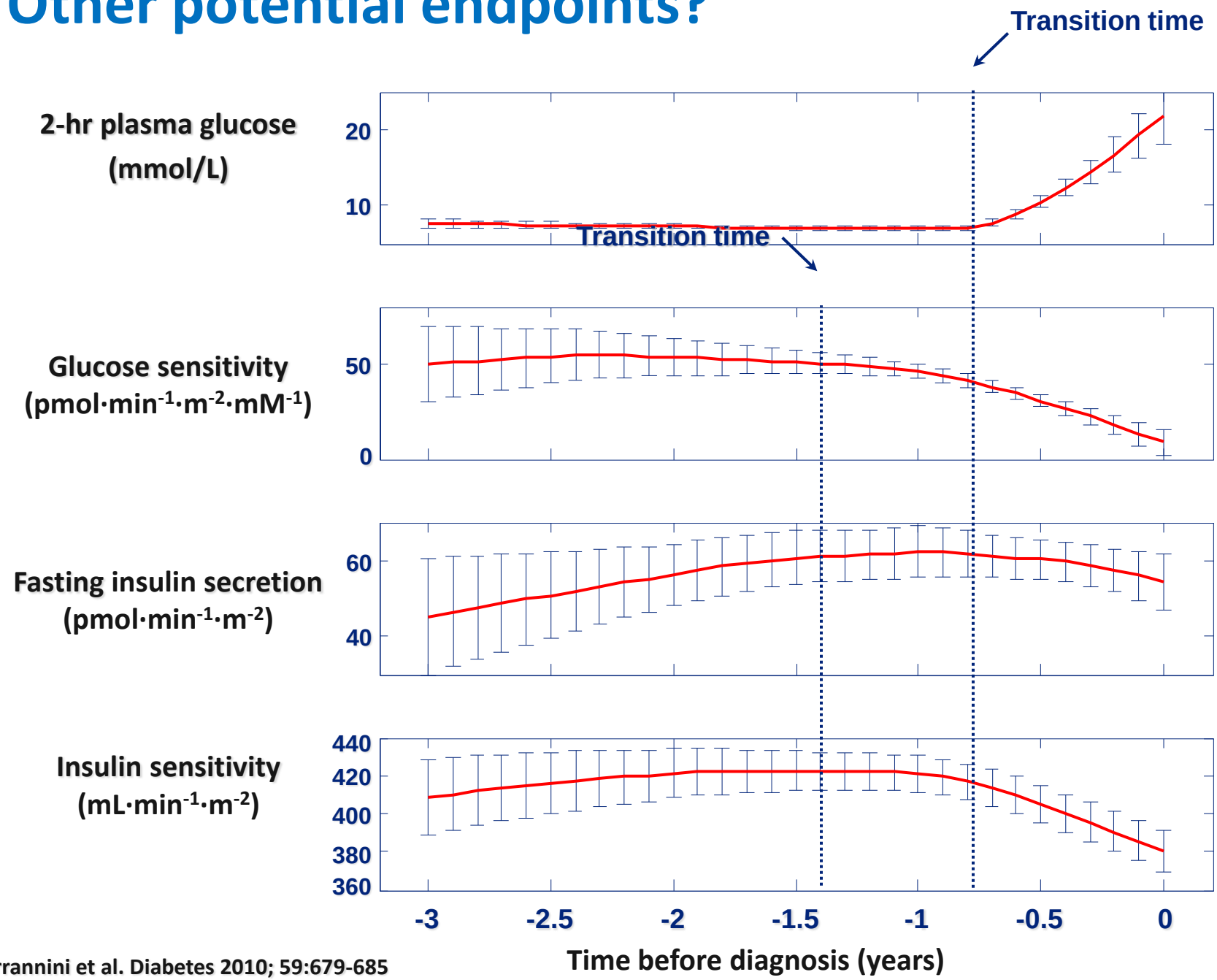
Teplizumab Prevention Trial

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

FUTURE THINKING: OTHER ENDPOINTS TO BE EXPLORED

Other potential endpoints?



Ferrannini et al. Diabetes 2010; 59:679-685

Summary

- Current Prevention Trials: Rationale, planning parameters
  - Oral Insulin
  - Abatacept
  - Teplizumab
- Additional Planned Prevention Trials: Rationale, planning parameters
  - Silent Diabetes
- Newer Considerations
  - Other intermediate risk parameters
  - Risk beyond 5 years
    - Islet autoimmunity as a disease
    - Islet autoimmunity prevention trial

defining the early stages of type 1 diabetes

T1D

Use of risk detection and staging for design of prevention clinical trials

Thank You

Type 1 Diabetes TrialNet

BENAROYA RESEARCH INSTITUTE Virginia Mason

defining the early stages of type 1 diabetes

T1D

Benefits of Screening/Risk Detection

Desmond Schatz MD

Professor of Pediatrics

University of Florida College of Medicine

We Cannot Afford to do Nothing

Current Status Quo in 2014 Unacceptable

- Epidemic worldwide
- Increasing burden to individual and society
- No reduction in acute complications
- Potential benefits of improved glycemic control reaching a minority of patients
- Even current `successful' immune interventions after diagnosis are of questionable translation

Burden of Diabetes in USA (2012)

Diabetes Rising + **Morbidity/Mortality** = **Economic Burden**

Prevalence/Incidence:

- 24.9 million Americans (29 million 2014)
- 6.3 million undiagnosed
- 1.6 million cases/year
- 10% type 1 (1/300)
  - 2 million

High rate as evidenced by:

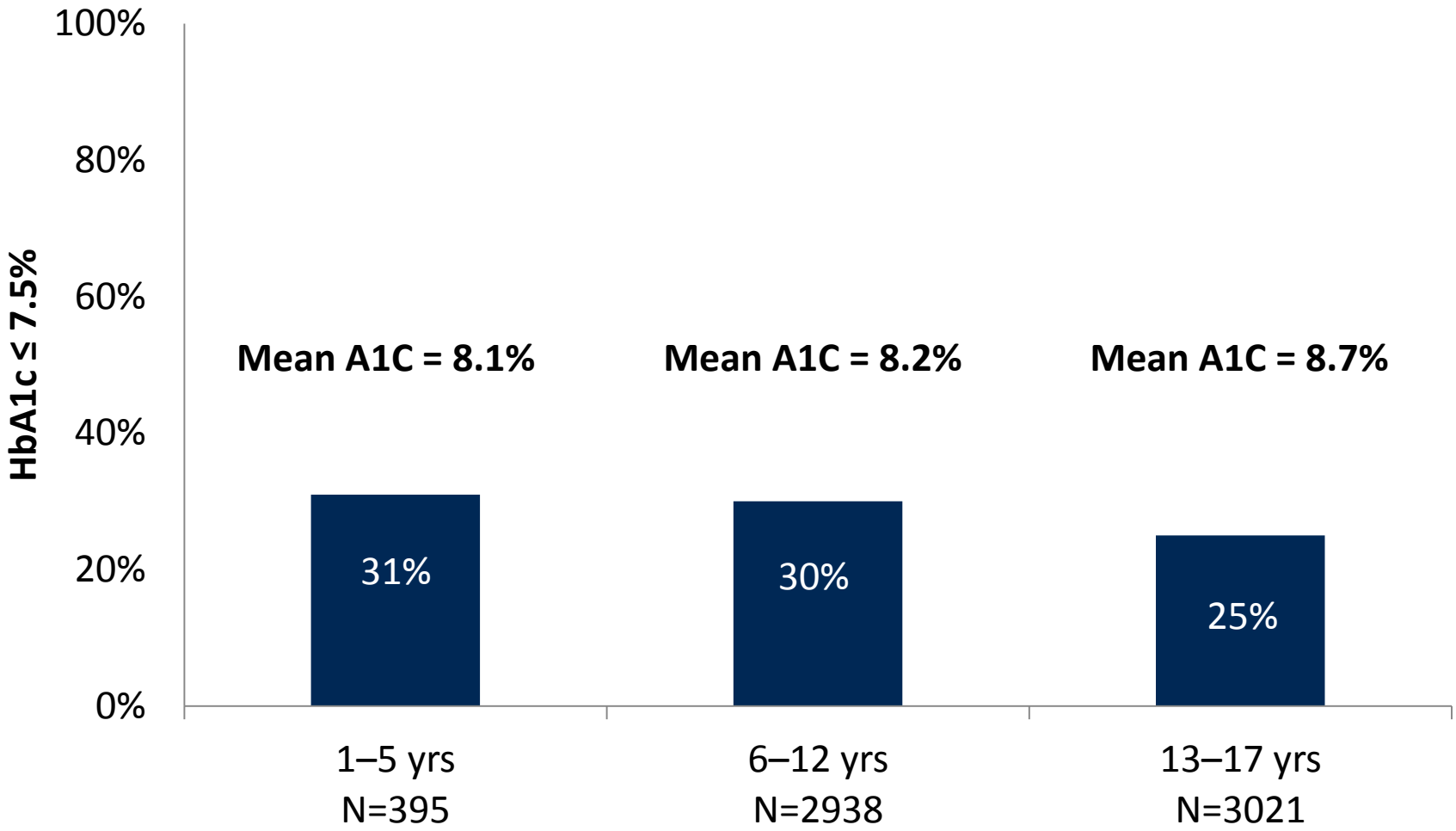
- > 246,000 deaths/ > 600/day
- Shortened life span
- 2-4x risk MI, stroke
- 75% hypertensive
- 47,000 new cases RD/yr
- 12,000 – 24,000 new cases blindness/yr
- >82,000 amputations/yr

2012 Medical costs:

- $245 billion
- ~ 1/8 health care dollars
- 27% of all medications ($77 billion of $286 billion)
- Type 1 disproportionately ↑

Diabetes Care 36: 1033-1046, 2013

Falling Short of Target: HbA1c ≤7.5% by Age Group



Wood JR et al Diabetes 2013 Jul;36(7):2035-7

defining the early stages of type 1 diabetes T1D

Ultimate Goal……..
Public Health Screening

Identification of a burdensome disease with the long-term goal of reducing the incidence and mortality for that disease in the subjects being examined

Does T1D Fulfill Requirements for a Public Health Screening Program?

- Cost/benefit to individual and society: YES
- Disease detected early enough to intervene: YES
- Effective method for identifying those eligible for intervention (sensitivity, specificity, positive predictive value): YES
- Credible intervention must be available, i.e., safe/efficacious: NOT YET

Current `Screening' = Risk Detection

Why Screen in 2014?

- **Better understanding of natural history of pre-diabetes**
- **Gain insight into immunopathogenesis**
- **Make early diagnosis (decrease morbidity/mortality)**
- **Identify individuals for prevention trials**

Without prevention there will NEVER be a cure….

Screening Enables Earlier “Diagnosis” ……Decreases Prevalence of DKA

NEWBORN GENETIC SCREENING

- Barker et al Diabetes Care 27 1399-1404, 2004
- Heikka et al Diabetes Care 30 861-66, 2007
- Winkler et al Pediatr Diabetes 13 308-13, 2012
- Larsson et al Diabetes Care 34 2347-52 2011

ISLET AUTOANTIBODY SCREENING

- Greenbaum et al Diabetes 2001; 50:470-476

DKA Morbidity and Mortality = Cerebral Edema

- UK study of DKA (Edge et al 2001 Arch Dis Child)
  - CE: 1.19%, 24% mortality, 35% morbidity. N= 2,940
- Canadian Study – Case:Control (Lawrence et al. J Peds 2005)
  - CE: 0.51% (13 cases). 23% mortality, 15% morbidity
- Swedish Study of DKA (Hanas et al. Diabet Med 2007)
  - CE: 0.68% (2 cases). No mortality, 1 neuro sequelae, n = 292

Newborn TEDDY Screening Reduces DKA Rates in < 2 year olds

Study	Total DKA	
	Under 2 years	P Value
TEDDY	**16.1%**	
Sweden Registry	39.5%	0.02
SEARCH	50.0%	<0.0001
Finland Registry	44.8 %	<0.0001
German Registry	54%	<0.0001

Larsson et al Diabetes Care 34, 2347-52 2011

Newborn TEDDY Screening Reduces DKA Rates in < 5 year olds

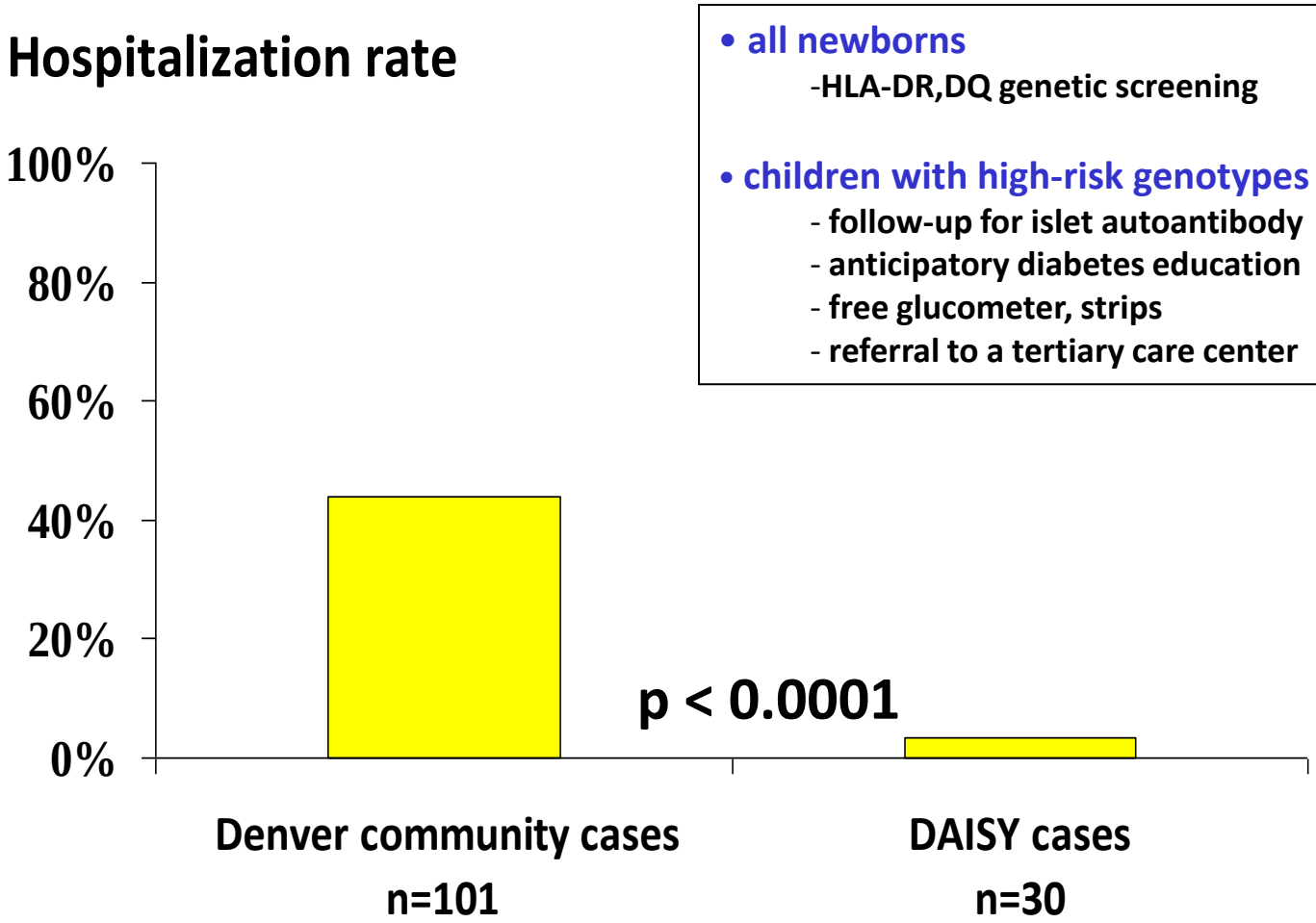
Study	Total DKA	
	Under 5 years	P Value
TEDDY	**13.1%**	
Sweden Registry	16.9%	0.45
SEARCH	36.4%	<0.0001
Finland Registry	18.7%	<0.11
German Registry	32.2%	<0.0001

