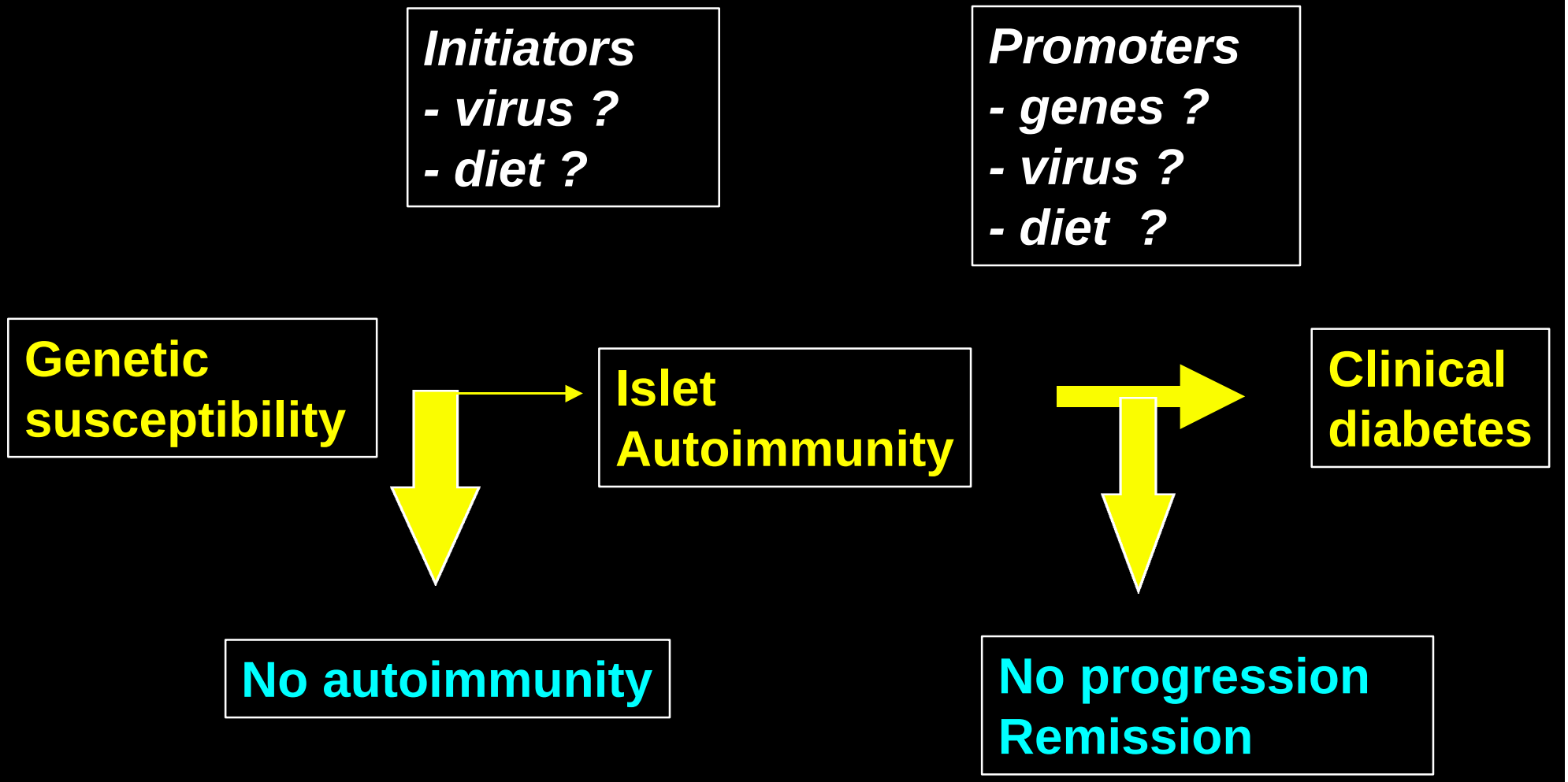
Natural History of Type 1 Diabetes (T1 DM)



