Differences in Risk of Progression and Attitudes in Adults and Children:
A Case-Based Review

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Disclosures

I have no conflicts of interest to disclose.

Adult-Onset Type 1 Diabetes (T1D)

- **Lower risk of progression, slower disease progression.**
  - **Immunologic differences across age groups.**
  - **Slower decline in beta cell function.**
    - **Lower rates of DKA at diagnosis.**

- **Data from relative or incident T1D cohorts, <45 years old.**
- **Adults often misdiagnosed.**

Wherrett, et al. (TrialNet Study Group). *Diabetes Care*. 2015
Leete, et al. *Curr Diab Report*. 2023.
Davis, et al. (T1D Exchange Clinic Network). *Diabetes Care*. 2015
Leslie, et al. *Diabetes Care*. 2021.
Casu, et al. (T1D Exchange Clinic Registry). *Diabetic Medicine*. 2020.

Case 1 - DAISY

- **3-year-old female enrolled in 1995**

- **Father with T1D**

- **Islet autoantibodies (IAs):**
  - **GADA+ at age 8.5**
  - **IAA+ at age 11**
    - **Intermittent, lost by age 15**

Age	GAD	IAA	IA-2A	ZnT8
3.09				
3.87	-0.027	27	-0.018	
4.92	-0.045	26	-0.042	
5.94	-0.038	-25	-0.003	
8.43	0.675	-0.003	-0.003	
8.64	0.611	0.006	0.018	
9.32	0.538	-0.007	-0.007	
9.92	0.627	-0.001	0.021	
10.55	0.521	-0.001	0.041	
11.17	0.782	0.014	0.029	
11.86	0.965	0.005	0.04	
12.49	1	0.012	-0.001	
12.88	1.057	0.05	-0.015	
13.32	0.882	0.026	-0.004	
14.06	1.061	0.01	0.003	
14.37	0.607	0.02	-0.006	
14.86	0.73	0.006	0.004	
15.39	0.505	0.002	0.006	
16.33	0.448	0.004	-0.017	
20.81	745	-0.003	0	-0.004
21.82	976	0.002	4	-0.006
24.09	625	0.004	0	0.003
25.48	517	0.001	0	0.006
26.69	868	0.001	0	0.001
27.24	661	0.001	0	-0.003
28.71	608	0.007	0	-0.001
28.76				
29.35	1022	-0.002	0	0.001
29.99	683	-0.001	0	-0.002
30.29	944	0.003	0	-0.001
30.72	943	-0.004	0	-0.001
30.97	1186	-0.002	0	0.001

DATE	OGTT		A1c (%)
	Time (mins)	Glucose (mg/dL)	
2001-2006			x10 Ranged 5.1-5.7%
2/21/2007	-10	98	5.1%
	0	93	
	30	172	
	60	144	
	90	100	
	120	101	
8/20/2007			5.3%
2/27/2008	-10	96	5.5%
	0	96	
	30	125	
	60	127	
	90	98	
	120	103	

DATE	OGTT		A1c (%)
	Time (mins)	Glucose (mg/dL)	
2/7/2009 - 1/21/2023			x12 Ranged 5.3-6.3%
6/27/2023 (31 years)	-10	117	6.4%
	0	120	
	30	213	
	60	262	
	90	132	
	120	222	
3/21/2024	-10	140	6.3%
	30	--	
	60	290	
	90	--	
	120	328	