Larsson et al Diabetes Care 34, 2347-52 2011

Prevention of hospitalization at T1 DM onset

DAISY, Denver, children, ages 0-11, 1999-2002

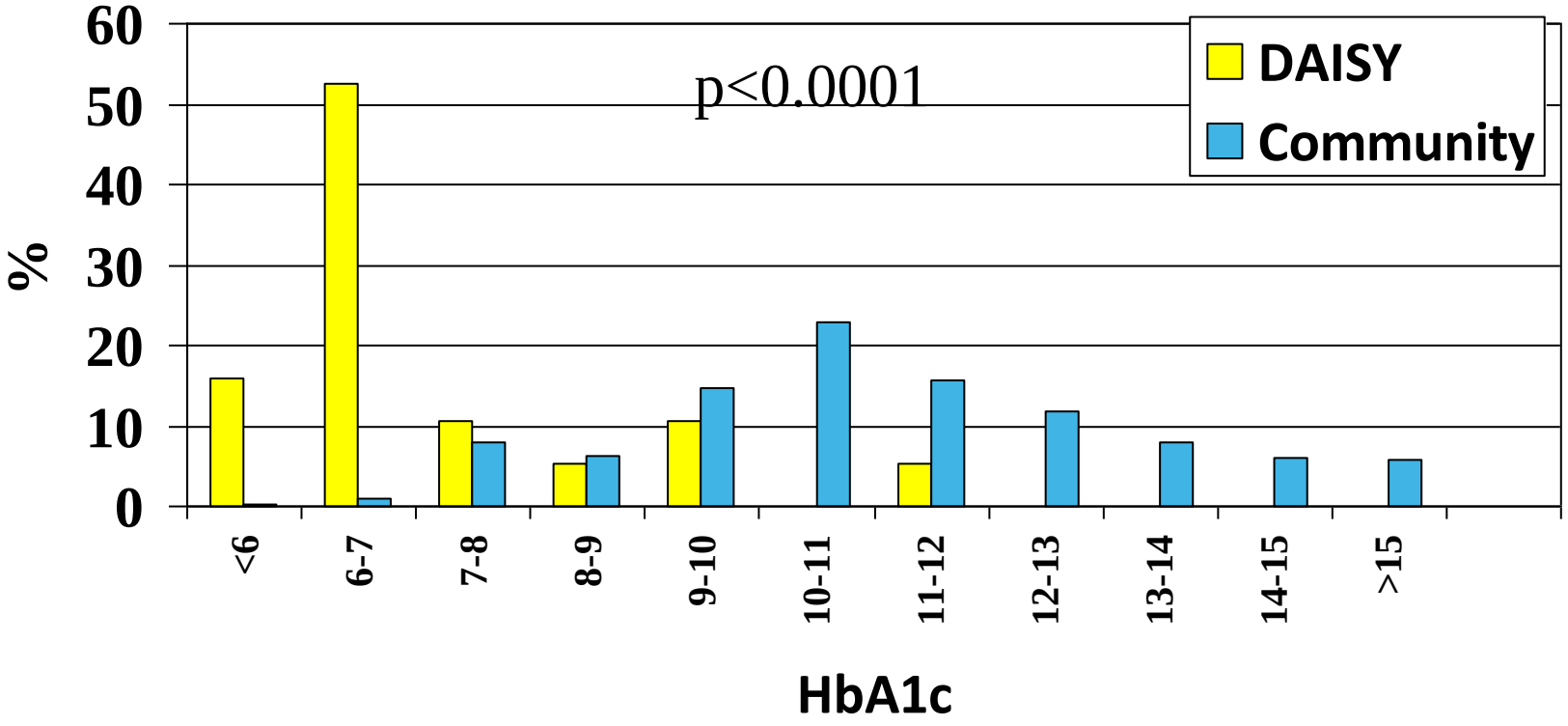
- **all newborns**
  - -HLA-DR,DQ genetic screening
- **children with high-risk genotypes (<10%)**
  - - follow-up for islet autoantibody
  - - anticipatory diabetes education
  - - free glucometer, strips
  - - referral to a tertiary care center



Barker J, et al. Diabetes Care 2004

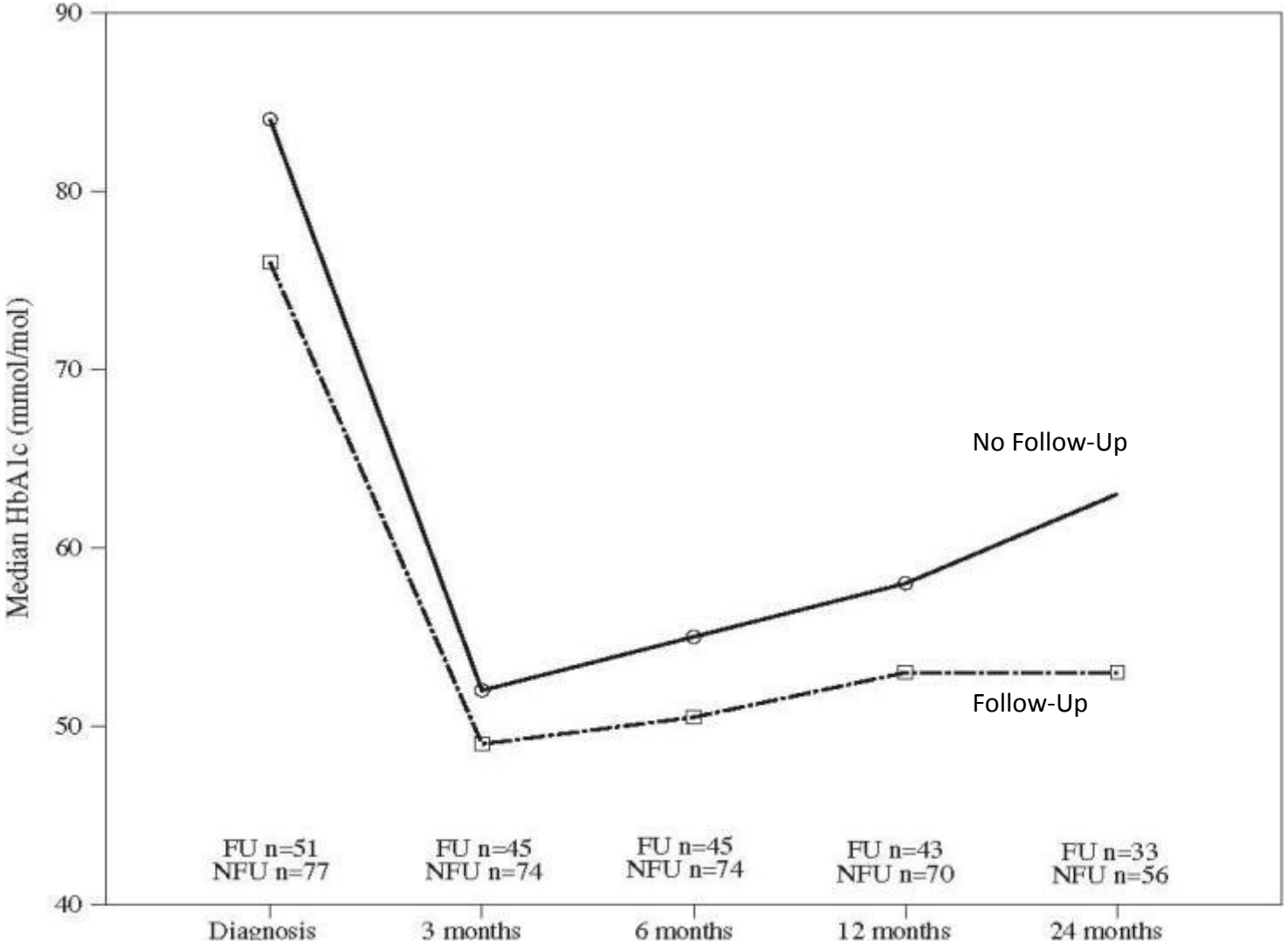
defining the early stages of type 1 diabetes T1D

HbA1c at Diagnosis in DAISY Cohort



defining the early stages of type 1 diabetes T1D

HbA1c At Diagnosis and First 2 Years in DiPiS

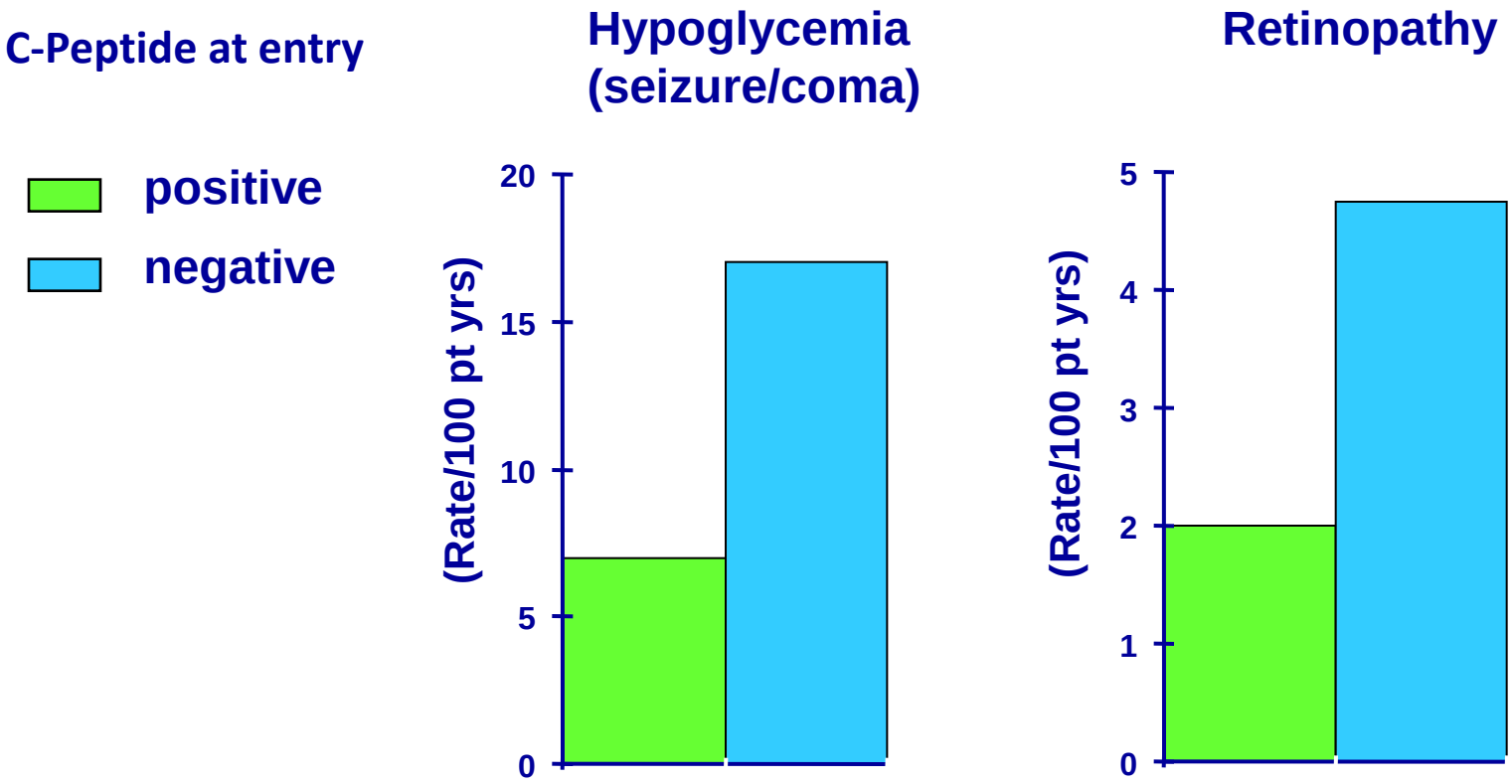


Pediatric Diabetes 2014 doi: 10.1111/pedi.12151

defining the early stages of type 1 diabetes T1D

Will earlier diagnosis and onset of insulin replacement therapy in T1D lead to greater preserved functional beta cell mass and decreased insulin dose requirements over time and decreased risk of hypoglycemia and long-term diabetic complications?

DCCT: Impact of Preserved C-Peptide on Hypoglycemia & Retinopathy



DCCT Research Group. Ann Intern Med 1998;128:517

defining the early stages of type 1 diabetes T1D

CONCLUSION

Screening should be performed in the context of defined research questions

Diabetes Care 37 (Suppl), 1 S18, 2014.

As soon as an intervention is shown to be safe and efficacious in slowing progression of Type 1 diabetes, wide-scale screening should begin

defining the early stages of type 1 diabetes T1D

defining the early stages of type 1 diabetes

T1D

Biomarkers in the Early Stages of T1D

Åke Lernmark, Professor
Department of Clinical Sciences
Lund University/CRC, Malmö, Sweden

Proposed Stages of Type 1 Diabetes

- **Stage 1: Autoimmunity+/Dysglycemia-/Asymptomatic T1D**

Multiple T1D-associated islet autoantibodies with normal glycemic control

- **Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D**

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

- **Stage 3: Symptomatic T1D**

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Current and Candidate Biomarkers: Risk Detection

1: Sensitivity, specificity and predictive value

2: ***Metabolomics:*** cord blood biomarkers

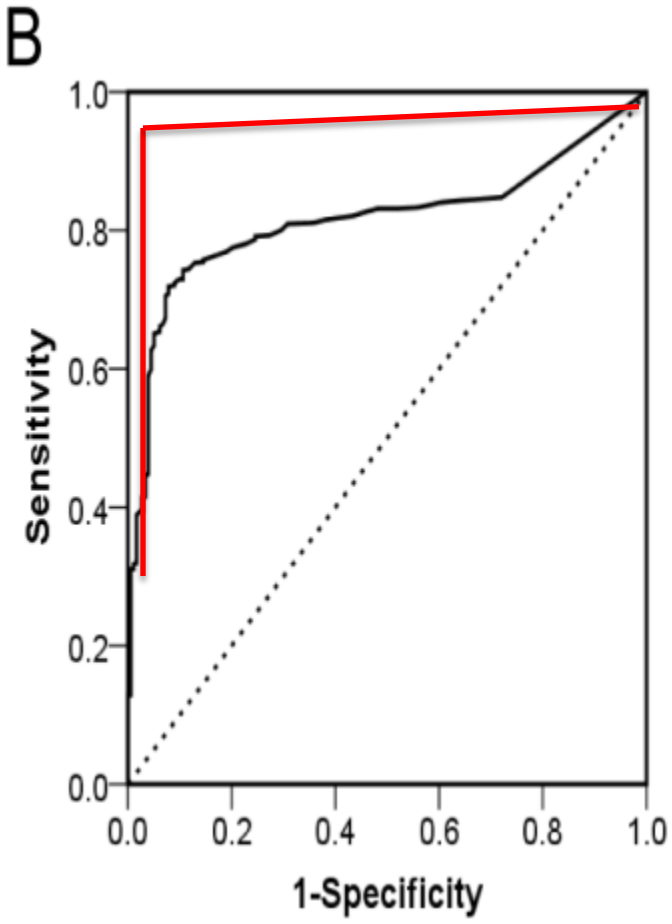
3: ***Systems Biology:*** will it define seroconversion to yield new biomarkers

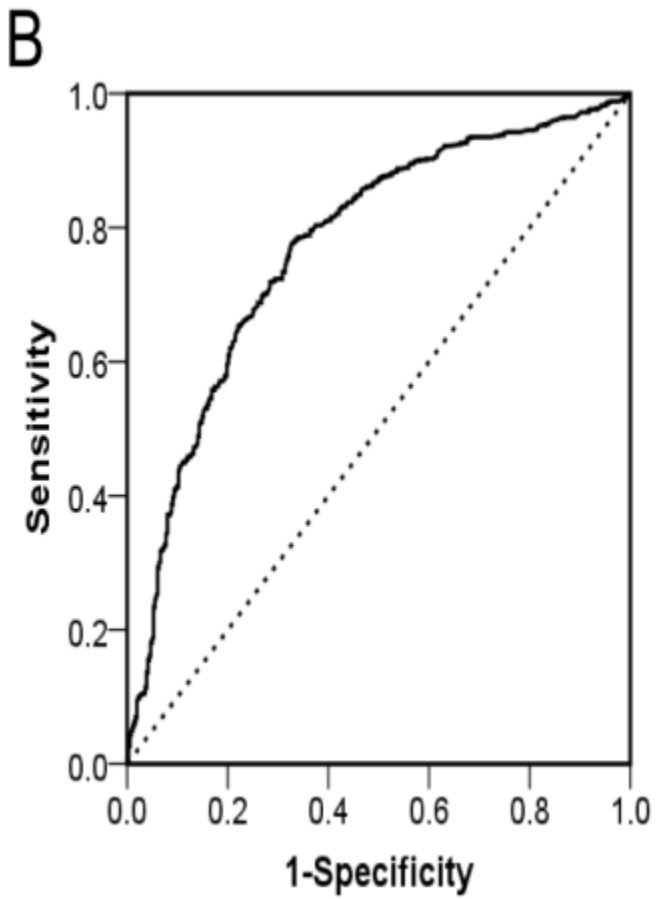
4: ***Genomics:*** HLA and Non-HLA genetic factors

5: ***Autoimmunity:*** next generation cellular and humoral tests

6: Summary

Sensitivity and specificity: Will “omics” do the trick?