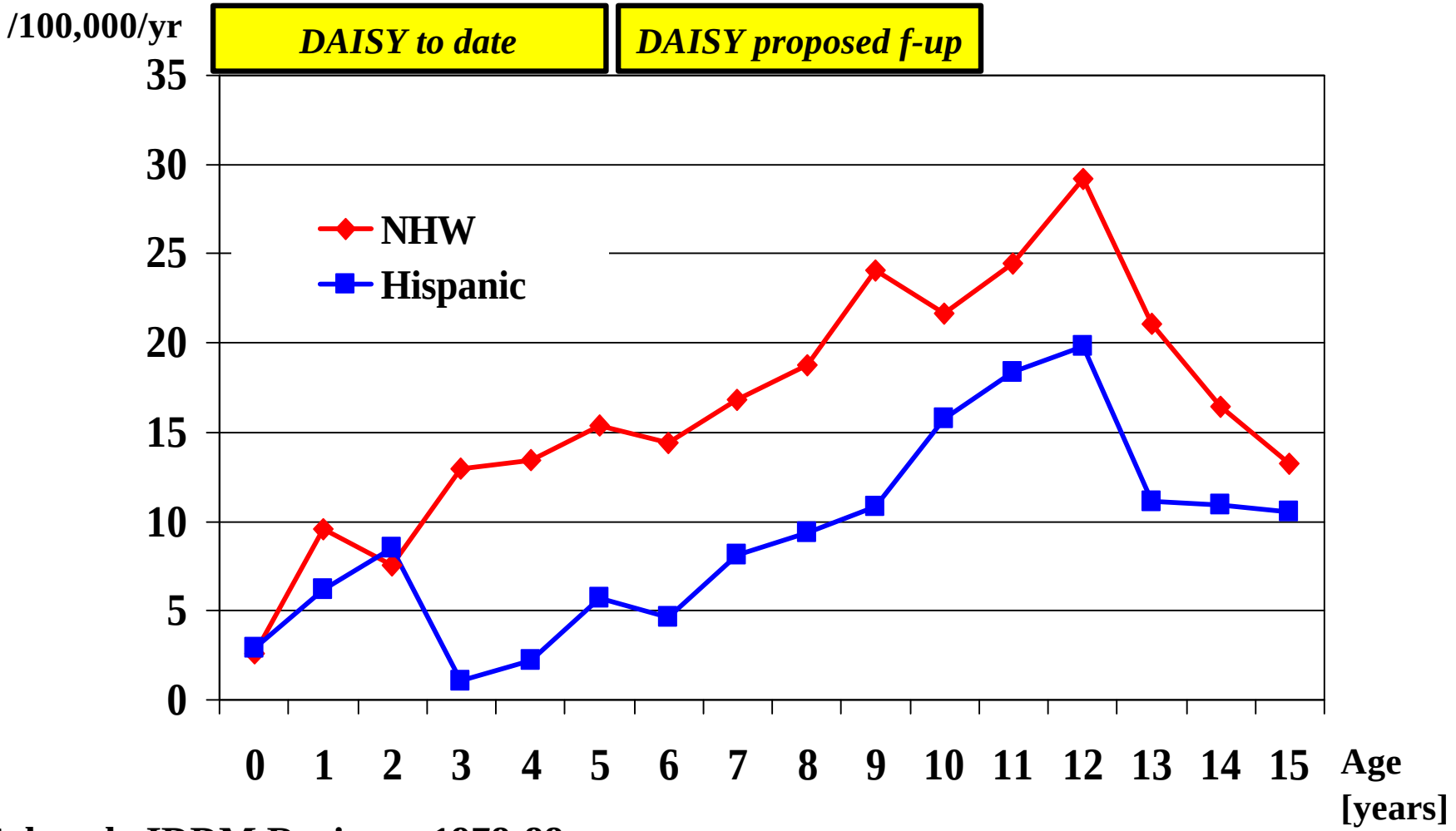
Islet Autoimmunity (IA)
Definition

- **IAA, GAD or ICA512 (IA-2) positive**
  on at least two consecutive visits including the last visit

- **or positive once before developing diabetes**

(would be nice to have a good T-cell assay or beta-cell mass measure)

Incidence of Type 1 diabetes



Colorado IDDM Registry, 1978-88

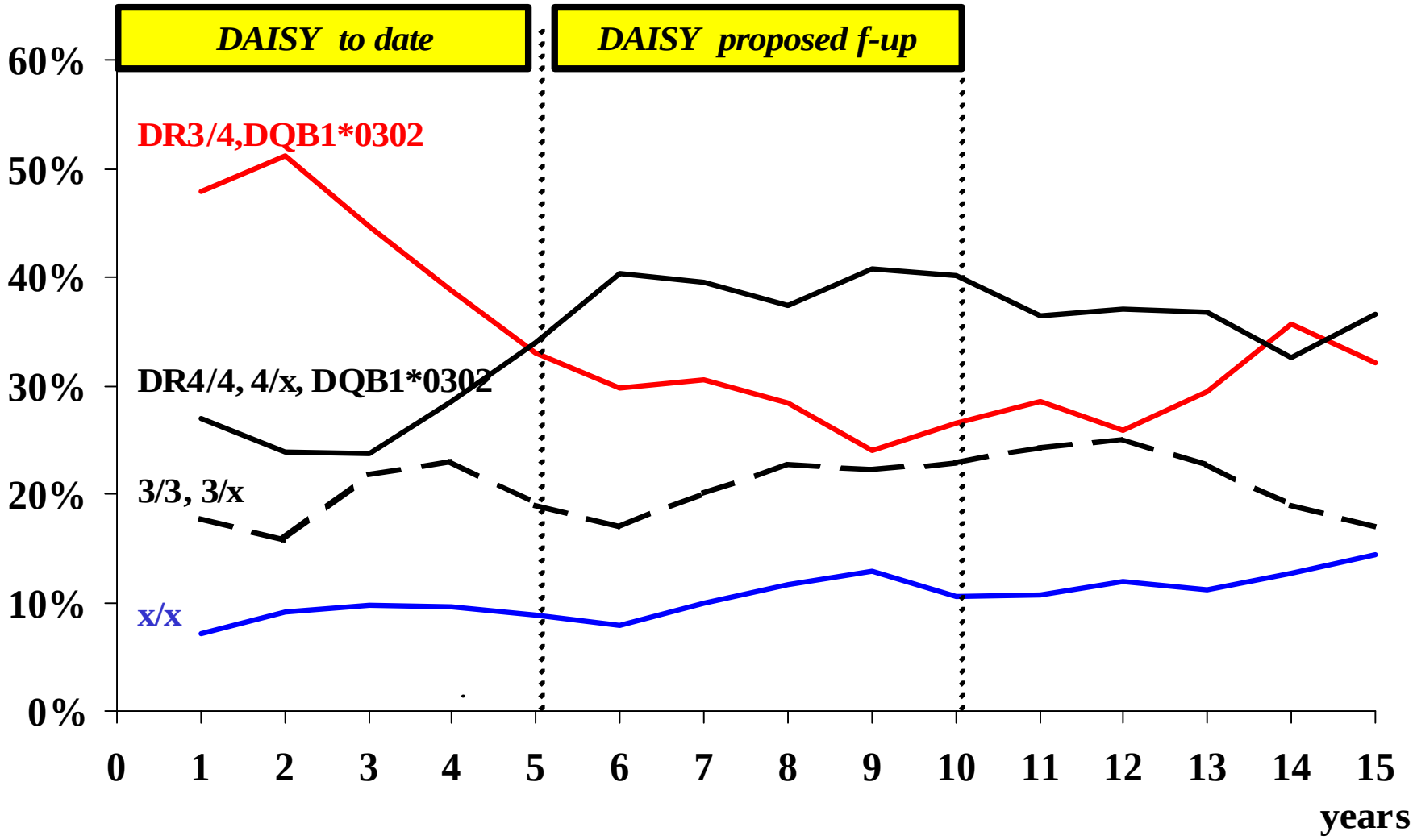
IDDM Loci Confirmed in Recent Genome Screens