Case 1 - DAISY

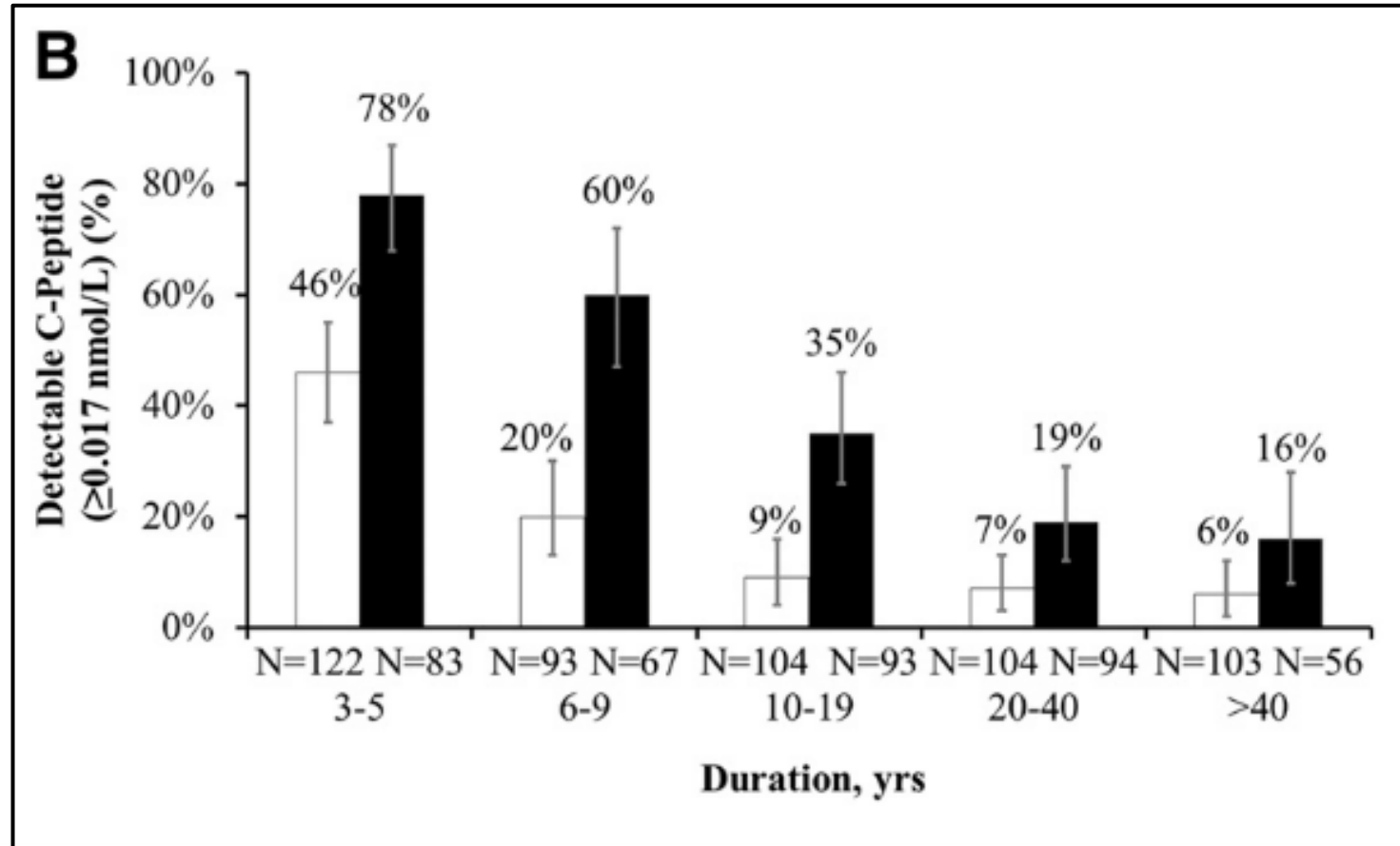## Case Summary:

- IA seroconversion occurred in childhood, persisted for decades before progression to clinical T1D.

- Even with diagnostic OGTT, A1c remained <6.5%.