Screening strategy: Step One: inclusive – false positives accepted.
Step Two: selective – false positives ruled out.

METABOLOMICS IN THE CORD BLOOD–
LOW PHOSPHOLIPIDS INCREASED THE RISK FOR T1D

CORD BLOOD LIPIDOMICS: Low phospholipids a biomarker for increased T1D risk.

ORIGINAL ARTICLE

Cord Serum Lipidome in Prediction of Islet Autoimmunity and Type 1 Diabetes

Matej Orešič,[1] Peddinti Gopalacharyulu,[1] Juha Mykkänen,[2,3] Niina Lietzen,[1] Marjaana Mäkinen,[2,3] Heli Nygren,[1] Satu Simell,[2,3] Ville Simell,[2,3] Heikki Hyöty,[4,5] Riitta Veijola,[6] Jorma Ilonen,[7,8] Marko Sysi-Aho,[1] Mikael Knip,[9,10,11,12] Tuulia Hyötyläinen,[1] and Olli Simell[2,3]

tidylcholines. A molecular signature was developed comprising seven lipids that predicted high risk for progression to T1D with an odds ratio of 5.94 (95% CI, 1.07–17.50). Reduction in choline-containing phospholipids in cord blood therefore is specifically associated with progression to T1D but not with development of β-cell autoimmunity in general. ***Diabetes*** **62:3268–3274, 2013**

ORIGINAL ARTICLE

Decreased Cord-Blood Phospholipids in Young Age–at–Onset Type 1 Diabetes

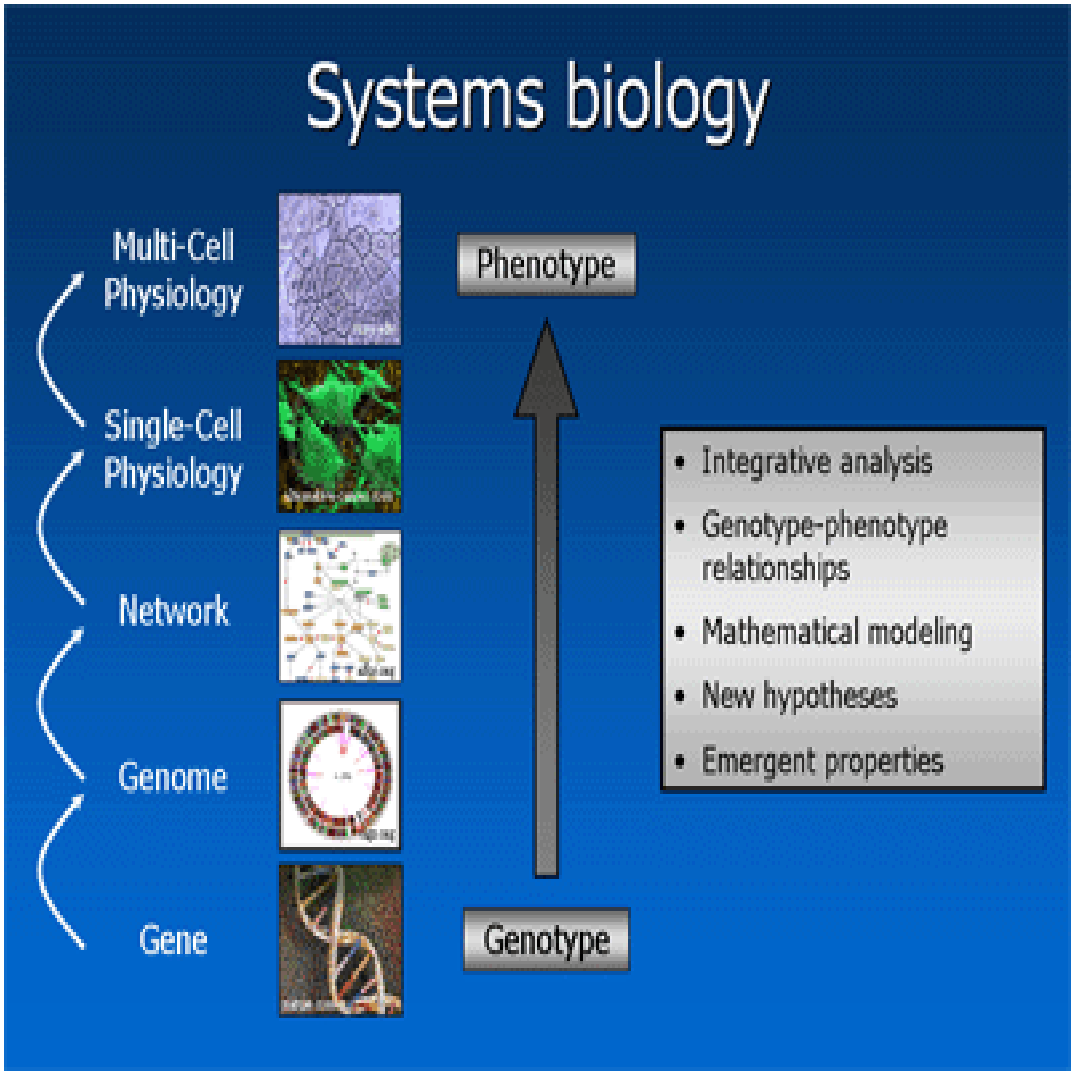
Daria La Torre,[1] Tuulikki Seppänen-Laakso,[2] Helena E. Larsson,[1] Tuulia Hyötyläinen,[2] Sten A. Ivarsson,[1] Åke Lernmark,[1] Matej Orešič,[2] and the DiPiS Study Group*

in index and control children. In conclusion, metabolomics of umbilical cord blood may identify children at increased risk for type 1 diabetes. Low phospholipid levels at birth may represent key mediators of the immune system and contribute to early induction of islet autoimmunity. ***Diabetes*** **62:3951–3956, 2013**

Future of phospholipids as a biomarker:
Recommendations to pregnant mothers to take folic acid should perhaps be complemented also to take phospholipids (lecithin)?

SYSTEMS BIOLOGY – WILL IT DETECT THE TRIGGER OF ISLET AUTOIMMUNITY?

Systems Biology Approach to detect trigger of seroconversion and beyond.



Analyses applicable to

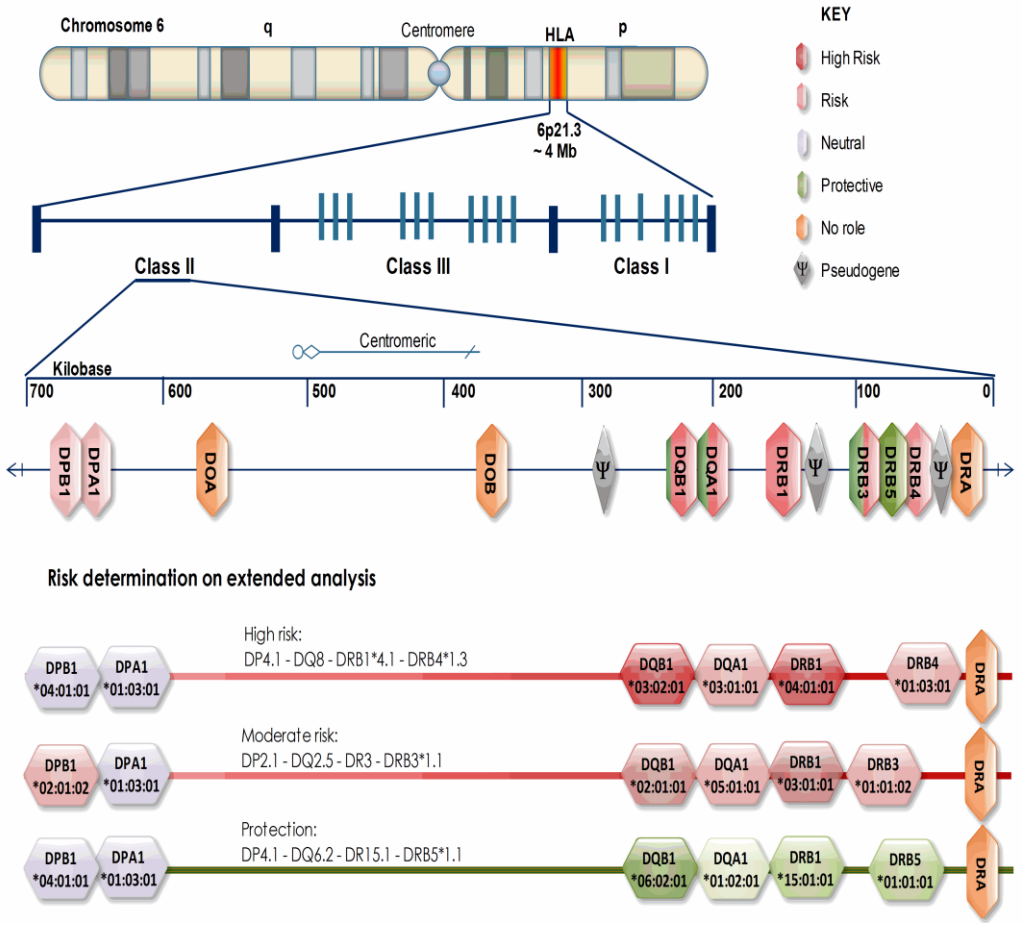
Pre-Stage I

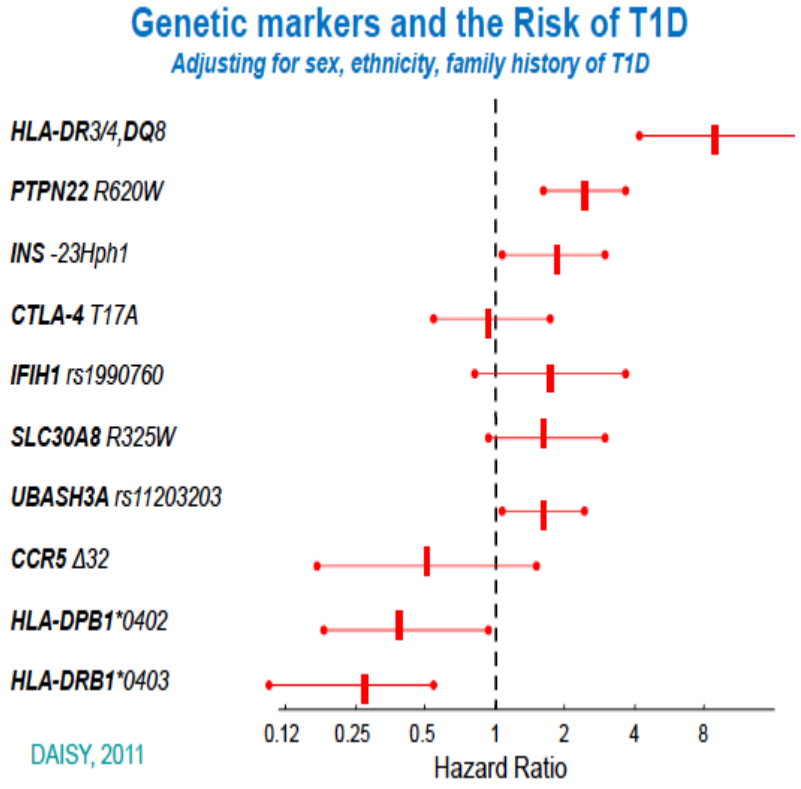
Stage I

Stage II

GENOMICS– IS THERE ROOM FOR INCREASED SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUE?

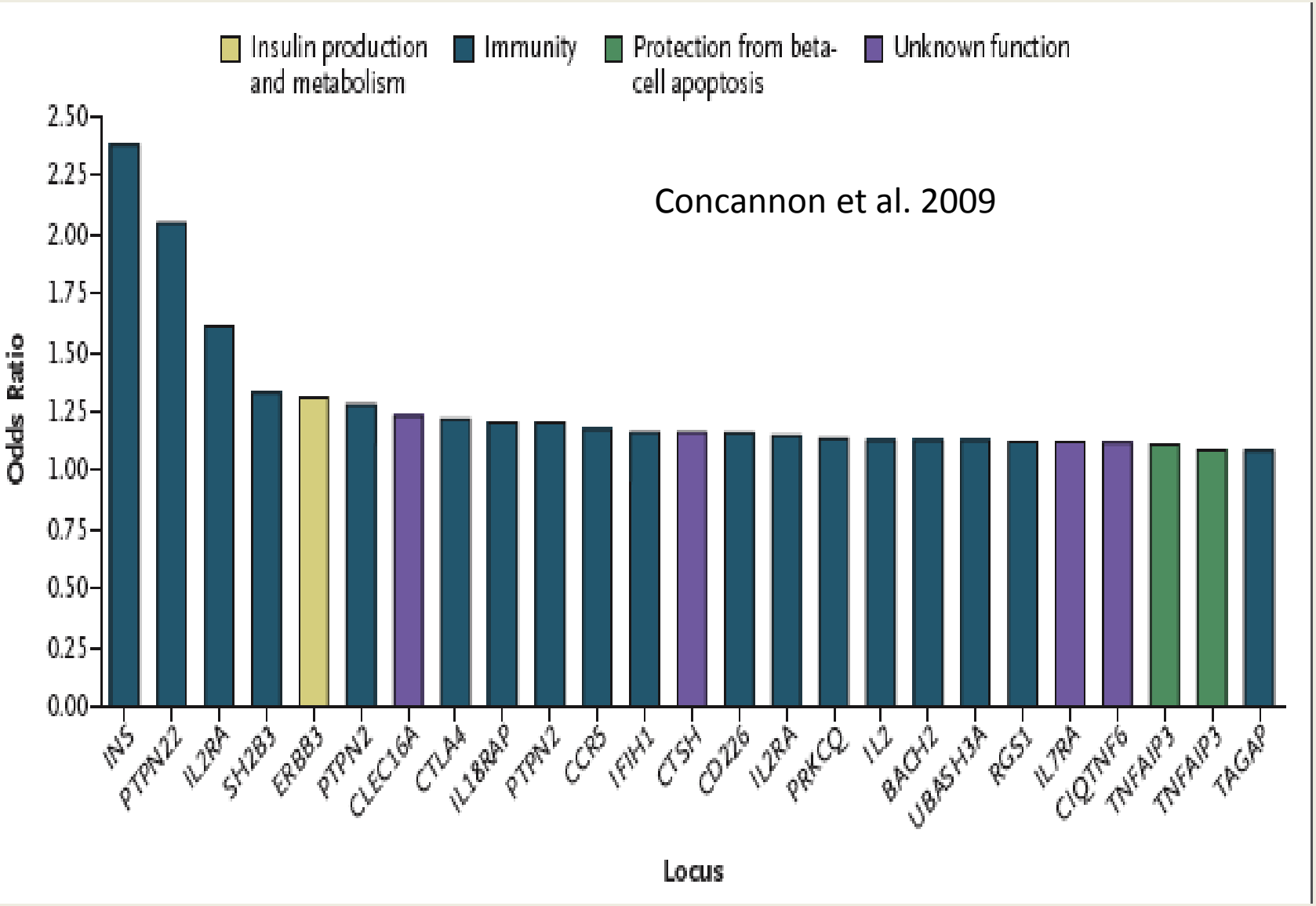
NEXT GENERATION SEQUENCING (NGS) – DO WE UNDERSTAND ALL VARIANTS? – WHAT IS THE ROLE OF NON-CODING SEQUENCES?





NGS may reduce the frequency of low risk individuals to be randomized to follow up for the risk of either T1D Stage I or II.

Non-HLA genetic factors for type 1 diabetes



Combining HLA with non-HLA genotypes for studies of seroconversion, Stage I or Stage II.

HLA AND 40 SNP

Winkler C, Krumsiek J, Buettner F, Angermüller C, Giannopoulou EZ, Theis FJ, Ziegler AG, Bonifacio E. :Feature ranking of type 1 diabetes susceptibility genes improves prediction of type 1 diabetes. Diabetologia. 2014 Sep 4. [Epub ahead of print]:

Feature selection identified HLA plus nine SNPs from the PTPN22, INS, IL2RA, ERBB3, ORMDL3, BACH2, IL27, GLIS3 and RNLS genes that could achieve similar prediction accuracy as the total SNP set.

T1DGC & DAISY

Valdes AM, Varney MD, Erlich HA, Noble JA. Receiver operating characteristic analysis of HLA, CTLA4, and insulin genotypes for type 1 diabetes. Diabetes Care. 2013 Sep;36(9):2504-7.