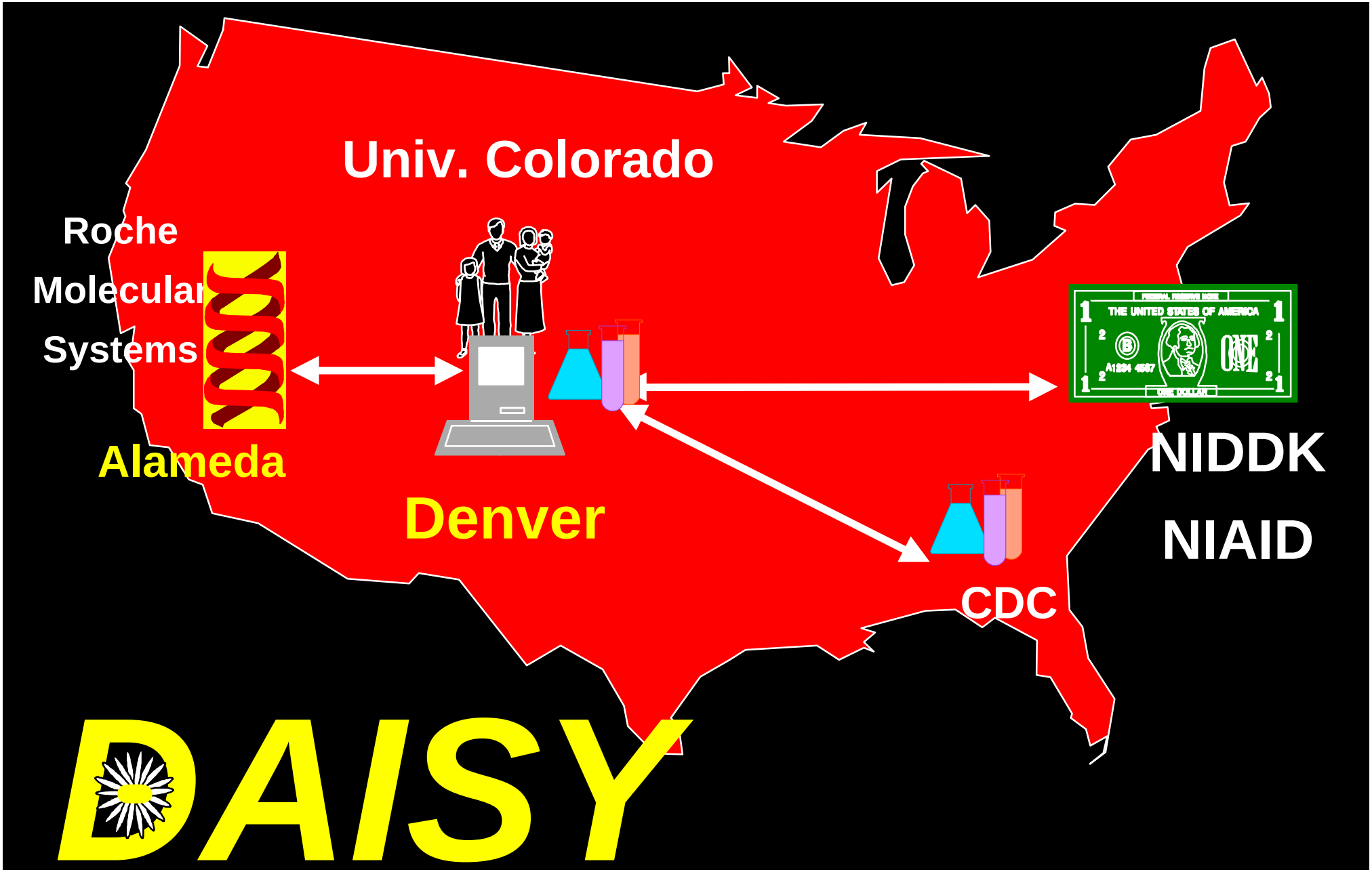
IDDM	Marker	Chromosome	LOD
IDDM1	MHC	6p21.3	65.8, 39.4*
IDDM2	Insulin	11p15.5	4.28
IDDM15	D6S283	6q21	2.36, 3.12*
IDDM10		10p13-q11	2.8
IDDM7		2q31	2.62
	D16S3098	16q	4.23
		16p*	2.34*
		1q42	2.27
		2*	2.1*
		5*	2.1*

Concannon et al. 768 families

*Julier et al. 485 sib pairs

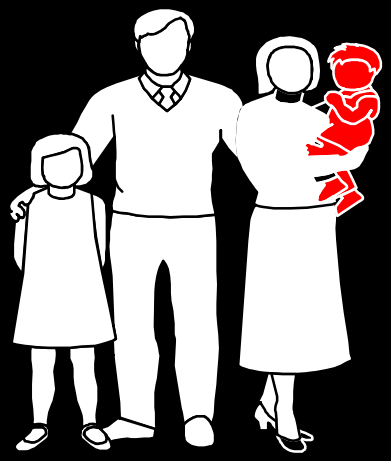
HLA-DR,DQ genotypes in Colorado T1 DM patients (n=1,509)



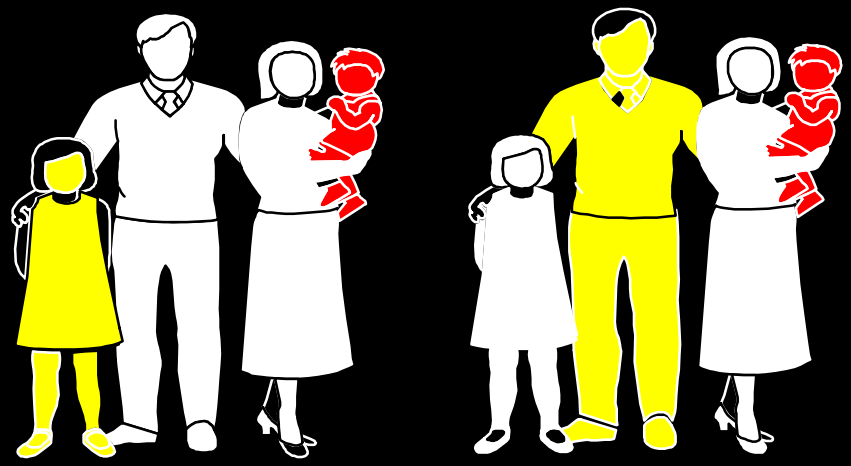

Univ. Colorado
Roche
Molecular
Systems
Alameda
Denver
NIDDK
NIAID
CDC
DAISY
Diabetes AutoImmunity Study in the Young