- IA status was fluid.

Risk of T1D Progression Strongly Relates to Age

Wherrett, et al. (**TrialNet Study** Group). *Diabetes Care*. 2015
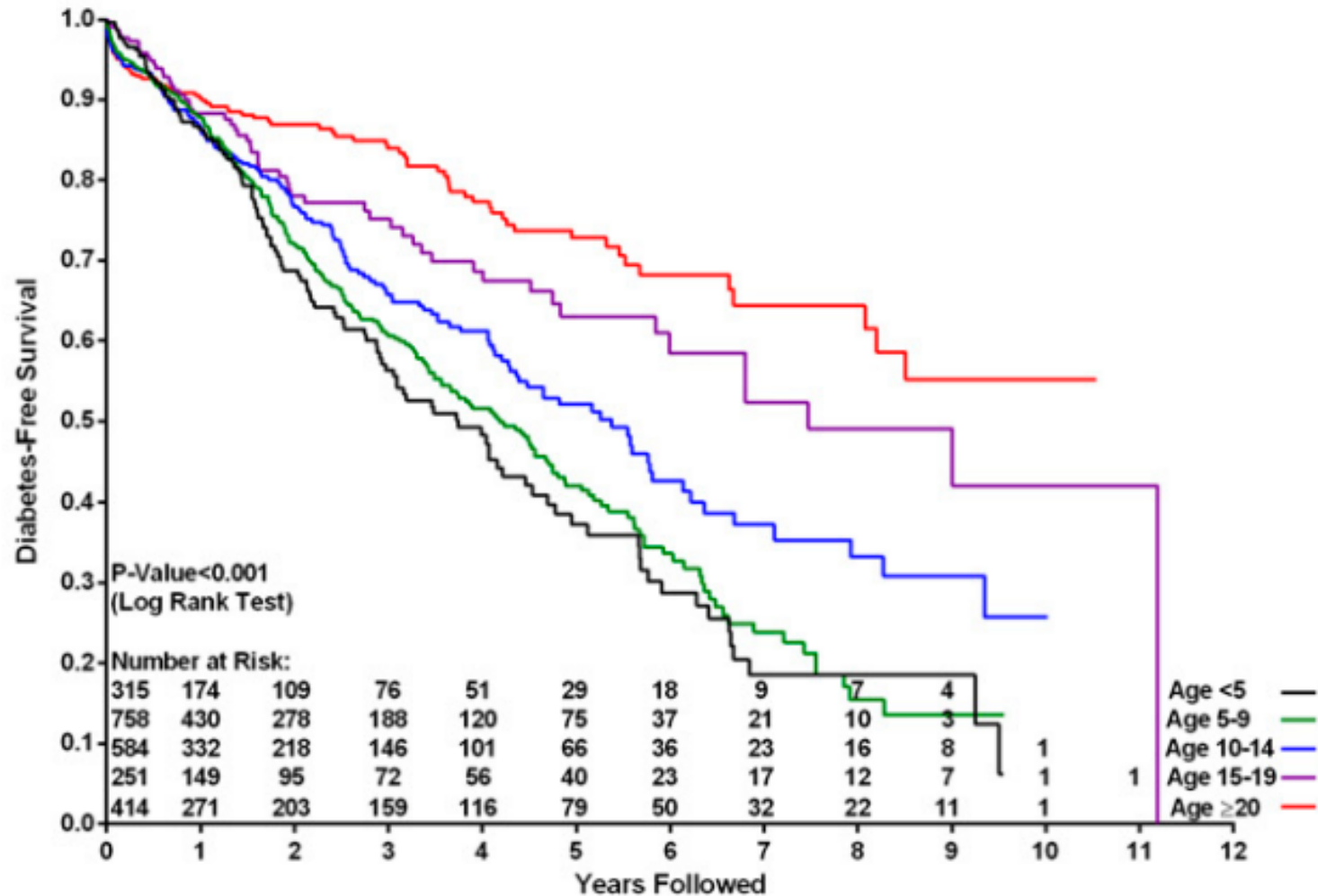
Insulin (C-Peptide) Production