*Genotyping data sufficient to tag DR3, DR4-DQB1*03:02, CTLA4, and INS were shown to distinguish between subjects with type 1 diabetes and their unaffected siblings.*

Source: Click to edit source for this chart

AUTOIMMUNITY– WHAT ARE THE NEXT GENERATION CELLULAR AND AUTOANTIBODY BIOMARKERS?

Stage I: Islet Autoantibodies

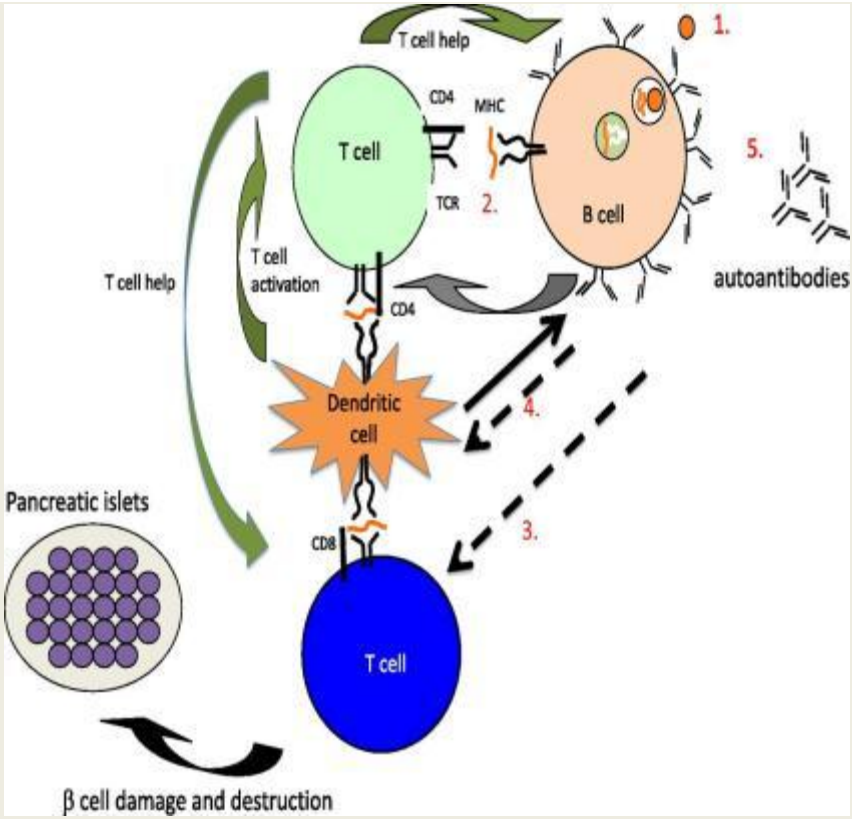
- Number
- Specificity (IA-2, ZnT8)
- Titer (IAA)
- Affinity (GAD)

ISLET AUTOANTIBODY STANDARDIZATION PROGRAM
1986 IMMUNOLOGY OF DIABETES WORKSHOPS (IDW)
WHO STANDARD: ICA , GADA AND IA-2A (JDF Units)
DIABETES AUTOANTIBODY STANDARDIZATION PROGRAM (DASP)
NIDDK STANDARD: GADA AND IA-2A (DK UNITS)
ISLET AUTOANTIBODY STANDARDIZATION PROGRAM (IASP)

Stage I and II Biomarker Challenge

- Biomarker that would predict seroconversion:
  - Antigen presentation
  - CD4+ T cell responses
  - CD8+ T cell activation
  - B cell activation – islet autoantibodies

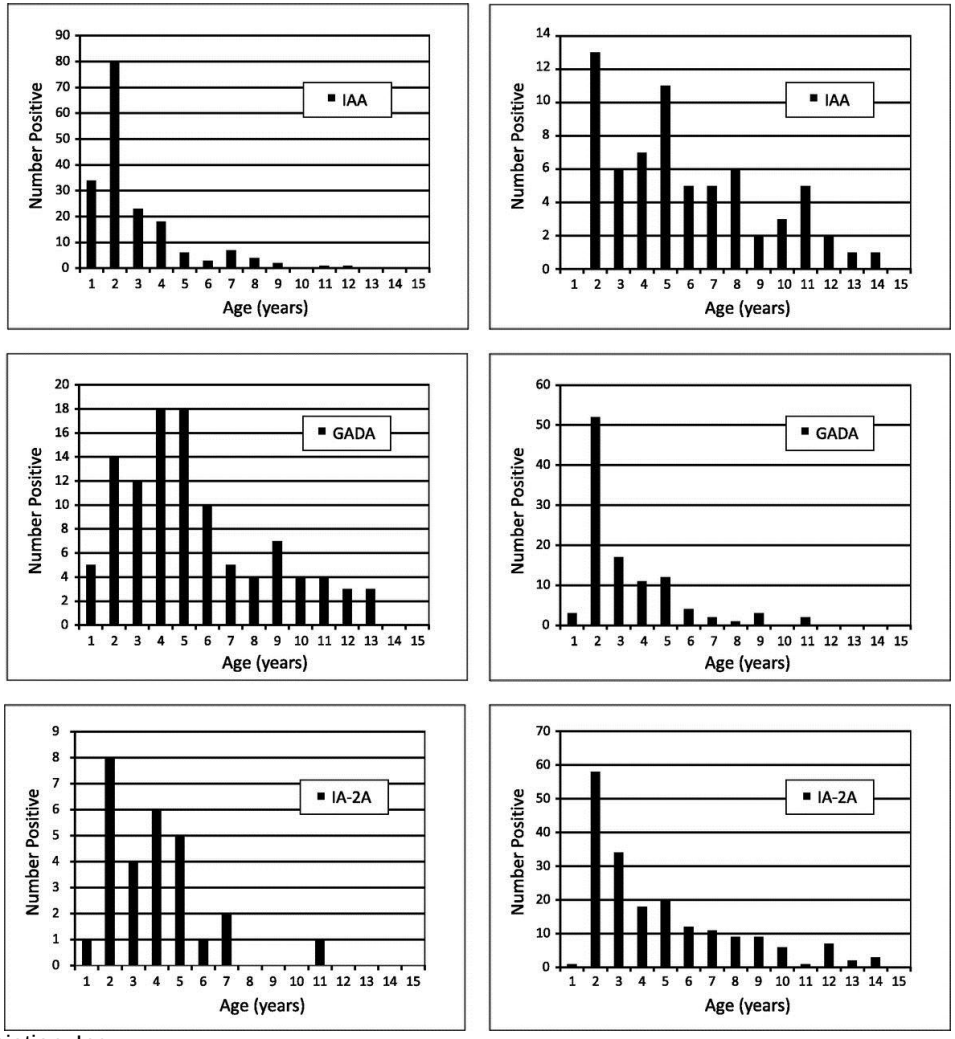
Stage I and II likely differ in cellular responses.



Wong S, Diabetes 83: 1855-1857, 2014

The age distribution for the appearance of the first autoantibody in the group of children with advanced β-cell autoimmunity (left panels) compared with the age distribution for the secondary autoantibodies appearing after the first autoantibody (right panels).

Ilonen J et al.
Diabetes 62:3636-3640, 2013



American Diabetes Association.

Possible next generation biomarkers for T1D Stage I and II

AUTOANTIBODY MARKERS
HIGH DENSITY PROTEIN ARRAYS
Massa et al. Serological Proteome Analysis (SERPA) as a tool for the identification of new candidate autoantigens in type 1 diabetes. J Proteomics. 82:263-73, 2013.
Miersch et al. Serological autoantibody profiling of type 1 diabetes by protein arrays. J Proteomics. 94:486-96, 2013.
Zhang et al. A plasmonic chip for biomarker discovery and diagnosis of type 1 diabetes. Nat Med. 20:948-53, 2014.
and others……..

BIOMARKERS OF ISLET AUTOIMMUNITY
REPORTER ASSAYS
Chen *et al.* Molecular signature differentiate immune states in Type 1 diabetes families. Diabetes. 2014 Apr 23.
GENE EXPRESSION INDIVIDUAL CELLS NEEDED FOR STAGE I AND II
McKinney et al. A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. Nat Med. 16:586-91,2010.

BIOMARKERS OF BETA-CELL FUNCTION
URINE C-PEPTIDE
Oram et al. The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. Diabetologia. 57:187-91, 2014.
DISCHARGE OF INTRACELLULAR MARKERS
Proinsulin, GAD65 and others
miRNA

Next generation biomarkers for T1D Stage I and II: Will they pass the acid tests?

ISLET AUTOANTIBODY STANDARDIZATION PROGRAM
1986 IMMUNOLOGY OF DIABETES WORKSHOPS (IDW)
WHO STANDARD: ICA , GADA AND IA-2A (JDF Units)
DIABETES AUTOANTIBODY STANDARDIZATION PROGRAM (DASP)
NIDDK STANDARD: GADA AND IA-2A (DK UNITS)
ISLET AUTOANTIBODY STANDARDIZATION PROGRAM (IASP)

NEWBORN SCREENING STUDIES
DiPP
BABYDIAB
DAISY
DiPiS
TEDDY

FDA REQUIREMENTS OF BIOMARKERS
INTEGRATION OF BIOMARKERS IN GLOBAL DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT
GENOMIC BIOMARKERS
DIFFERENTIAL GENE EXPRESSION SIGNATURE
FACILITATE DRUG OR BIOTECHNOLOGY PRODUCT DEVELOPMENT

Conclusion: Biomarkers in the Early Stages of T1D

1: Sensitivity, specificity and predictive value should improve above existing assays

2: ***Metabolomics:*** cord blood biomarkers – low level phospholipids

3: ***Systems Biology:*** will it yield novel biomarkers of the events leading to seroconversion?

4: ***Genomics:*** HLA and Non-HLA genetic factors show promise

5: ***Autoimmunity:*** next generation cellular and humoral tests will be needed for Stage I and II

6: **Stage I and II defined on autoantibodies:** what are the next generation assays?

defining the early stages of type 1 diabetes

T1D

THANK YOU

JDRF IMPROV LIVES. CURING TYPE 1 DIABETES

DiPiS

Battre Diabetes Diagnos

DIAPREV-IT
Diabetes Prevention - Immun Tolerans

TEDDY

defining the early stages of type 1 diabetes

Current and Candidate Biomarkers for Staging of Progression in Early Stages of Type 1 Diabetes

Kevan C. Herold, MD

Departments of Immunobiology and Internal Medici

Yale University

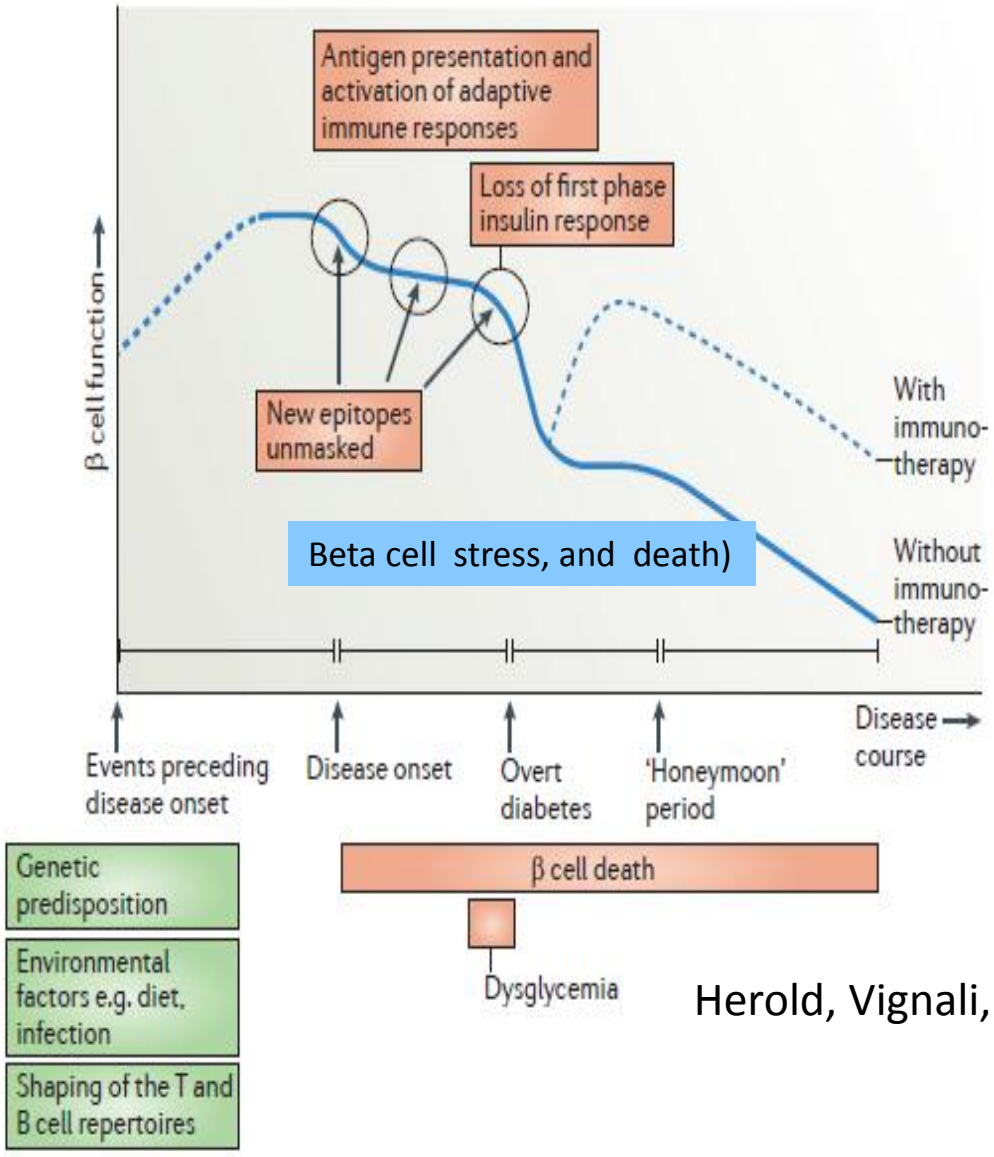
Biomarkers in At-Risk Setting of T1D

- Identification, validation, and use of biomarkers in the at-risk setting to understand the progression of Type 1 diabetes and identify subjects for clinical trials. Biomarker development will need to go hand-in-hand with characterizing the heterogeneity and pathogenesis of the disease that may improve selection of subjects for prevention studies.

Outline

- Current biomarkers of dysglycemia
- Can beta cell stress and beta cell death be detected in at-risk individuals with normal glucose tolerance?
- Analysis of glucose tolerance in the prediabetic period. What accounts for the heterogeneity of progression?
- Can the cellular immune process that leads to T1D be identified?
- What other modalities may be useful for evaluating individuals at risk?