Diabetes Autoimmunity Study in the Young

General population cohort



Sibling/offspring cohort



screened = 23,305

enrolled	=	349	high risk	83
		448	moderate risk	230
		347	average - low risk	500
		1,144	All	813
relatives		1,491		1,007

7/01

General Population HLA screening

DAISY 1999 +		
HLA-DR,DQ	**%**	**RR**
3/4, 0302 (not *0403,6)	**2.1**	**26**
4/4, 0302 (not *0403,6)	**2.4**	**11**
4/1, 8, 9 or 13 (not *0403,6)	**3.4**	**6**
3/3	**1.5**	**4**
	9.4%	

Add *IDDM2*, CTLA-4, other HLA- and non-HLA markers ?

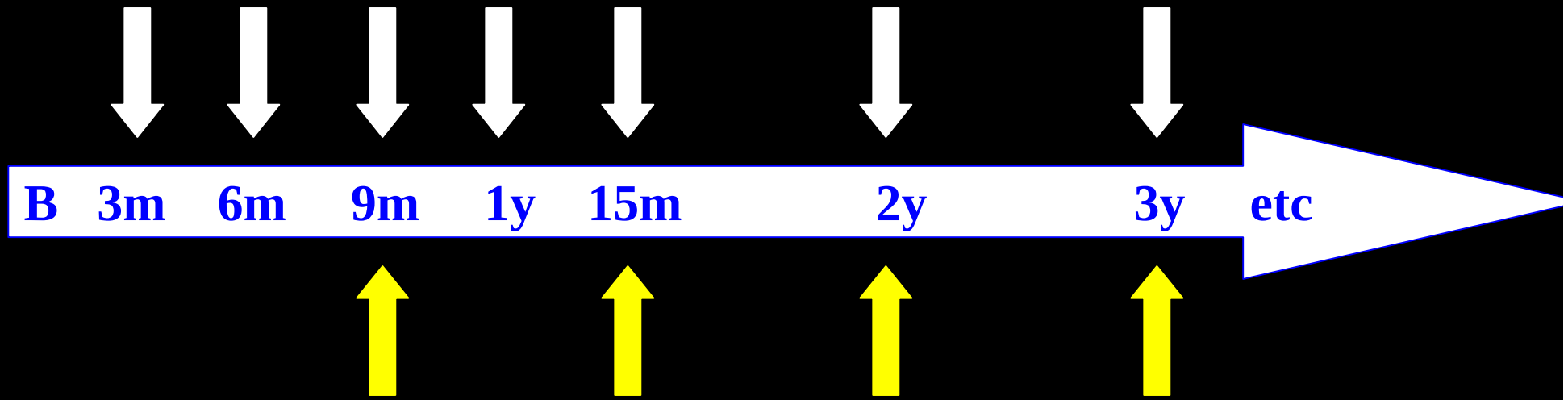
DAISY Strip (18 BSA-SSO probes) for DRB1 and DQB1

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

General Population High/Moderate-Risk Cohort Follow-up Protocol (N=5,200)

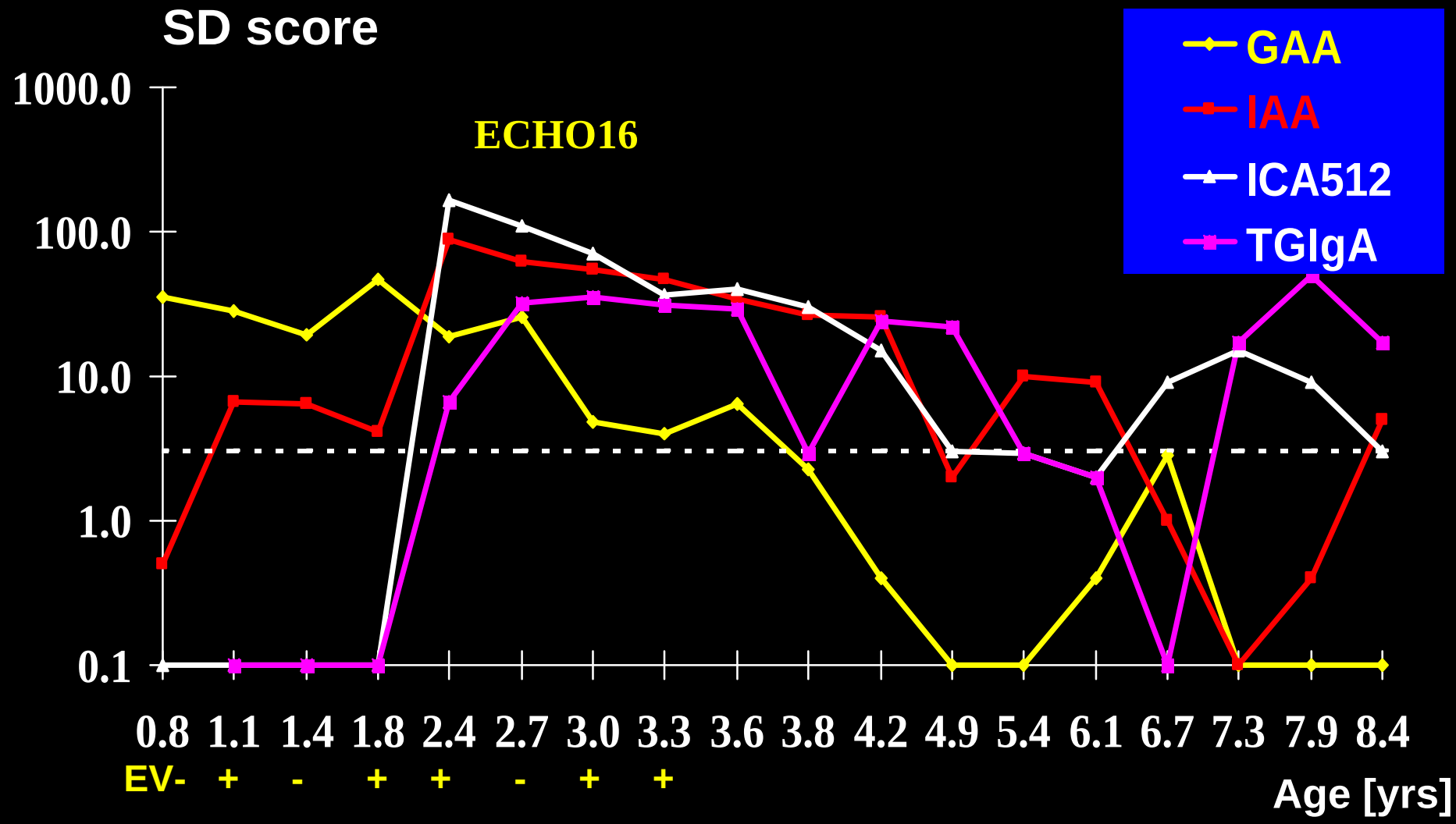
Interviews: diet, infections, immunizations
allergies, stress