Black bars = T1D diagnosed in <u>adulthood</u>
White bars = T1D diagnosed in <u>youth</u>

Davis, et al. (**T1D Exchange Clinic Network**). *Diabetes Care*. 2015

Case 1 - DAISY

Case Summary:

- IA seroconversion occurred in childhood, persisted for decades before progression to clinical T1D diagnosis.
- Even with diagnostic OGTT, A1c remains <6.5%.
- IA status was fluid.

Risk of T1D Progression Relates to Number of IAs

Figure 1. Development of Diabetes in Children Stratified for Islet Autoantibody Outcome
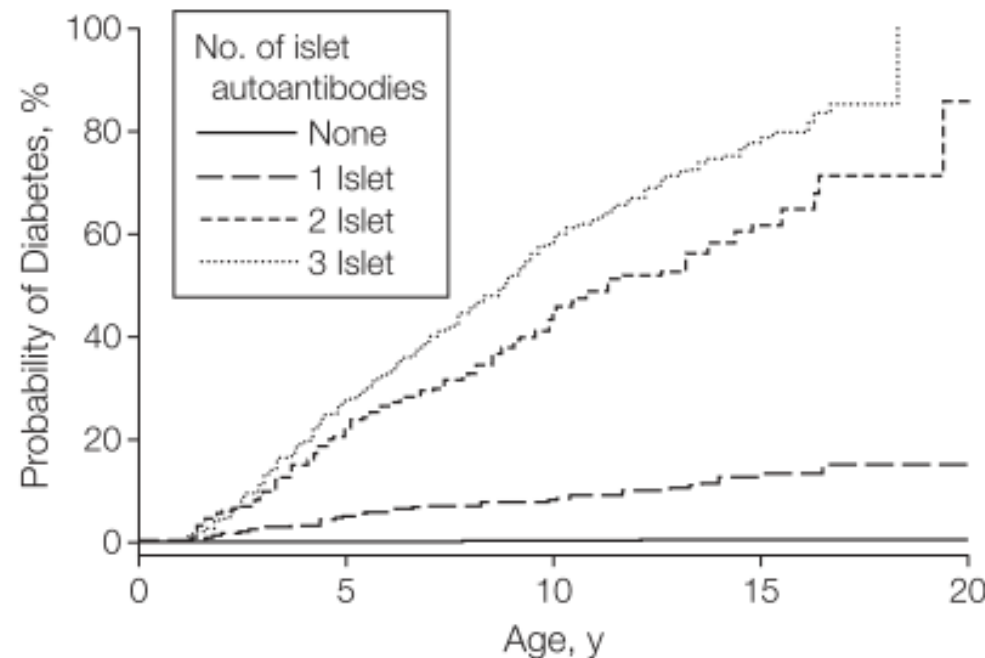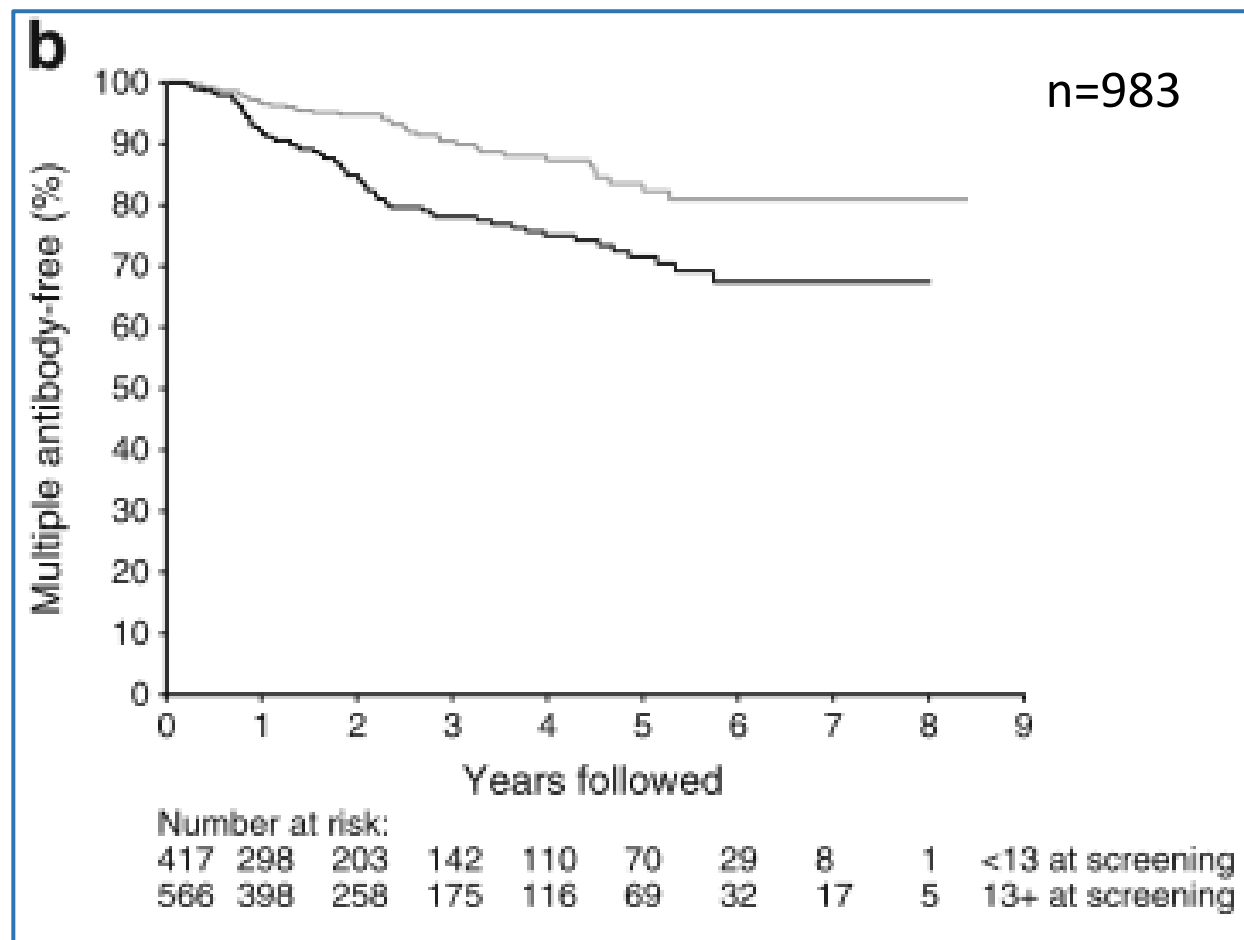

- **Multiple IAs (youth) = ~100% lifetime risk**

- **Multiple IAs (adults) = ~15% 5-year risk**
  (Jacobson, et al.)

- **Single IA = variable**

Risk of IA Expansion Relates to Age

b

n=983

☐ = >13 years

■ = <13 years

Overall 5-year risk of expansion to multiple IAs was 22.0% (95% CI 17.9, 26.1)

Bingley, et al. (**TrialNet Pathway to Prevention Study**). *Diabetologia.* 2015.