Natural History of Type 1 Diabetes



Herold, Vignali, Cooke, Bluestone, NRI,

Dysglycemia in the prediabetes setting:

- OGTT
  - 120 min plasma glucose: ≥ 140mg/dL (≥7.8mmol/L)
  - 30, 60, or 90 min plasma glucose: >200 mg/dL (≥11.1mmol/L)
- IVGTT: FPIR, other
- Fasting plasma glucose: >110mg/dL (≥6.1mmol/L)
- HbA1c
  - Rising- 10% change
  - Absolute level

Patterns of Metabolic Progression to Type 1 Diabetes in the Diabetes Prevention Trial-Type 1

Jay M. Sosenko, MD[1]
Jerry P. Palmer, MD[2]
Carla J. Greenbaum, MD[3]
Jeffrey Mahon, MD[4]
Catherine Cowie, PhD[5]
Jeffrey P. Krischer, PhD[6]
H. Peter Chase, MD[7]
Neil H. White, MD[8]
Bruce Buckingham, MD[9]
Kevan C. Herold, MD[10]
David Cuthbertson, MS[6]
Jay S. Skyler, MD[1]
the Diabetes Prevention Trial–Type 1 Study Group

[redacted]

tes Care 2006; 29:643-649

Glucose and C-Peptide Changes in the Perionset Period of Type 1 Diabetes in the Diabetes Prevention Trial-Type 1

Jay M. Sosenko, MD[1]
Jerry P. Palmer, MD[2]
Lisa Rafkin-Mervis, MS, CDE[2]
Jeffrey P. Krischer, PhD[3]
David Cuthbertson, MS[4]
Della Matheson, RN[2]
Jay S. Skyler, MD[1]

[redacted]

tes Care 2008; 31:2188-2192

PERSPECTIVES IN DIABETES

The Metabolic Progression to Type 1 Diabetes as Indicated by Serial Oral Glucose Tolerance Testing in the Diabetes Prevention Trial–Type 1

Diabetes 2012; 61:1331-1337

Jay M. Sosenko,[1] Jay S. Skyler,[1] Kevan C. Herold,[2] Jerry P. Palmer,[3] and the Type 1 Diabetes TrialNet and Diabetes Prevention Trial–Type 1 Study Groups

defining the early stages of type 1 diabetes T1D

Key features of metabolic progression in individuals at-risk for T1D

- Glucose levels are increasing at least 2 years before dx
- Despite increasing glucose levels, fasting and overall measures of C-peptide change little until 6 mos before dx
- Peak C-peptide is delayed at least 2 years before dx. It occurs even later as diagnosis approaches.
- Although glucose levels increase during

Glucose (mg/dL) and C-peptide (ng/mL) values of DPT-1 participants (n = 115) with OGTTs 6 months before diagnosis and at diagnosis

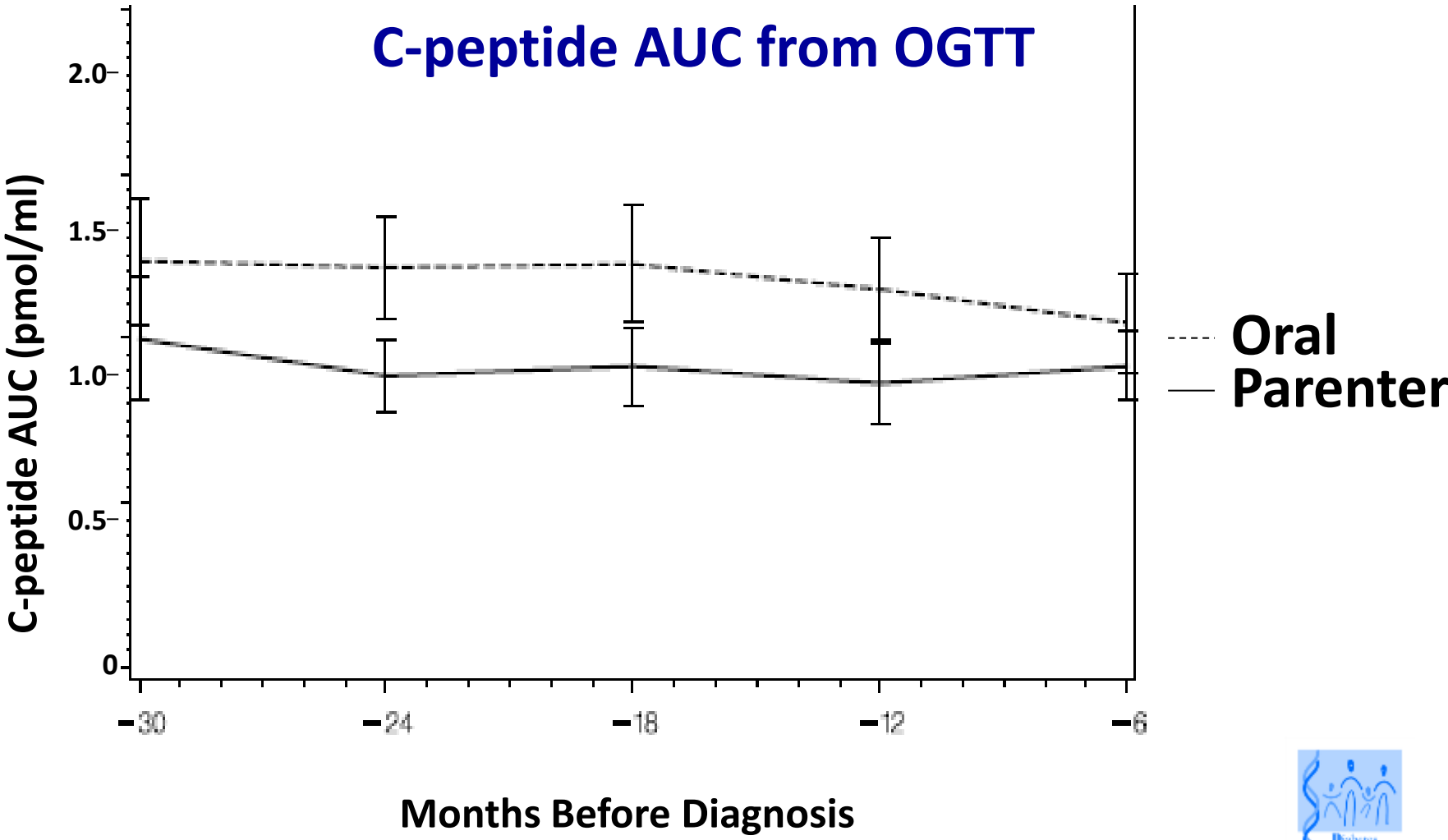
	6 months before diagnosis	At diagnosis
Fasting glucose	93 ± 13	113 ± 29++
2-h glucose	155 ± 29	289 ± 71++
AUC glucose/120 min	165 ± 23	240 ± 48++
Fasting C-peptide	1.16 ± 0.72	1.41 ± 1.16+
Peak C-peptide	4.57 ± 1.86	3.86 ± 2.29++
AUC C-peptide/120 min	3.44 ± 1.42	2.92 ± 1.74++
Fasting C-peptide/fasting glucose	0.013 ± 0.008	0.012 ± 0.009
AUC C-peptide/AUC glucose	0.021 ± 0.009	0.013 ± 0.009++

Data are shown as mean ± SD. +$P < 0.01$. ++$P < 0.001$ for differences from 6 months before diagnosis.

Sosenko et al, Diabetes 2012

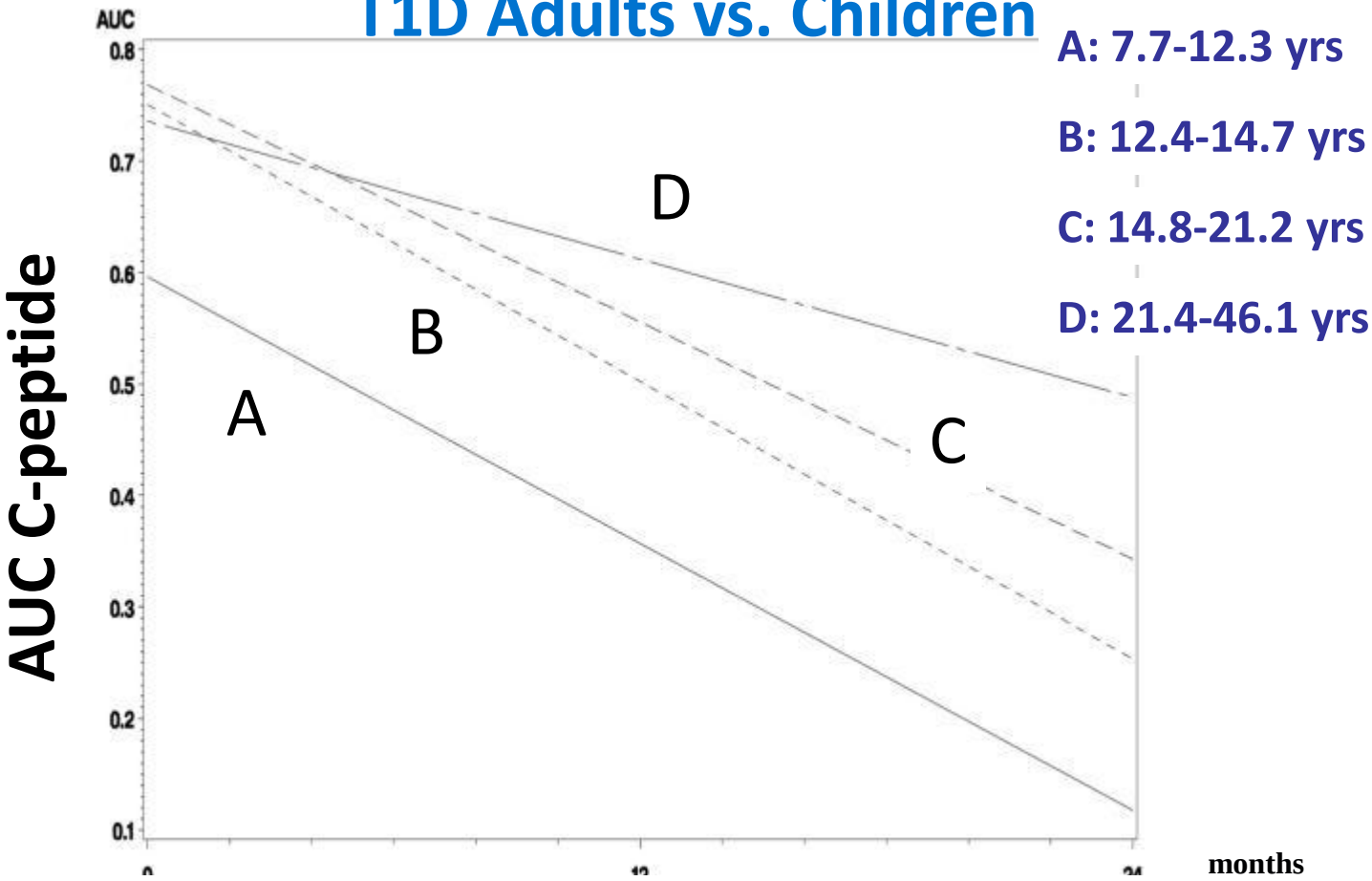
defining the early stages of type 1 diabetes T1D

C-Peptide AUC Is Relatively Flat for the Period Up to 6 months Prior to Diagnosis



Sosenko et al. Diabetes Care 2006; 29:643-649

Functional Beta Cell Mass is Better Preserved in New Onset T1D Adults vs. Children



Model-based estimates of average slopes of AUC C-peptide over time according to age quartiles

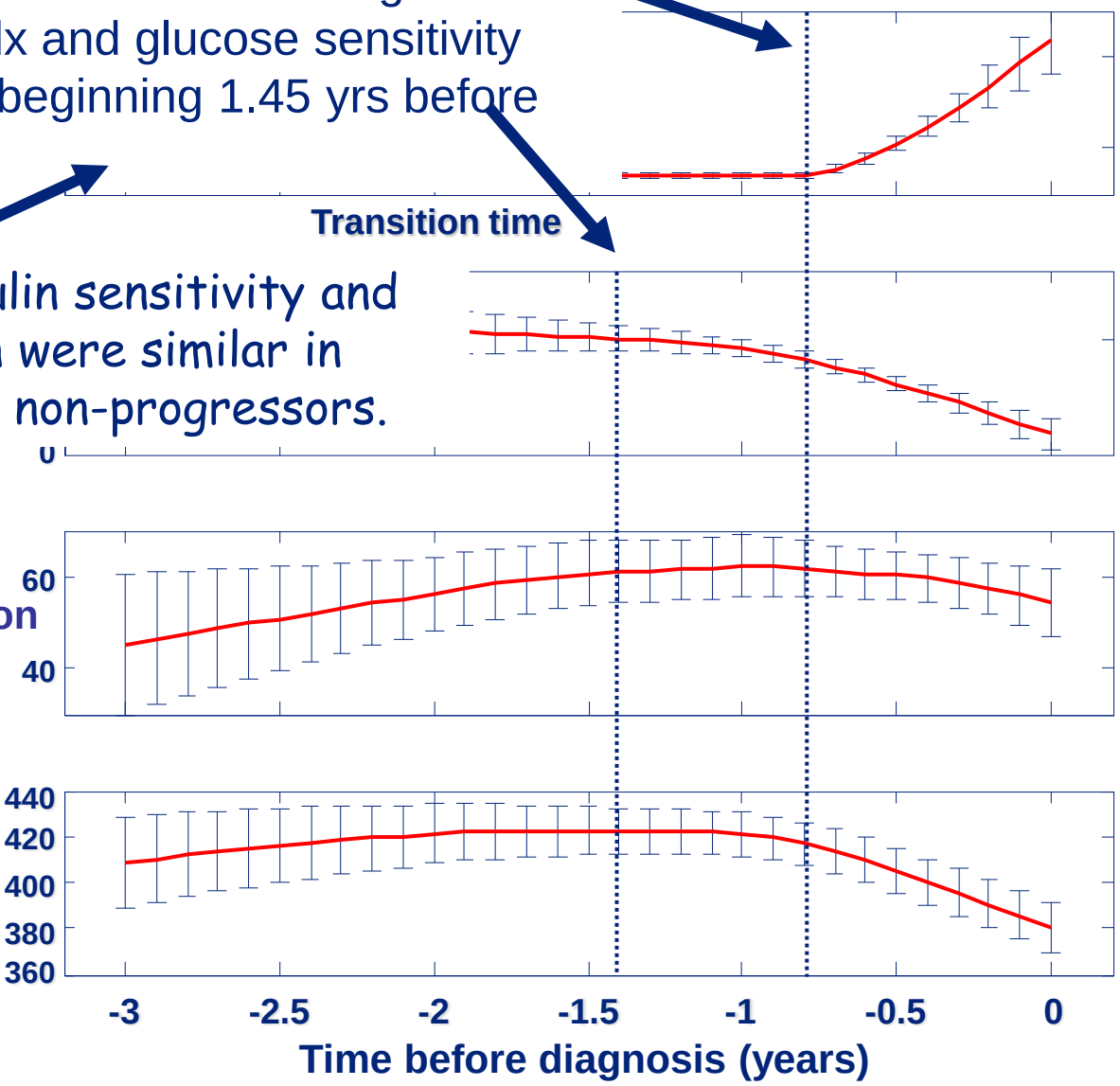
. Diabetes 2012;61:2066-2073

Type 1 Diabetes TrialNet

-cell Glucose Sensitivity Decreases Earlier than Other Paramete

In progressors 2 hr glucose levels changed little until 0.78 yrs before dx and glucose sensitivity declined significantly beginning 1.45 yrs before dx.

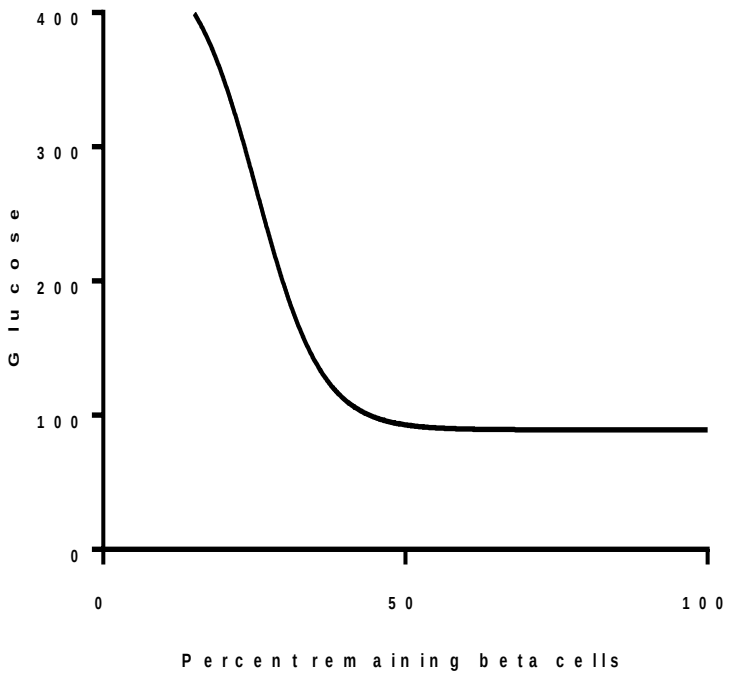
At baseline, insulin sensitivity and insulin secretion were similar in progressors and non-progressors.