Clinical Visits: blood sample for GAA, IAA, ICA512, DNA
throat and rectal swabs, saliva sample

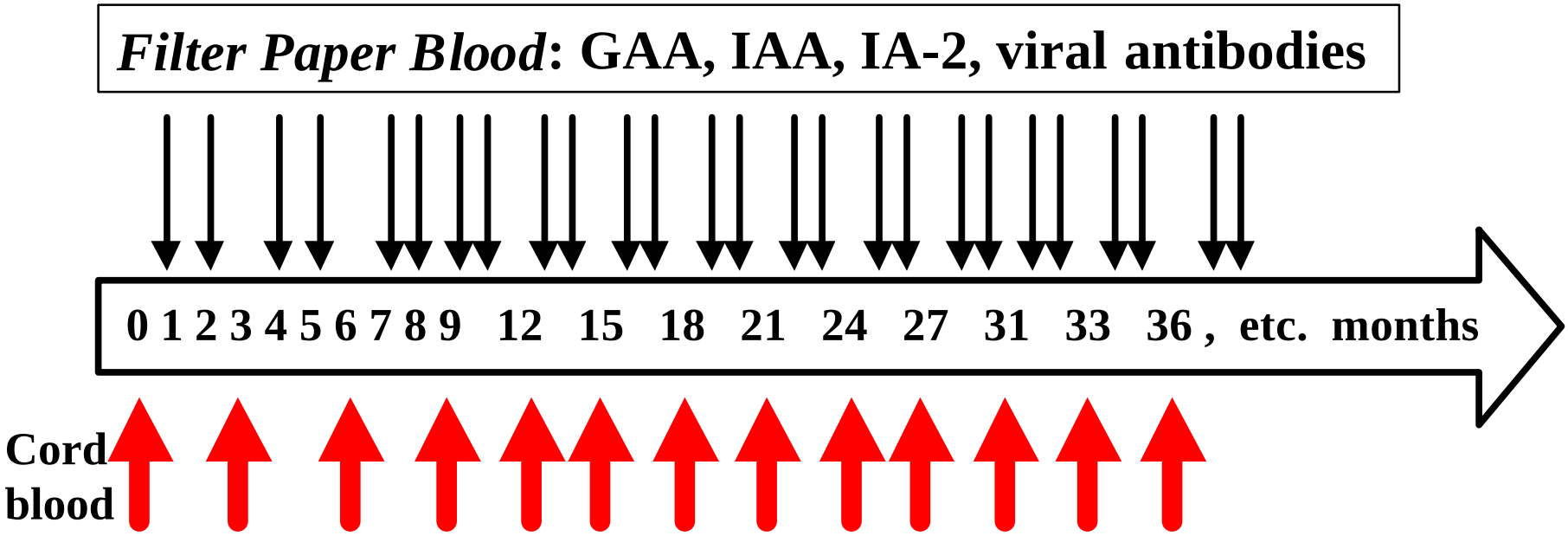
Autoantibody development in a sibling

HLA-DR3/4,DQB1*0302 DAISY ID 00060



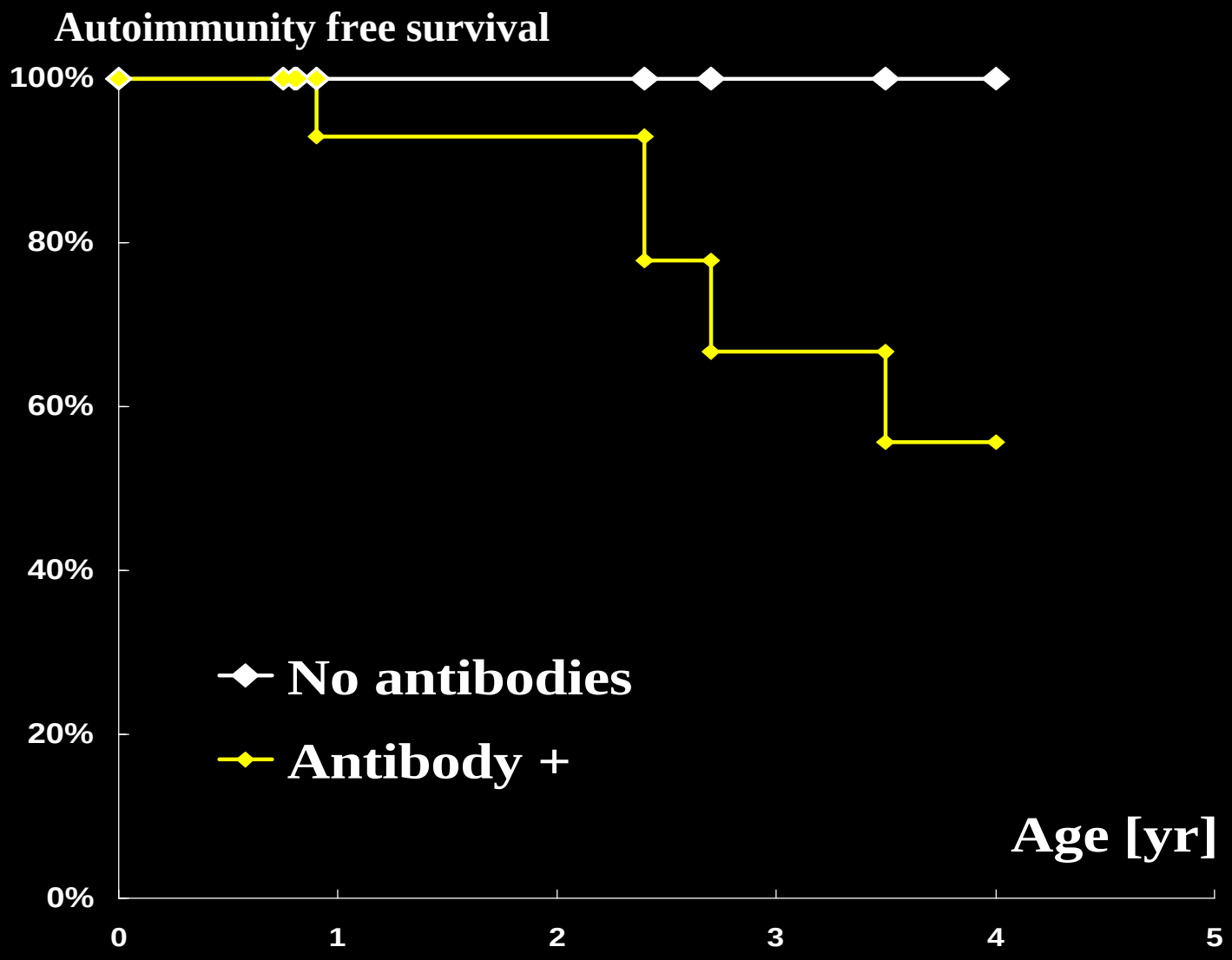
Intensive follow-up protocol (N=500)

Siblings & offspring, DR3/4,DQB1*0302, DR4/4, DR 3/3