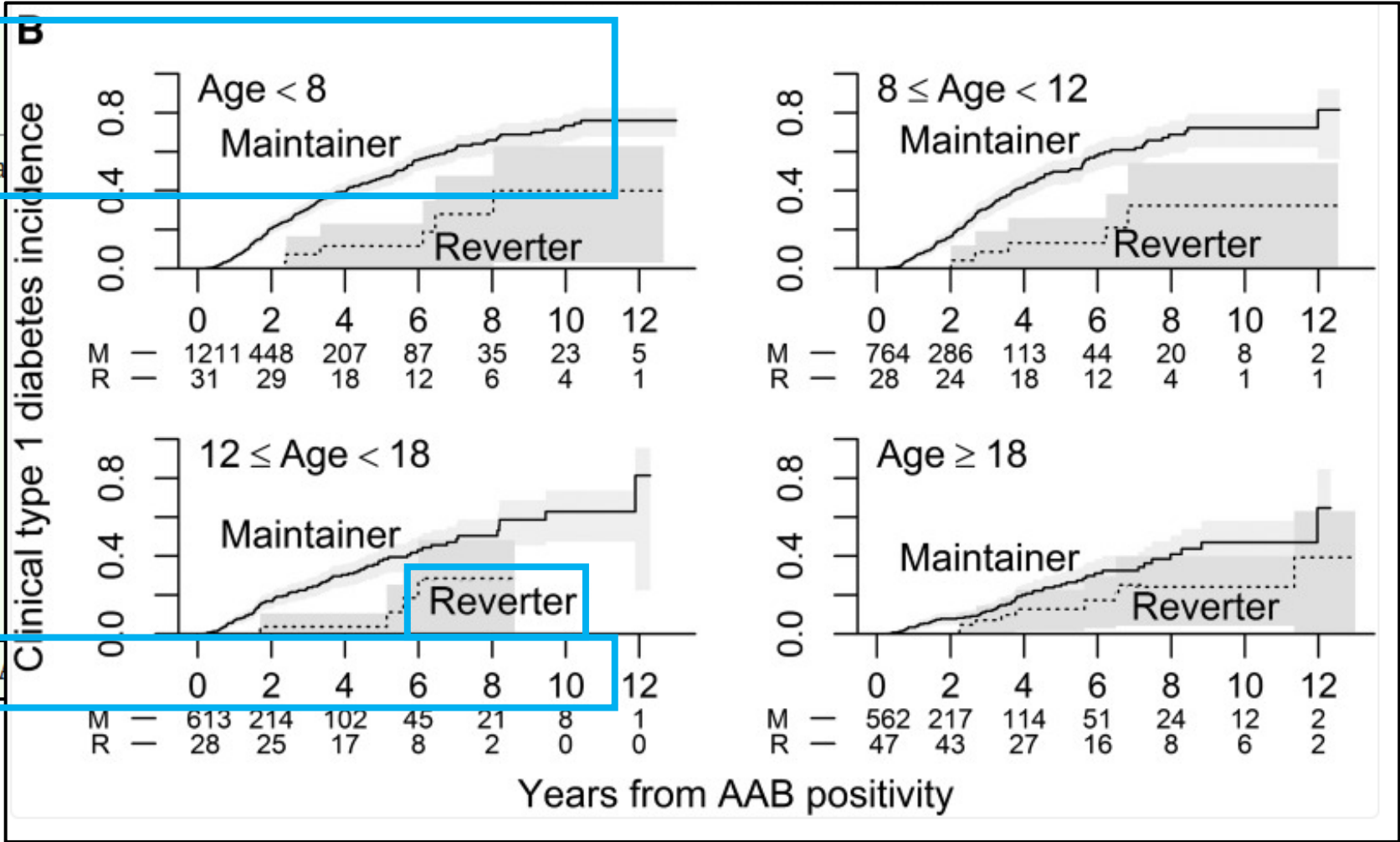# IA Expansion Impacts Risk of Progression to Stage 3 T1D
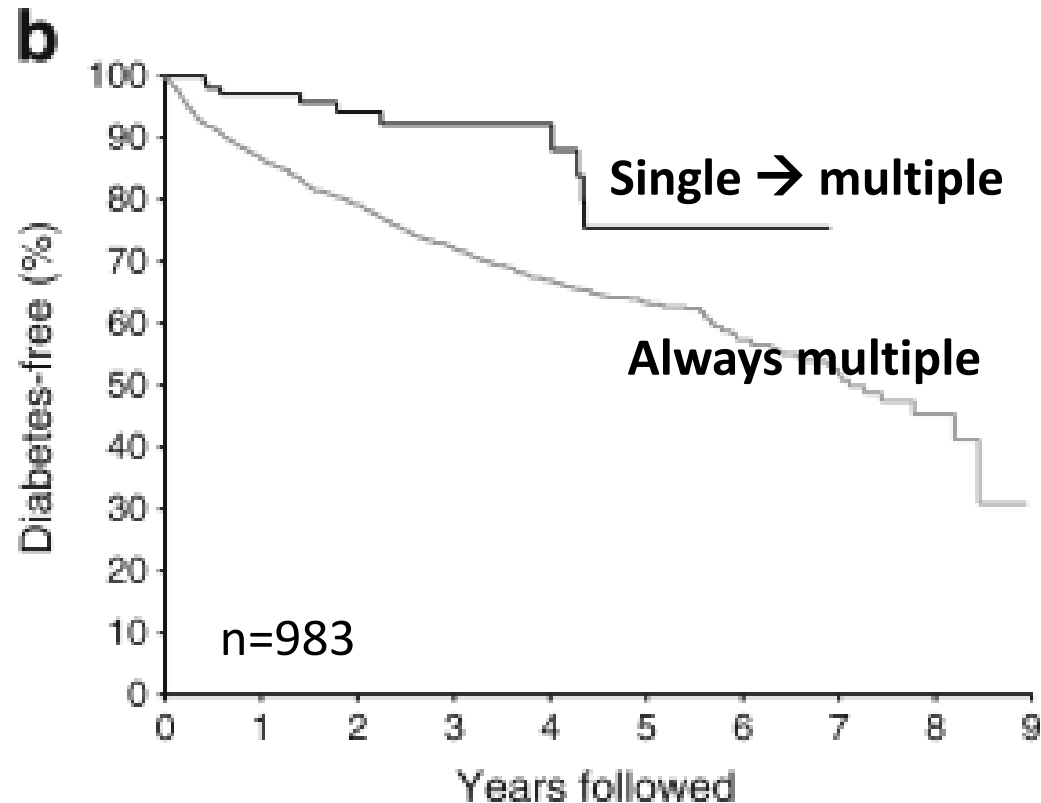
5-year risk of T1D:

- Single IA+ → multiple IA+: 24.5%
- Persistent multiple IA+: 36.8%
  - Not statistically different (p=0.06)

IA Reversion

So, et al. (**TrialNet Pathway to Prevention Study**). *Diabetes Care.* 2020.

Case 1 - DAISY

Take-home points:

- Increasing age associated with retained insulin production.
- Increasing age associated with decreased risk of IA expansion/progression.
- IA fluidity (expansion, reversion) impacts risk.
  - Reversion associated with older age.
  - Reversion less impactful in older age.

Case 2 - ASK

- **43-year-old obese female screened by ASK Study in 2021.**
  - **No family history of T1D (1st degree).**

Visit	GADA RBA	GADA ECL	IA-2A RBA	IA-2A ECL	IAA RBA	IAA ECL	ZnT8 RBA	ZnT8 ECL
Screening	**379**	**0.115**	**0**	**0**	**0**	**0.005**	**-0.003**	**0**
Confirmation (6 mos after screen)	**568**	**0.058**	**0**	**0.002**	**-0.003**	**-0.002**	**0**	**-0.001**
Follow Up (9 mos after confirm)	**476**	**0.361**	**0**	**-0.003**	**-0.003**	**-0.001**	**-0.002**	**-0.001**

Case 2 - ASK

- **19 months after screening:**
  - **A1c: 5.7%**
  - **CGM data:**
    - **Time >140: 67.2%**
      - **Increased from 3 months prior: 15.4%.**
    - **Glucoses >200? - YES**
  - **Symptomatic: polyuria, polydipsia**
  - **Not in DKA**
- **Clinical T1D diagnosis: symptoms, glucoses >200.**

Case 2 - ASK

Case Summary:

- **Short time from screening to diagnosis.**
  - **Unclear when seroconversion occurred.**
- **Single IA+ (GADA) progressed to clinical T1D.**
- **Met some (but not all) diagnostic criteria.**

Effect of GADA is Age Dependent

- **GAD is prevalent in IA+, especially in older youth and adults.**

- **Associated with lower risk in young children but increased risk in older youth/adults.**

single GADA+
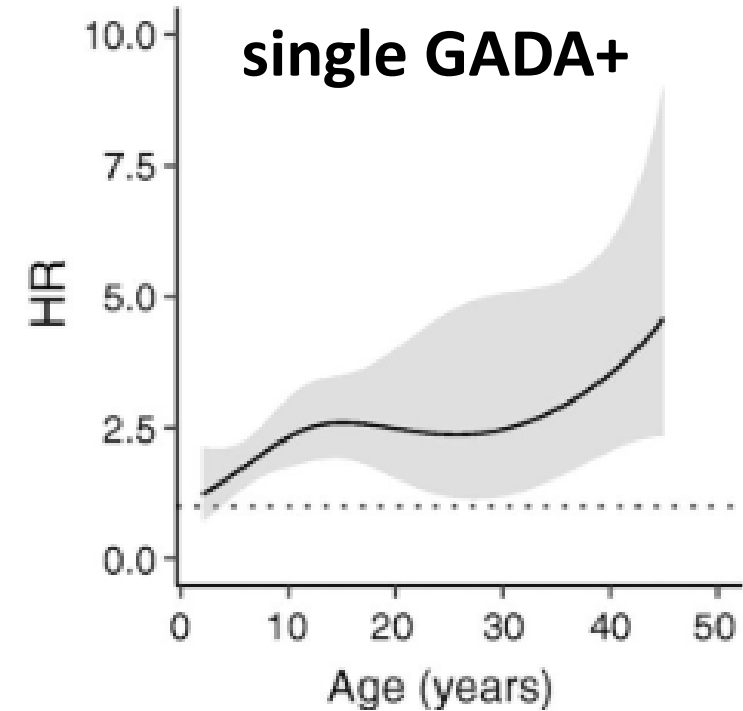
"Increasing HR with increasing age… amongst older adults to be greater than 4x that of the youngest children."