Ferrannini et al. Diabetes 2010; 59:679-685

The need for a direct measurement of beta cell killing: Problems with existing approaches

- Glucose and HbA1c levels normal until close to diagnosis (Sosenko et al, Diabetes Care 2006; Sosenko et al, Diabetes 2012)
- Elevated glucose levels may only occur after extreme beta cell loss.
- Autoantibodies do not provide direct information on the pathologic process.
- T-cell assays can differentiate patients with T1D from HC, not all labs can perform these and the relationship between the appearance of these cells and beta cell killing has not been evaluated. (Herold et al, Diabetes 2012)



defining the early stages of type 1 diabetes T1D

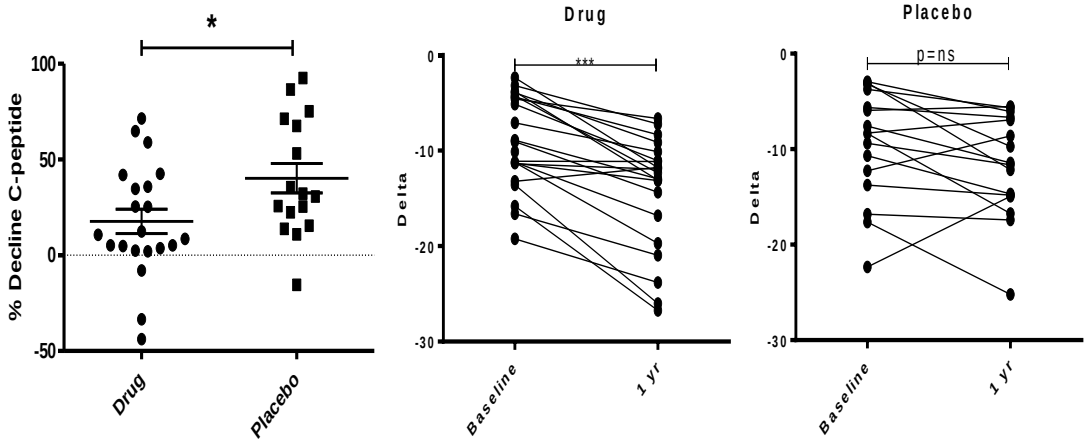
Rationale for an Assay to Measure Beta Cell Death In-Vivo

- Beta cell function affected by environmental factors
- Beta cell death is a silent event
- Methylation is one epigenetic control mechanism that can affect gene transcription.
- When cells die, they release their DNA into the bloodstream.
- The only source of unmethylated insulin DNA should be dead beta cells. This assay is based on the detection of unmethylated *INS* DNA in the serum. Two methods have been used: nested PCR ("delta") and droplet digital PCR

Akirav PNAS, 2011; Lebastchi Diabetes 2013; Usmani-Brown Endocrinology, 2014

Identification of beta cell death following autologous islet transplants or successful immune therapy

Anti-CD3 (teplizumab) treatment of recent onset T1D

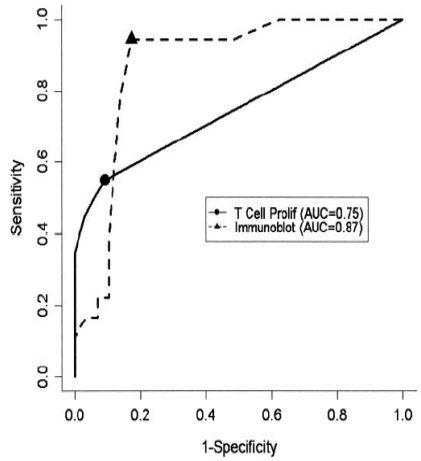


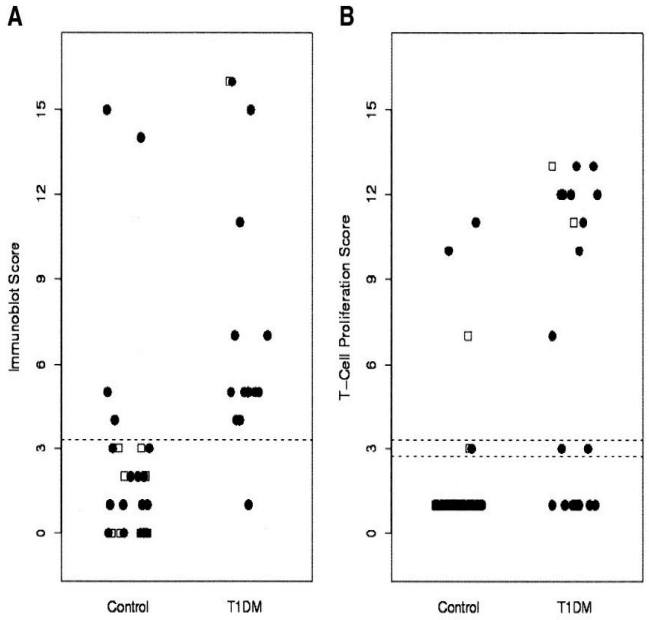
(Lebastchi Diabetes 2013)

Outline

- Current biomarkers of dysglycemia
- Can beta cell stress and beta cell death be detected in at-risk individuals with normal glucose tolerance?
- Analysis of glucose tolerance in the prediabetic period. What accounts for the heterogeneity of progression?
- **Can the cellular immune process that leads to T1D be identified?**
- What other modalities may be useful for evaluating individuals at risk?

Cellular assays: T cell immunoblot and T cell proliferation assays





Sensitivity and specificity of the assays

	n	Sensitivity	Composite 95% CI	Specificity	Composite 95% CI
T-cell proliferation	52	0.58	0.37–0.79	0.91	0.79–1.0
Immunoblot	47	0.94	0.83–1.0	0.83	0.69–0.97
GAD65	62	0.74	0.57–0.91	0.85	0.72–0.95
ICA512	62	0.52	0.30–0.74	0.97	0.92–1.0

Seyfert-Margolis, Diabetes, 2006

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TrialNet Analysis of Immune Cellular Studies

TABLE 2
Numbers of specimens assayed and measures* of the ability to discriminate between subjects with and without type 1 diabetes for autoantibodies alone† and each T-cell assay

	Specimens evaluable‡	Indeterminant§	Sensitivity	Specificity	Correct classification	Positive predictive value	Negative predictive value	Odds ratio‖	*P*
Autoantibodies (one or more)	296 (99.7)	—	83	92	88	91	84	56.9	<0.0001
Anti-GAD65	296 (99.7)	—	68	98	83	98	76	124.8	<0.0001
Anti-ICA512	296 (99.7)	—	58	99	78	98	70	119.3	<0.0001
Anti-ICA	296 (99.7)	—	59	94	76	91	69	22.6	<0.0001
Cellular immunoblot	122 (68.2)	6 (4.9)	74	88	81	86	77	21.7	<0.0001
T-cell proliferation	151 (84.4)	0	60	69	64	66	63	3.36	0.0041
Tetramer	117 (76.5)	32 (27.4)	46	72	59	63	57	2.10	0.076
U.S.-ELISPOT	87 (56.8)	0	35	65	50	51	50	1.09	0.95
U.K.-ELISPOT	109 (100)	8 (7.3)	61	69	65	66	64	3.44	0.0026

Herold et al, Diabetes 2009

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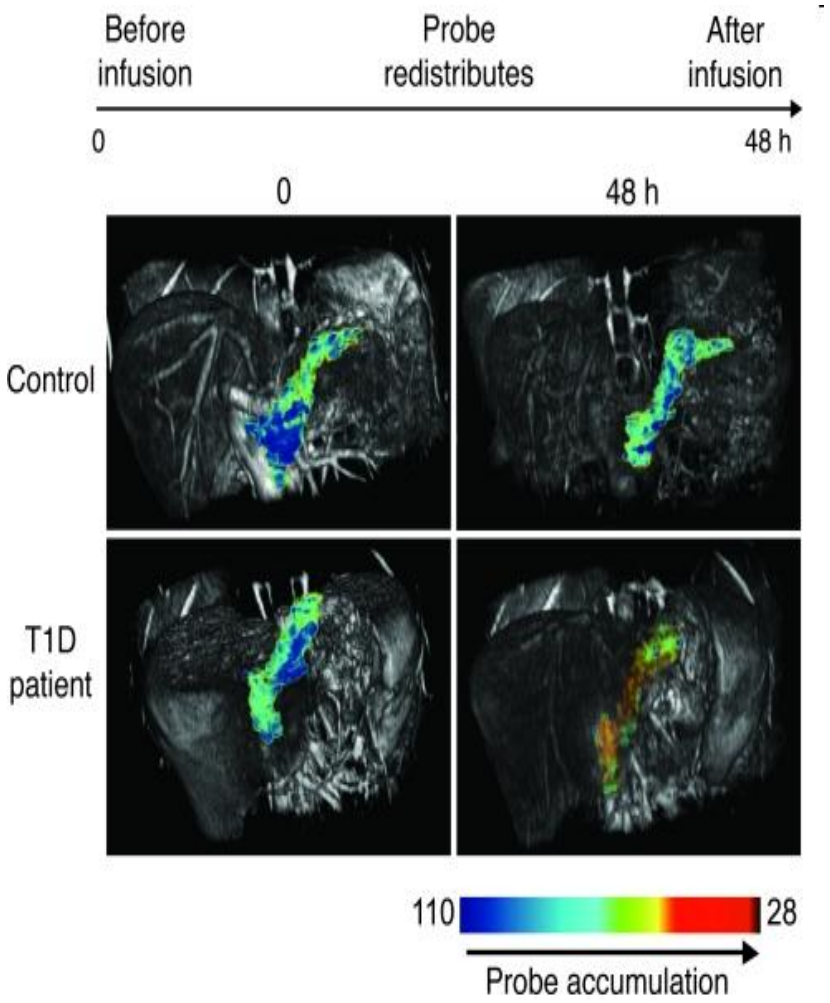
Insulitis May be Visualized by MRI



Gaglia JL et al, J Clin Invest. 2011 Jan 4;121(1):442-5

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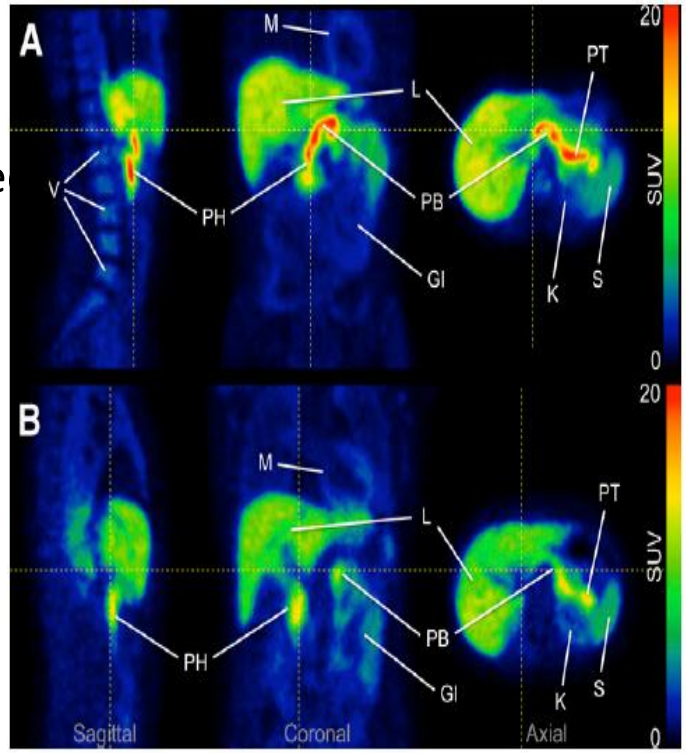
Imaging beta cell mass with ^{18}F-fluoropropyl-Dihydrotetrabenazine and PET

Non-diabetic subje

Subject with T1D



Normadin et al, J Nucl Med 2012

defining the early stages of type 1 diabetes T1D

Conclusions

- Increased levels of unmethylated *INS* DNA (reflecting beta cell death) can be detected about 1 ½-2 yrs before the diagnosis of T1D
- Insulin secretory dysfunction corresponds to episodes of increases in levels of unmethylated *INS* DNA in at-risk subjects
- Individuals at very high risk for T1D have elevated levels of unmethylated INS DNA in their serum
- Insulin secretory dysfunction is the feature that distinguishes individuals who meet diagnostic laboratory criteria of “diabetes” from those who do not

What else do we need?

- The reason for the delayed insulin secretion is not known. This is associated with an increase in unmethylated *INS* (beta cell death) but there is a reversible component.
- Additional measures of beta cell stress may identify more frequent episodes that warrant interventions with cellular protective agents.
- The relationship between cellular immune assays and beta cell killing and stress are under investigation.
- Insulitis imaging and quantitative measurement of

Acknowledgements

- Jeff Bluestone
- Eitan Akirav
- Sahar Usmani-Brown
- Michel Ledzet
- Jasmin Lebastchi
- Nicole Sherry
- Jake Kushner
- Craig Beam

- Funding
  - ITN
  - TrialNet
  - NIDDK
  - NIAID
  - JDRF
  - Brehm Coalition
  - Howalt family

defining the early stages of type 1 diabetes T1D

defining the early stages of type 1 diabetes

T1D

Early Stages of T1D

Richard Insel

JDRF

Scientific Framework of the Workshop

- T1D is a disease continuum that begins prior to symptomatic disease √
- Risk of developing T1D can be identified and quantified √
- T1D has well-defined, reproducible early stages that reach a point of inevitability of symptomatic T1D √
- Relative rate of progression to symptomatic T1D can be predicted with appreciable accuracy √
- The ability to screen for risk and stage T1D prior to symptomatic T1D has benefit today, and in the future, will provide a unique opportunity to intervene to delay, and ultimately prevent, the onset of clinical symptoms and life-long insulin dependence √

Proposed Stages of Type 1 Diabetes

Stage 1: Autoimmunity+/Dysglycemia–/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Autoimmunity+/Dysglycemia+/Asymptomatic T1D

Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

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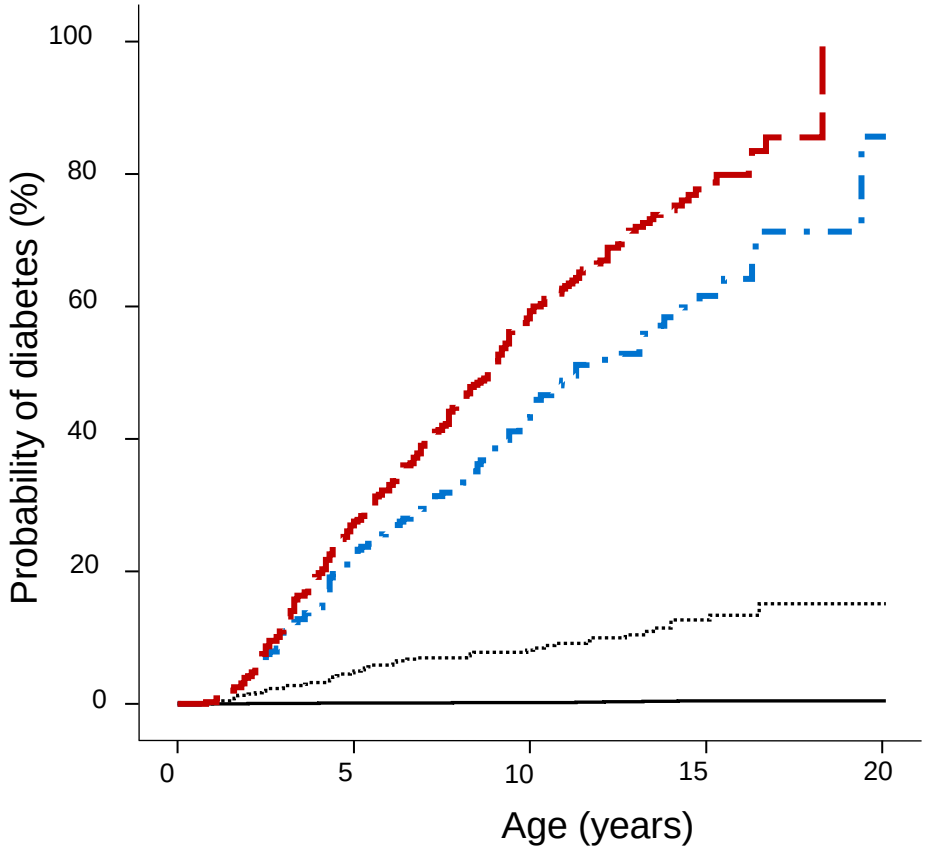
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Children with Multiple Islet Autoantibodies Progress to Symptomatic Diabetes