Clinic Visits: blood for GAA, IAA, IA-2, viral antibodies, DNA
T-cell studies
throat & rectal swabs, saliva samples, interviews

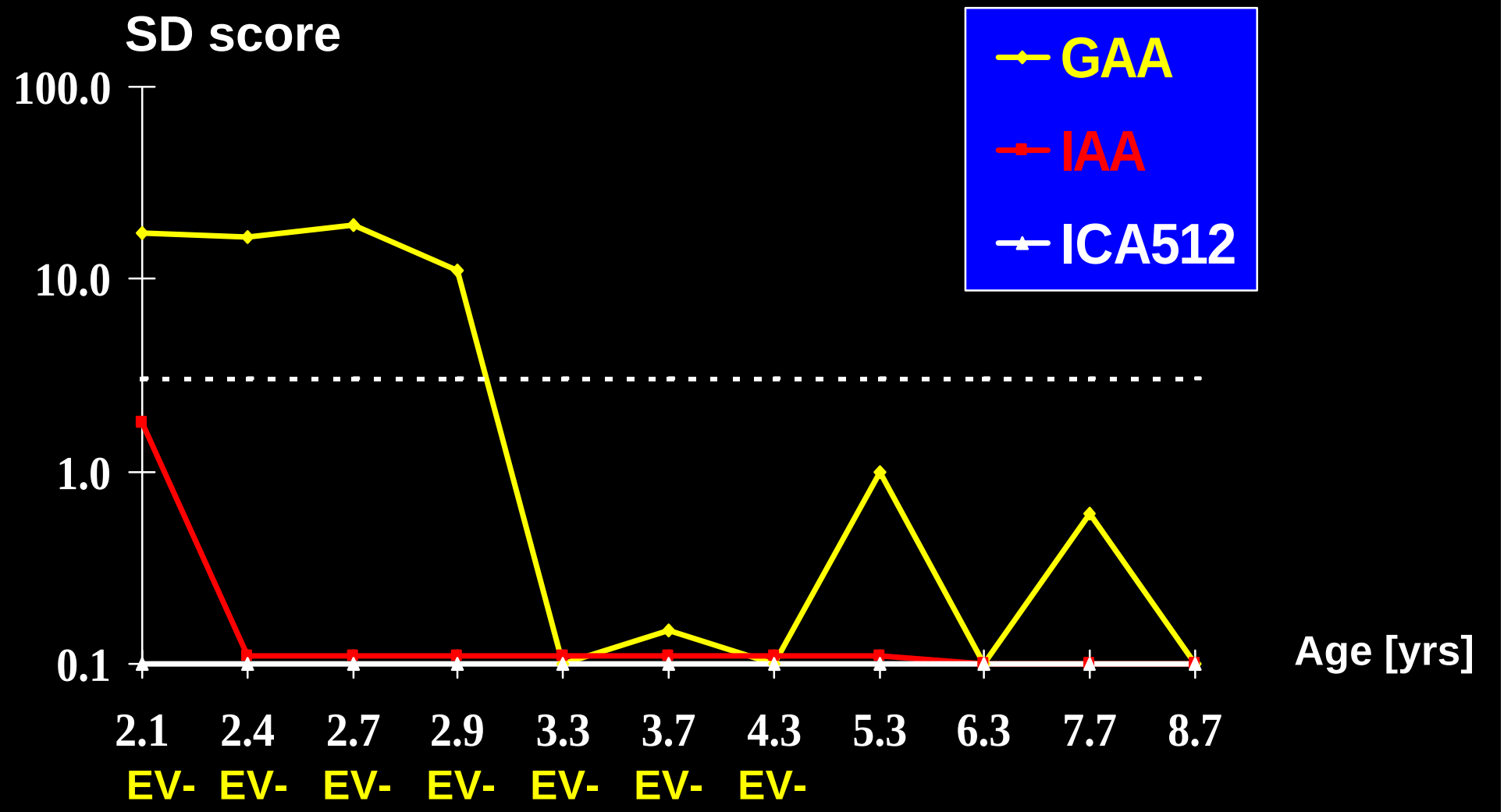
Risk of diabetes in siblings and offspring



DAISY, 10/01

Remission in a HLA-DR4/x sibling

HLA-DR4/x, DAISY ID 00130



Early childhood diet and T1 DM ?