Case 3 – ASK the Experts

- **48-year-old female enrolled in ASK the Experts in 2022.**
  - **Relevant FHx: children IA+**
  - **PMH:**
    - **Autoimmune thyroid disease**
    - **Endocrinologist ordered GADA:** *positive*
      - **Initially treated with functional medicine, restrictive diet.**

	GADA RBA	GADA ECL	IA-2A RBA	IA-2A ECL	IAA RBA	IAA ECL	ZnT8 RBA	ZnT8 ECL
ASK Screening	721	0.632	0	-0.001	0	-0.001	0.105	0.905

Case 3 – ASK the Experts

- **10 months later:**
  - **A1c: 6.3%**
  - **Underwent OGTT:**
  - **Not in DKA**
  - **No T1D symptoms (restrictive diet)**

- **Clinical T1D diagnosis: fasting glucose, OGTT**

OGTT	
Time (min)	Glucose (mg/dL)
0	145
30	236
60	285
90	256
120	234

Case 3 – ASK the Experts

Case Summary:

- **Short time from screening to diagnosis.**
  - **Unclear when seroconversion occurred.**
- **Met some (but not all) diagnostic criteria.**
- **GADA+ and ZnT8+.**

Impact of ZnT8+

- **Younger incidence, less commonly initial IA.**
    - <u>**TrialNet:**</u>
        - **ZnT8+ associated with increased risk in univariate setting, but not after adjustment for number of IAs.**
    - <u>**ENDIT:**</u>
        - **Improved prediction in age >20, low genetic risk.**
        - **Did not improve prediction in young, high genetic risk, another IA+.**
- **Risk prediction: older groups, high-affinity detection.**

Jiu, et al. *J Clin Endocrinol Metab. 2021.*
Jacobsen, et al. (**TrialNet Pathway to Prevention Study.** *Diabetologia*. 2020.

Long, et al. (**ENDIT** Cohort). *J Clin Endorinol Metab.* 2012.
So, et al. *Endocrine Reviews*. 2021.

Cases 2 & 3 – ASK, Experts

Take-Home Points:

- **GADA+ is the dominant IA in adults.**

- **GADA+ prevalence and impact on risk increases with age.**

- **ZnT8+ impact on risk likely greatest in single IA+, older cohorts.**

- **Elevated BMI and T1D are not mutually exclusive.**

Conclusions & Knowledge Gaps

- **Utilized cases to highlight and review major themes.**
- **Remaining knowledge gaps:**
  - **IA prevalence and associated risk.**
  - **Possible benefits of early detection and monitoring.**
  - **Psychological and behavioral health outcomes.**
  - **Differences across diverse races/ethnicities.**