3 AB pos

2 AB pos

1 AB pos

AB neg

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

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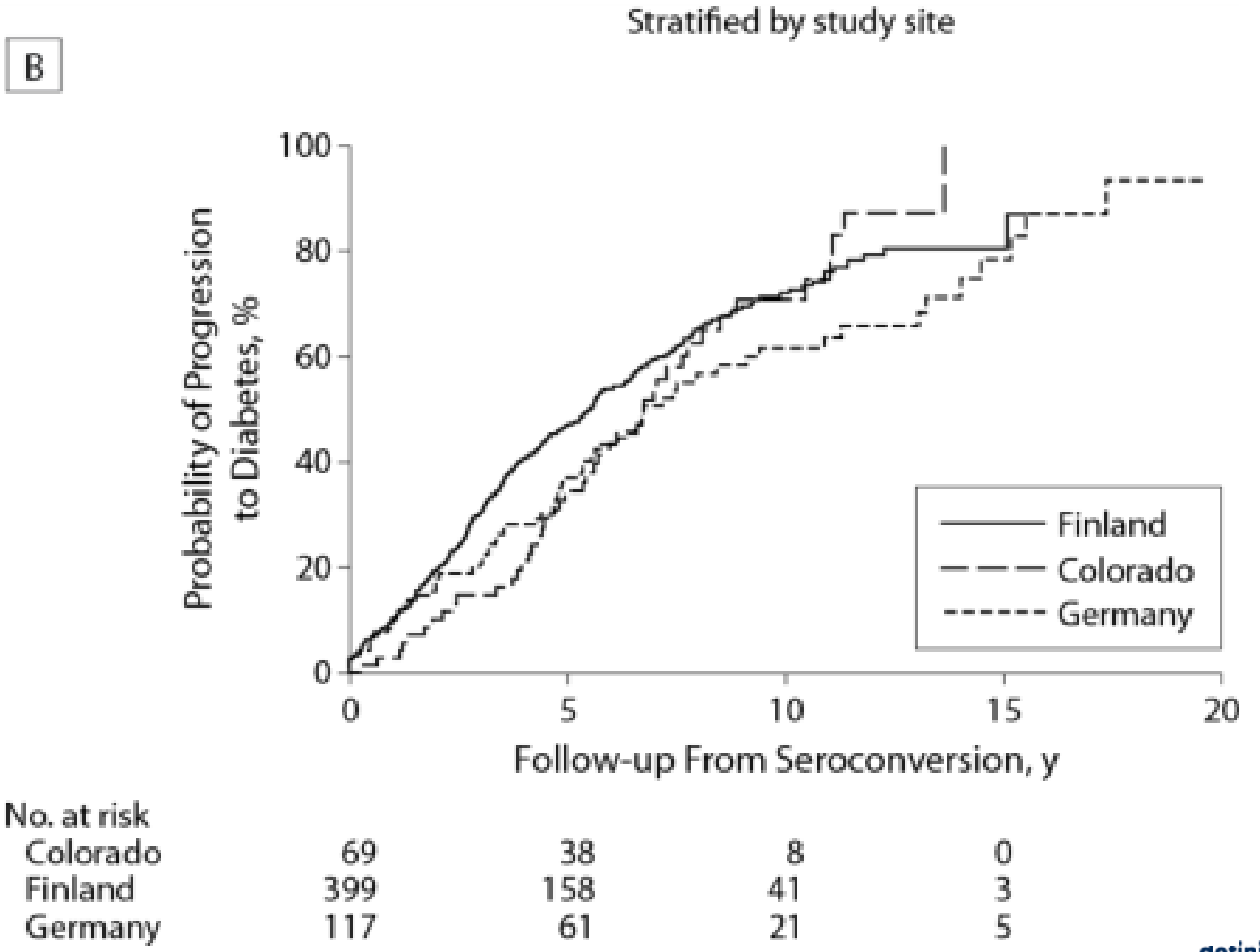
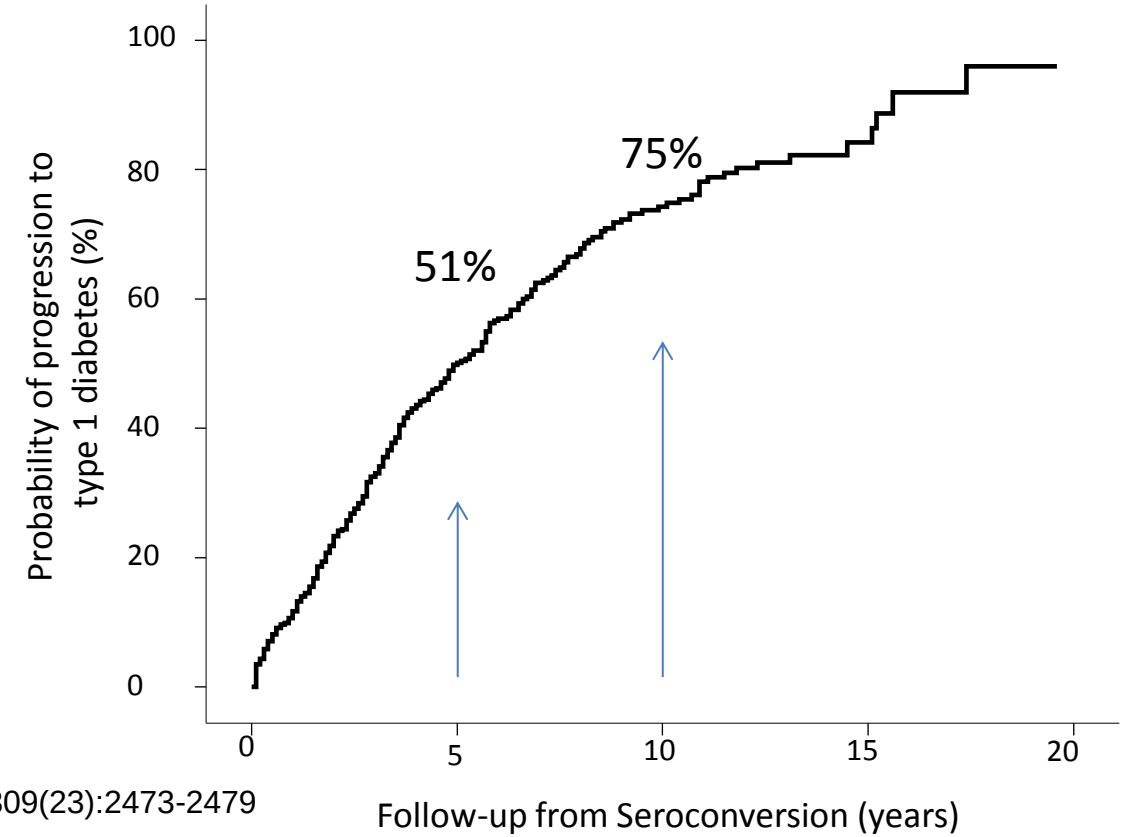
Also in General Population Children



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

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



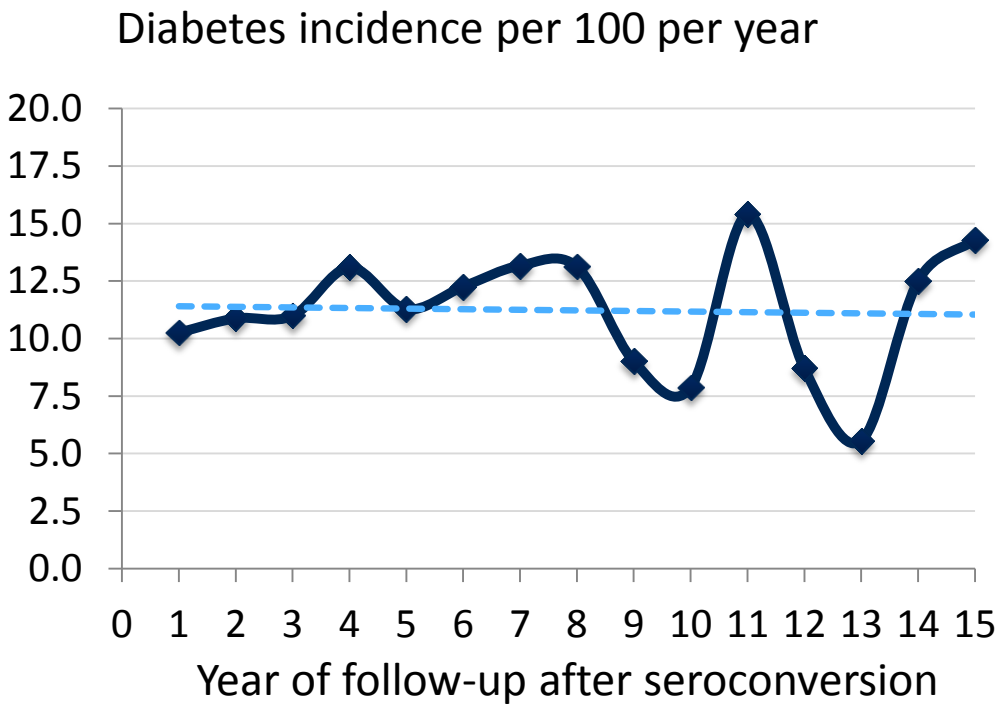
JAMA. 2013;309(23):2473-2479

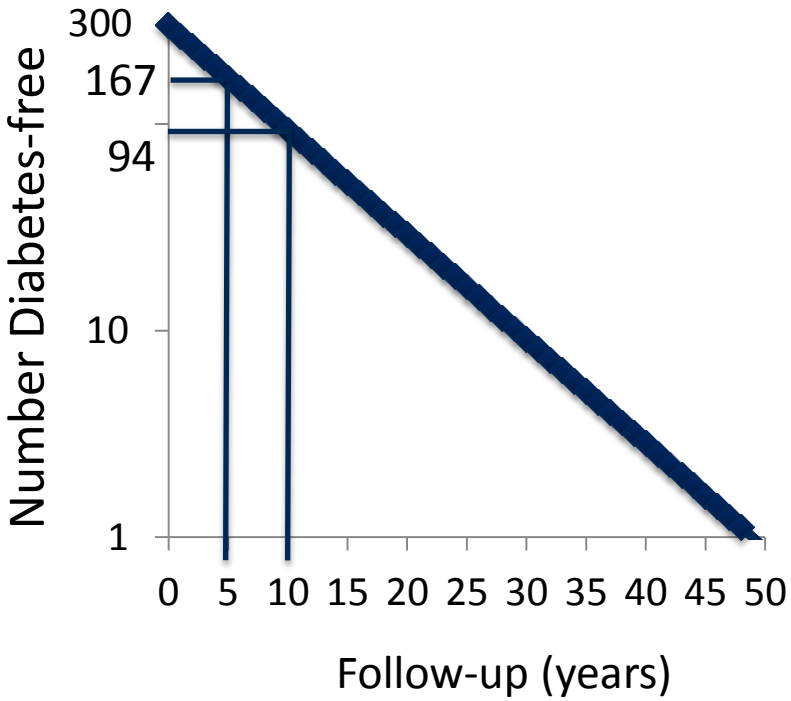
And the Lifetime Risk Approaches 100%

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**

Estimated Progression to Symptomatic T1D

Risk is persistently around 11% per year





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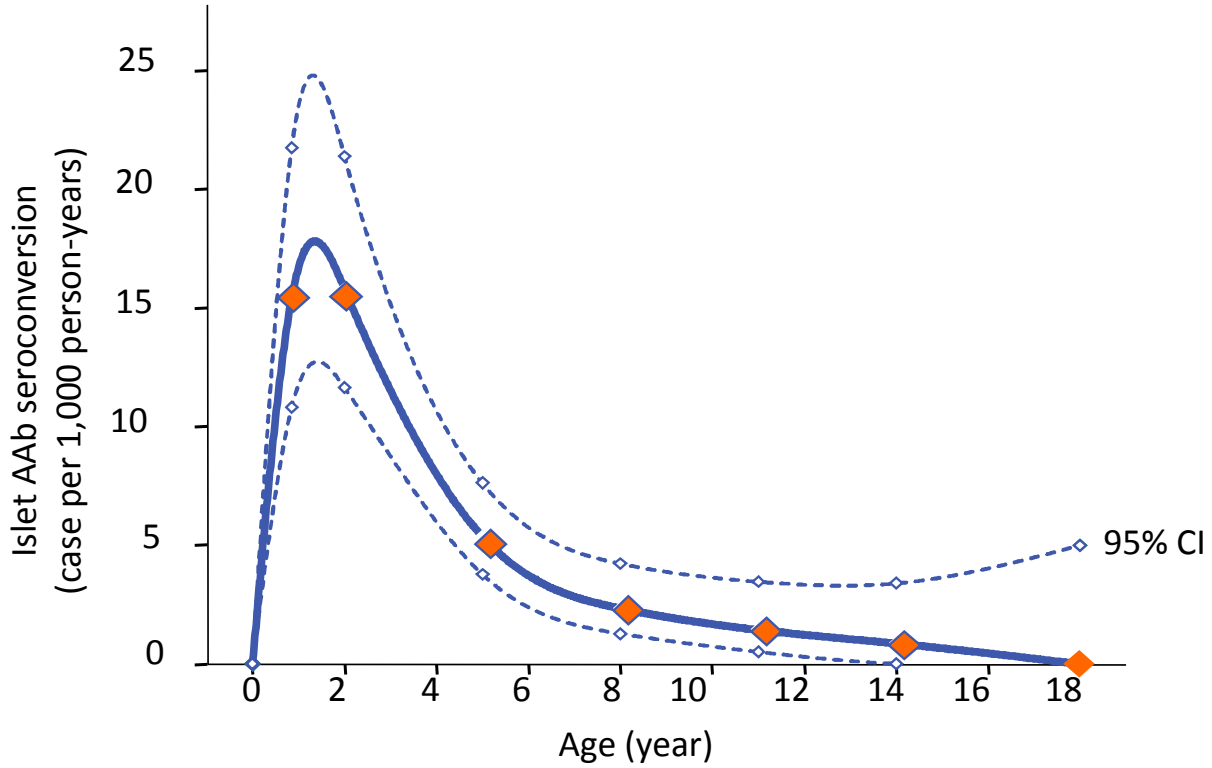
Multiple Islet Autoantibodies Are Detected Early in Life

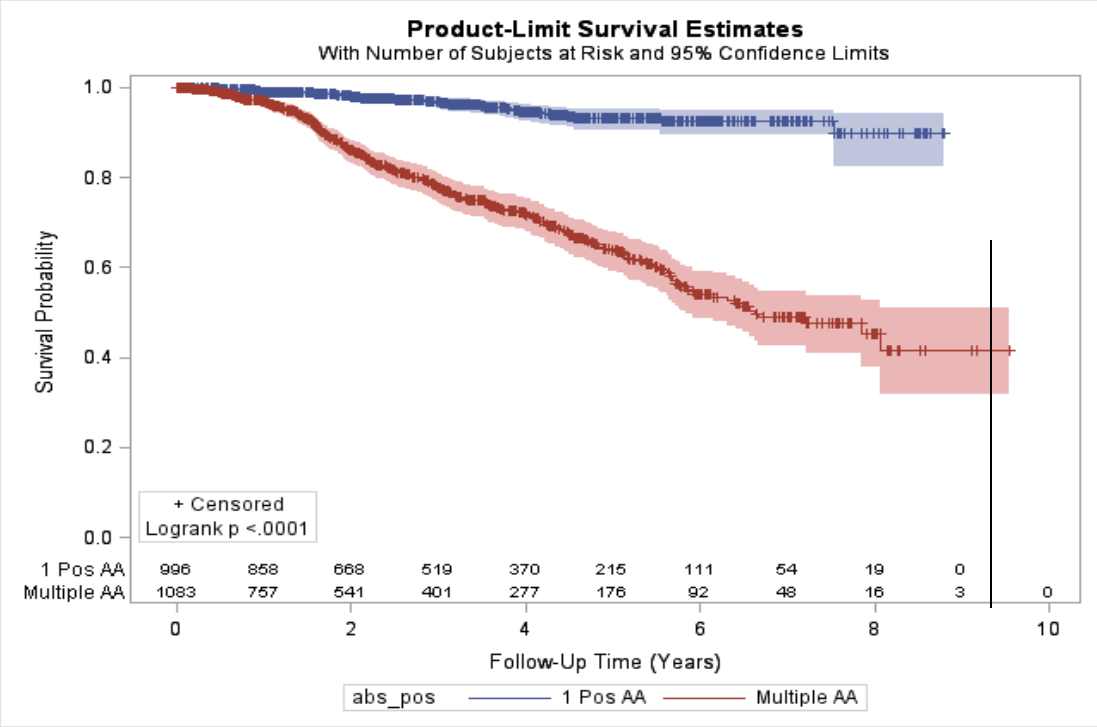
Incidence of islet autoantibodies in cases that become multiple Abs amongst unselected FDRs