Associations between exposure to specific foods in the infant diet and risk of BCA

Exposed by 6 Months to:	Cases (n = 27)	Controls (n = 1022)	P-value	Hazard ratio (95% CI)
Cereal	**77.8%**	**92.9%**	**0.003**	**0.29 (0.12-0.72)**
Gluten	**33.3%**	**58.3%**	**0.01**	**0.41 (0.18-0.92)**
Fruits/vegetables	**70.4%**	**83.5%**	**0.11**	**0.42 (0.18-0.96)**
Cow's milk	74.1%	75.4%	0.87	1.17 (0.49-2.79)
Meat	22.2%	15.8%	0.42	1.46 (0.58-3.61)

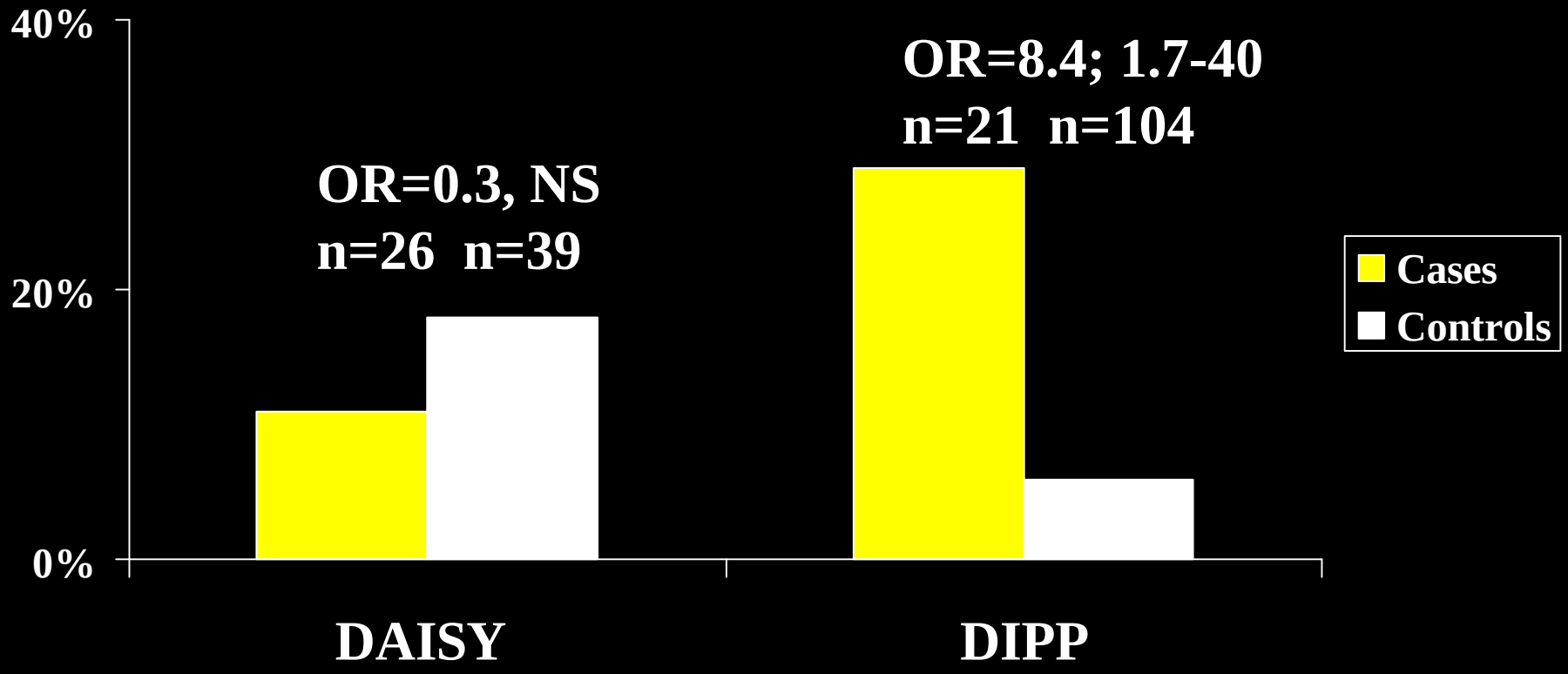
Norris et al. DAISY, 10/00

Infections and T1 DM ?