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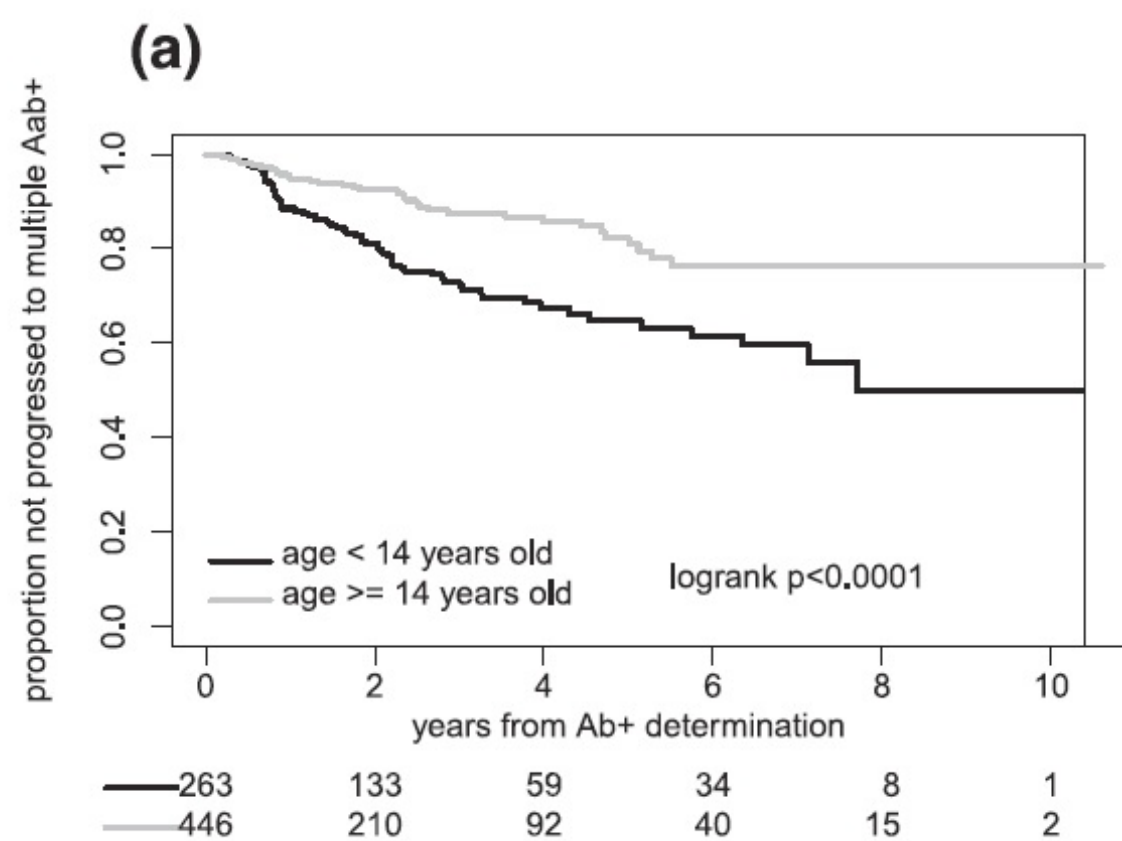
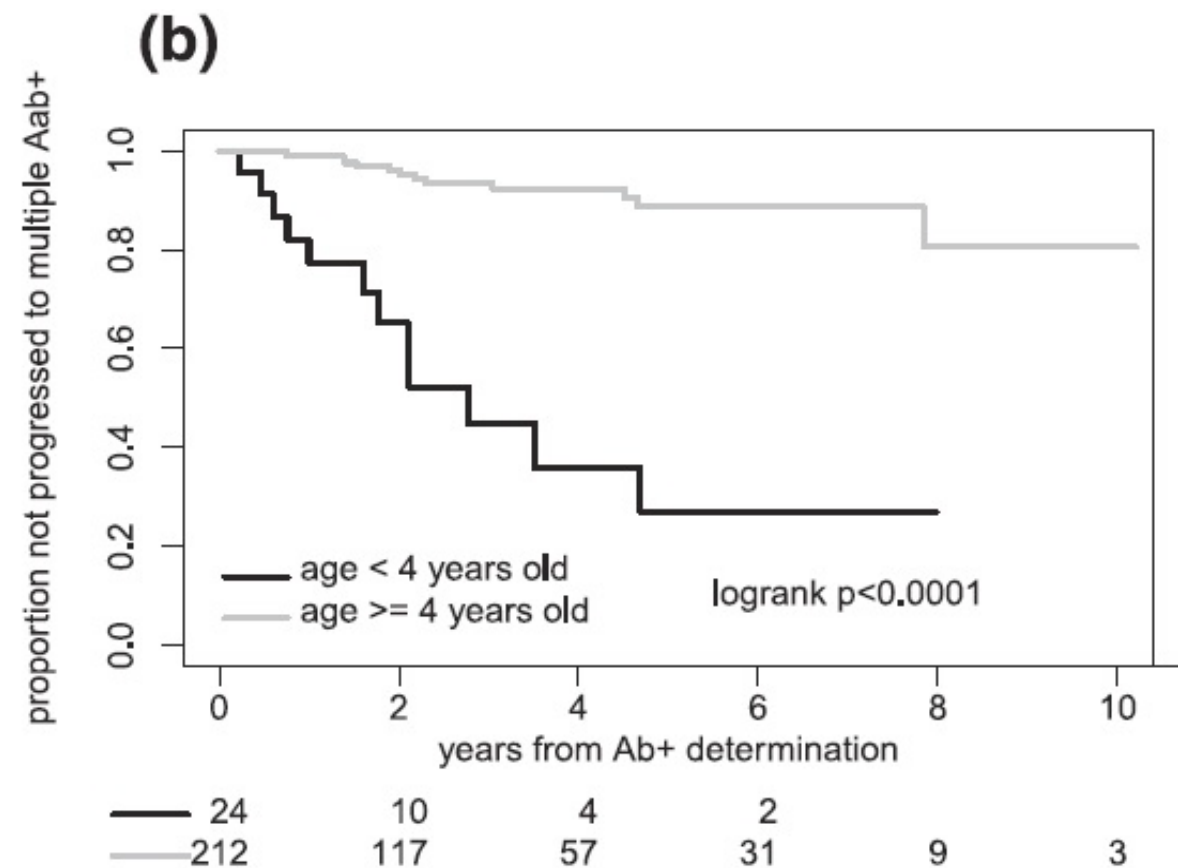# Thank you!

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Impact of Age and IA Type on IA Expansion

single GADA+   single IAA+

Bosi, E. et al. (**TrialNet Pathway to Prevention Study**). *J. Clin. Endocrinol. Metab.* 2017.