Ziegler, Bonifacio, Diabetologia 2012

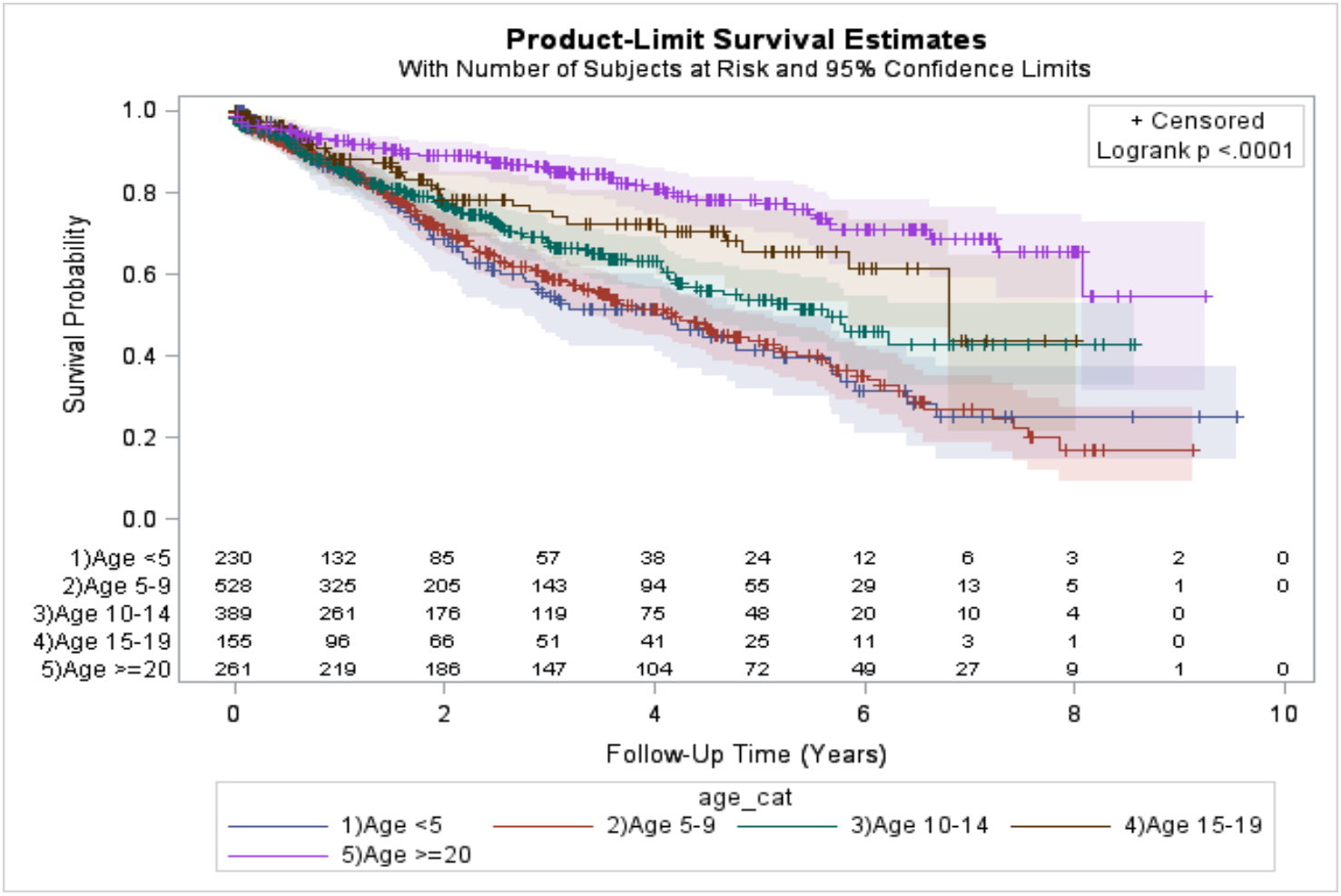
Immune Markers of Symptomatic Diabetes Risk in First Degree Relatives

	5-Year Risk	Prevalence
▪ Single antibody	<10%	3.1%
▪ Multiple antibodies	30-50%	2.2%



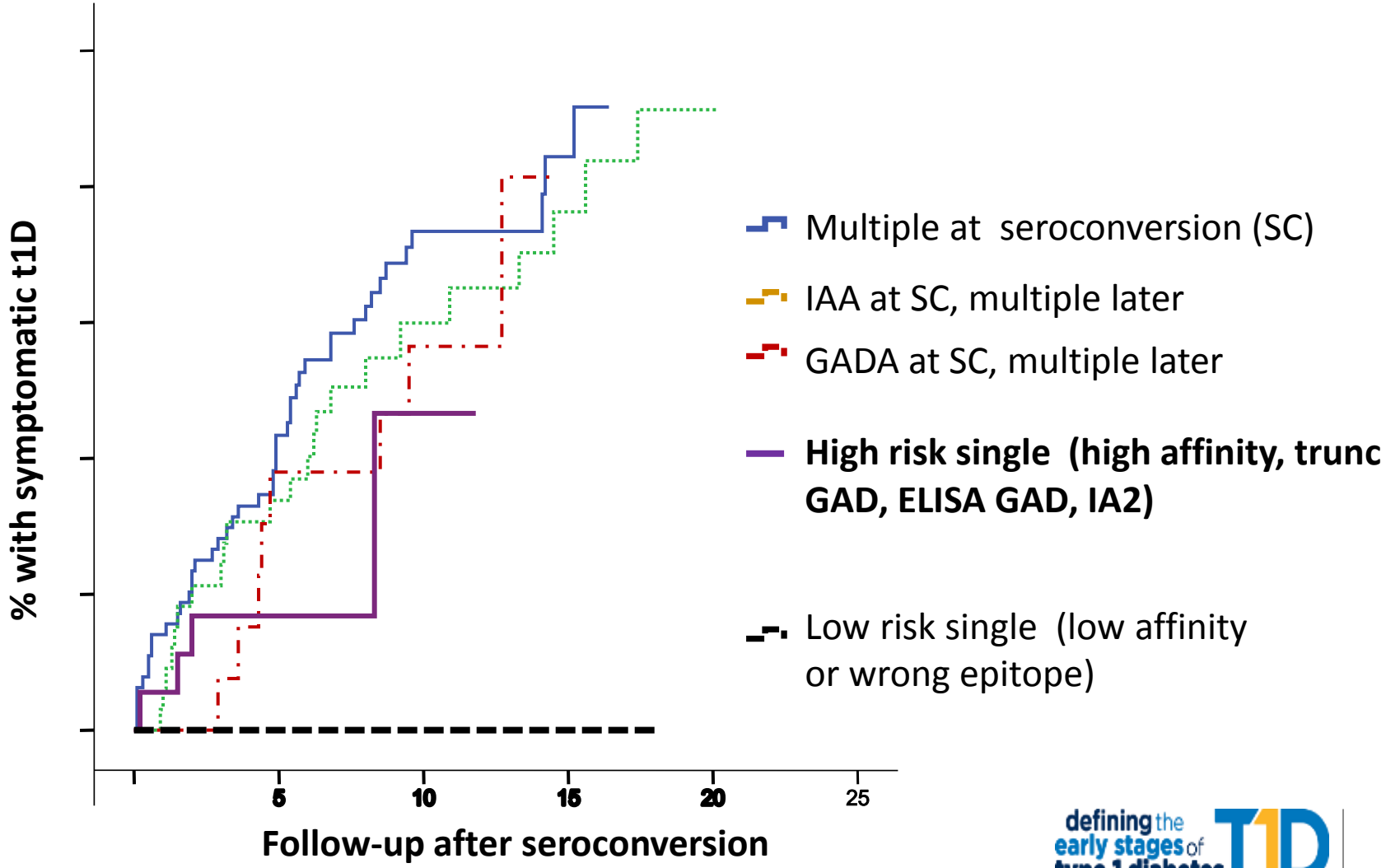
Even in the presence of other risk markers, age is important.

T1D-free curves by age categories among first degree relatives with multiple autoantibodies.



What about children with single islet autoantibodies?

Certain single Ab positives have a risk



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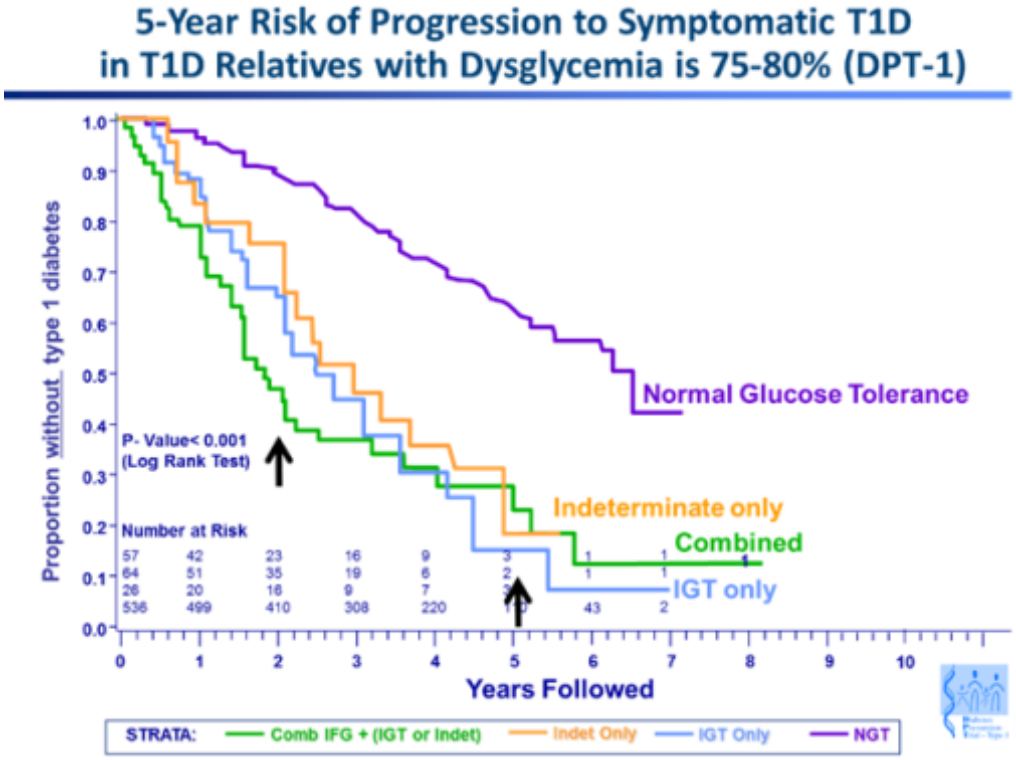
Stage 3: Symptomatic T1D

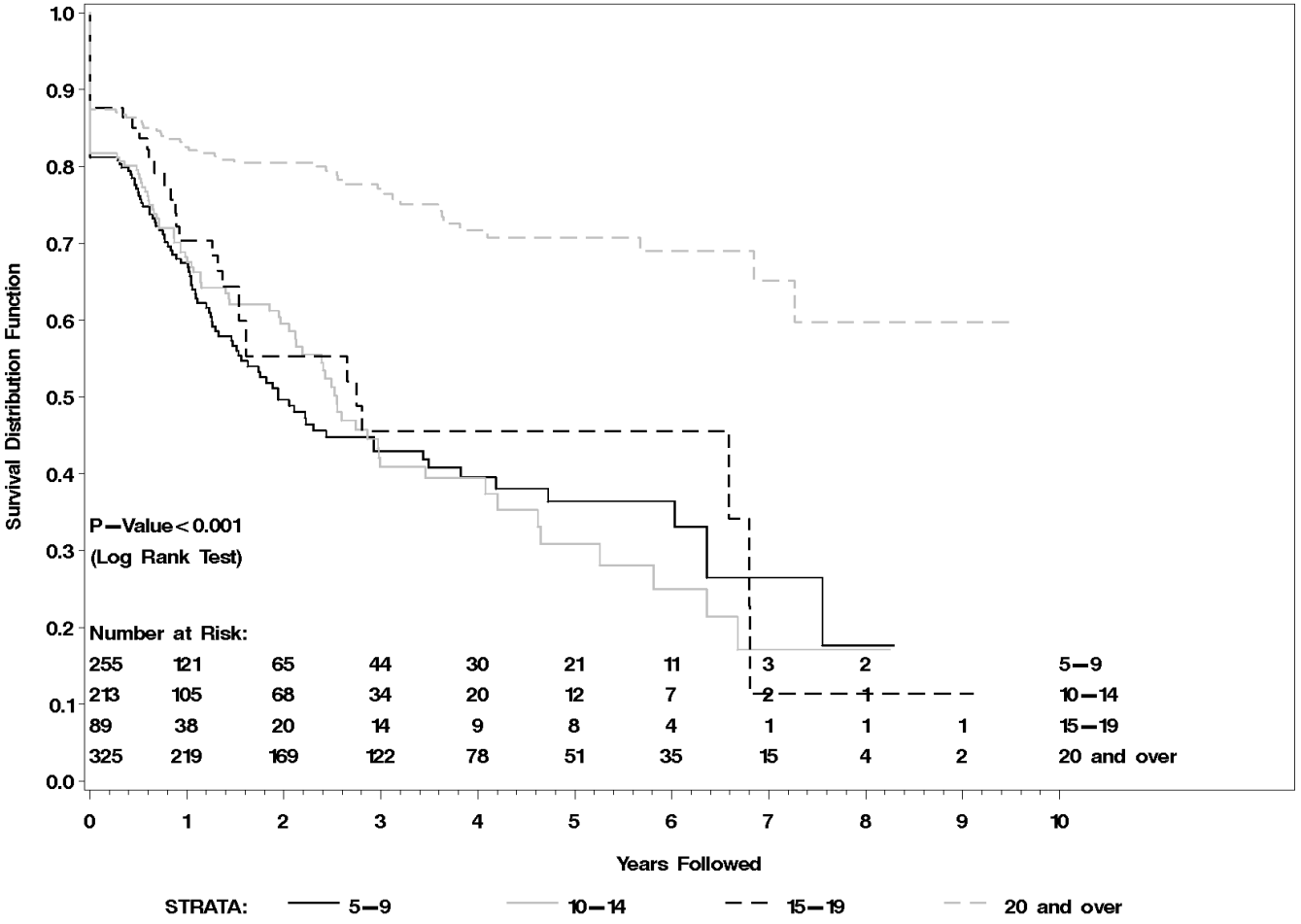
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Metabolic Markers of Symptomatic Diabetes Risk in Multiple Antibody Positive, First Degree Relatives

	5-Year Risk	Prevalence
▪ Abnormal Oral Glucose Tolerance Test	75-80%	0.7%



Again, age is a modifying factor.



Early Stages of Type 1 Diabetes: Diagnostic Criteria

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic	Stage #3 New Onset Symptomatic T1D
Diagnostic Criteria	▪ Multiple AutoAbs ▪ No impaired glucose tolerance or impaired fasting glucose	▪ Multiple AutoAbs ▪ Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose • FPG >100 mg/dL • OGTT: 2h PG ≥140mg/dL; 30, 60, 90 min PG ≥200 mg/dL • Random plasma glucose ≥200 mg/dL • HbA1c ≥5.7% • Increasing HbA1c	▪ Clinical Symptoms

Early Stages of Type 1 Diabetes: Diagnostic Criteria

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic	??Stage #2A Autoimmunity + Diabetic IGT +/- Diabetic OGT Asymptomatic
Diagnostic Criteria	▪ Multiple AutoAbs ▪ No impaired glucose tolerance or impaired fasting glucose	▪ Multiple AutoAbs ▪ Dysglycemia: Impaired Glucose Tolerance and/or Impaired Fasting Glucose • FPG >100 mg/dL • OGTT: 2h PG ≥140mg/dL; 30, 60, 90 min PG ≥200 mg/dL • Random plasma glucose ≥200 mg/dL • HbA1c ≥5.7% • Increasing HbA1c	▪ Multiple AutoAbs ▪ "Diabetic" Impaired Glucose Tolerance and/or Impaired Fasting Glucose • FPG ≥126 mg/dL • OGTT: 2h PG ≥200mg/dL • HbA1c ≥6.5%

Early Stages of Type 1 Diabetes: Diagnostic Criteria

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic	Stage #3 New Onset Symptomatic T1D
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Oral Insulin Prevention Trial

Abatacept Prevention Trial

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Teplizumab Prevention Trial

Stage 3: Symptomatic T1D

Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)

Early Stages of Type 1 Diabetes: Potential Clinical Trial Endpoints

Stage	Stage #1 Autoimmunity + Dysglycemia – Asymptomatic	Stage #2 Autoimmunity + Dysglycemia + Asymptomatic
Potential Endpoints of Clinical Trials	▪ Dysglycemia prevented ▪ Autoimmunity regulated ▪ Symptoms delayed, Insulin dependence delayed, prevented	▪ Dysglycemia reversed ▪ FPG normalized ▪ IGT fails to progress to IFG ▪ HbA1c restored to normal levels; Increasing HbA1c reversed ▪ Autoimmunity regulated ▪ Symptoms delayed; Insulin dependence delayed, prevented

defining the early stages of type 1 diabetes T1D

Desired Outcomes of the Workshop

- Provide a new standardized taxonomy and staging approach for human T1D
- Accelerate clinical development of therapies to prevent symptomatic T1D
- Aid design of clinical trials through use of risk profiles, subject stratification, and stage-specific trial endpoints
- Promote precision medicine: Tailoring of optimal therapies to specific individuals at specific stages of T1D
- Provide an approach for the benefit/risk framework in the early stages of T1D

October 10, 2014
Bethesda, MD