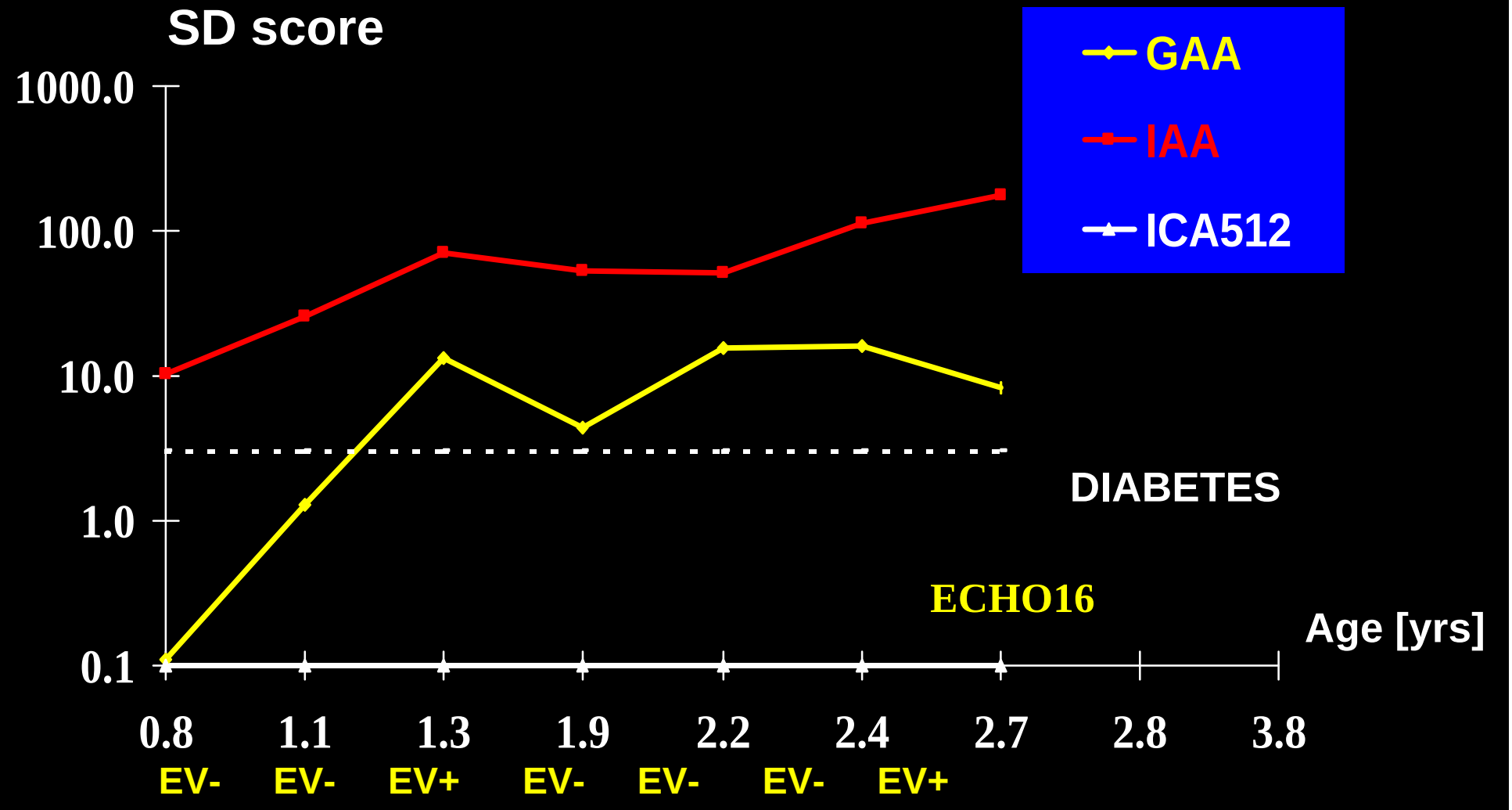
Enteroviruses - recent studies

Study	Autoimmunity	Diabetes
Frisk 1992, Dahlquist 1995		CVB 1-5 IgM
Hyoty 1995 Hiltunen 1997	IgM, IgG CVB	CVB IgM, IgG
Clements 1995 Andreoletti 1997		EV RNA
Graves (DAISY) 1996, 1998	- EV RNA - EV IgM	- EV RNA
Lonnrot 2000	+ EV RNA	- EV RNA

PCR-detected EV infections during a 6-months prior to development of islet autoantibodies



Autoantibody development in a sibling with HLA-DR3/4,DQB1*0302 DAISY ID 00132



Immunizations and Type 1 diabetes

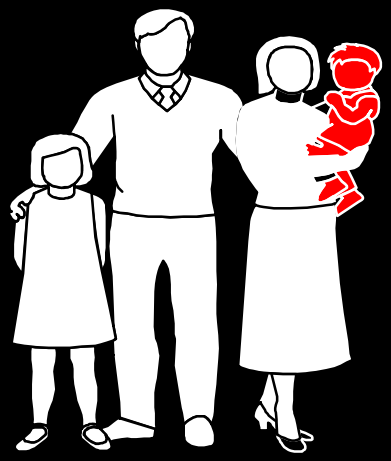
P. Graves at al, DAISY 1998

- **There was no difference between cases or controls in the timing or number of doses of Polio, DTP or MMR vaccines.**
- **There was no difference between cases and controls in the proportion receiving HBV, receiving HBV at birth, or age at first HBV.**
- **There was a trend towards earlier Hib immunization in cases.**
- **There is no suggestion that earlier administration of childhood vaccines would prevent BCA or type 1 DM.**

A future multi-center study

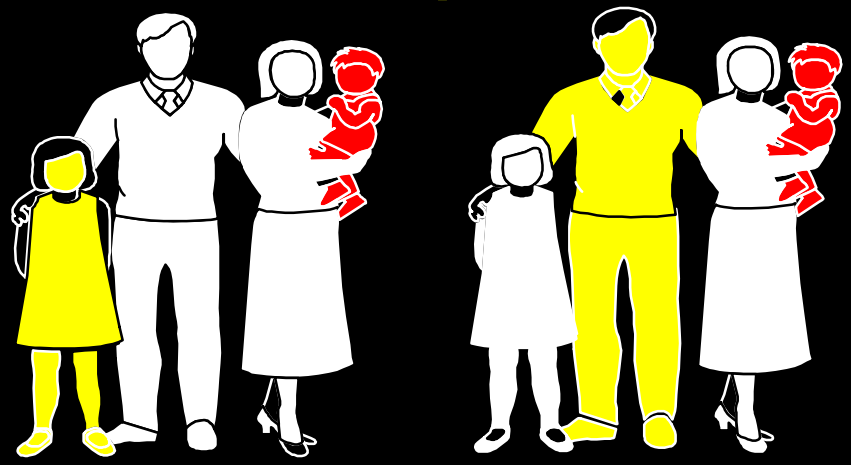
General population cohort

3-4 centers, NHW, AA, Hisp., other



Sibling/offspring cohort

4-5 centers (TrialNet, others)



screen = 100,000 /2-3 yrs

screen = 5,000

enroll =	1,500 (75%)	high risk enroll =	300 (60%)
	3,700 (50%)	moderate risk	200 (40%)
	3,120 /5,200 (60%)	15-yr f-up	400 / 500 (80%)
	200 / 100	cases IA/DM	120 / 80
	10,000	Parents	1,000

DAISY follow-up participation rates