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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ghalwash M, Dunne JL, Lundgren M. Two-age islet-autoantibody screening for childhood type 1 diabetes: a prospective cohort study.
Lancet Diabetes Endocrinol 2022; published online July 5. https://doi.org/10.1016/S2213-8587(22)00141-3.

"Sensitive and Efficient Islet Autoantibody screening…." Supplemental Materials

Table of Contents **(Page 1)**

Inverse Probability Censoring Weighting Algorithm:

The inverse probability censoring weights method accounts for right-censored outcomes – those who were type 1 diabetes free and lost follow up before age 15 – by using all 24,662 subjects and weight each subject by 1/p(t) where p(t) is the probability of censoring at time point t. In this case, subjects who were diagnosed at later age are assigned higher weights to account for those who would have had diagnosed but were censored. The algorithm to define weights for each subject is defined using the following steps:

1. Estimate the probability of censoring after time t using the Kaplan Meier estimator:

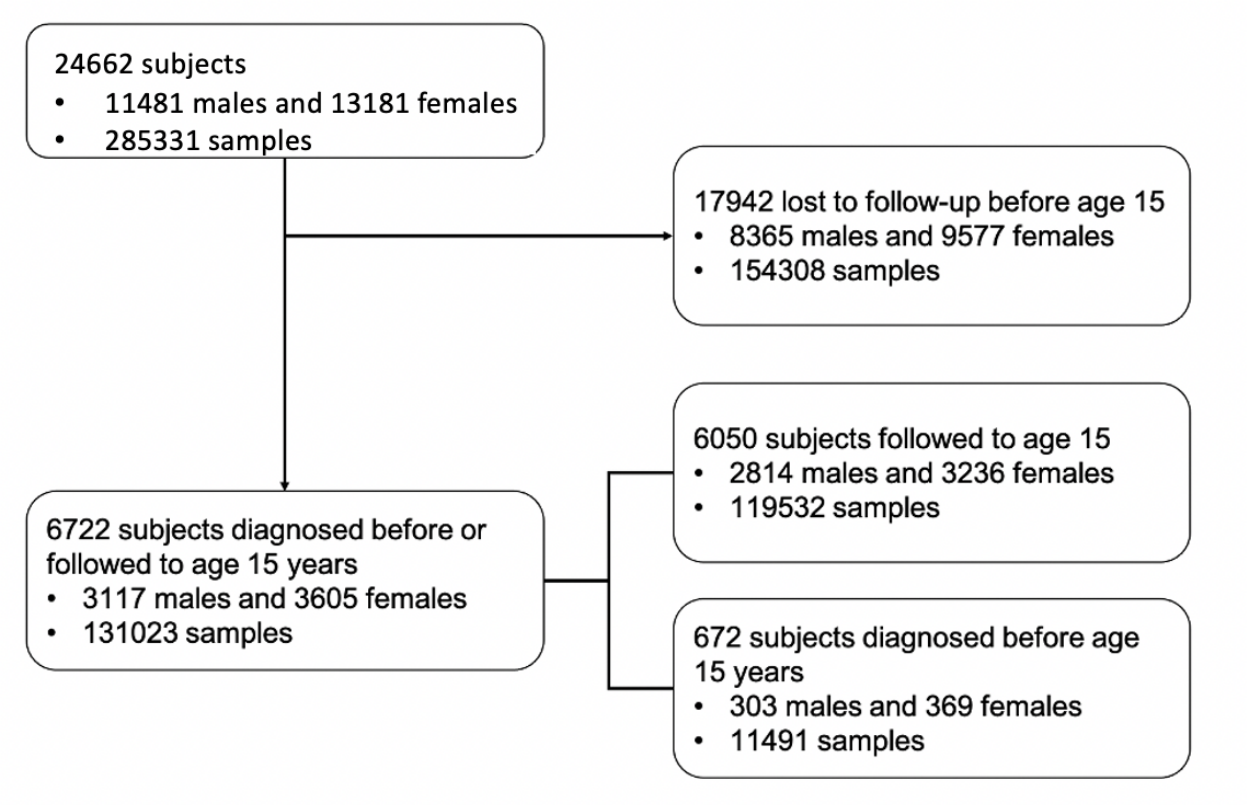
$$C(t) = \prod_{i:\, t_i < t} (1 - \frac{d_i}{n_i}) \quad \text{..... (1)}$$

   where d_i is the number of subjects censored at time t_i and n_i is the number of subjects who are not yet diagnosed or censored at time t_i.

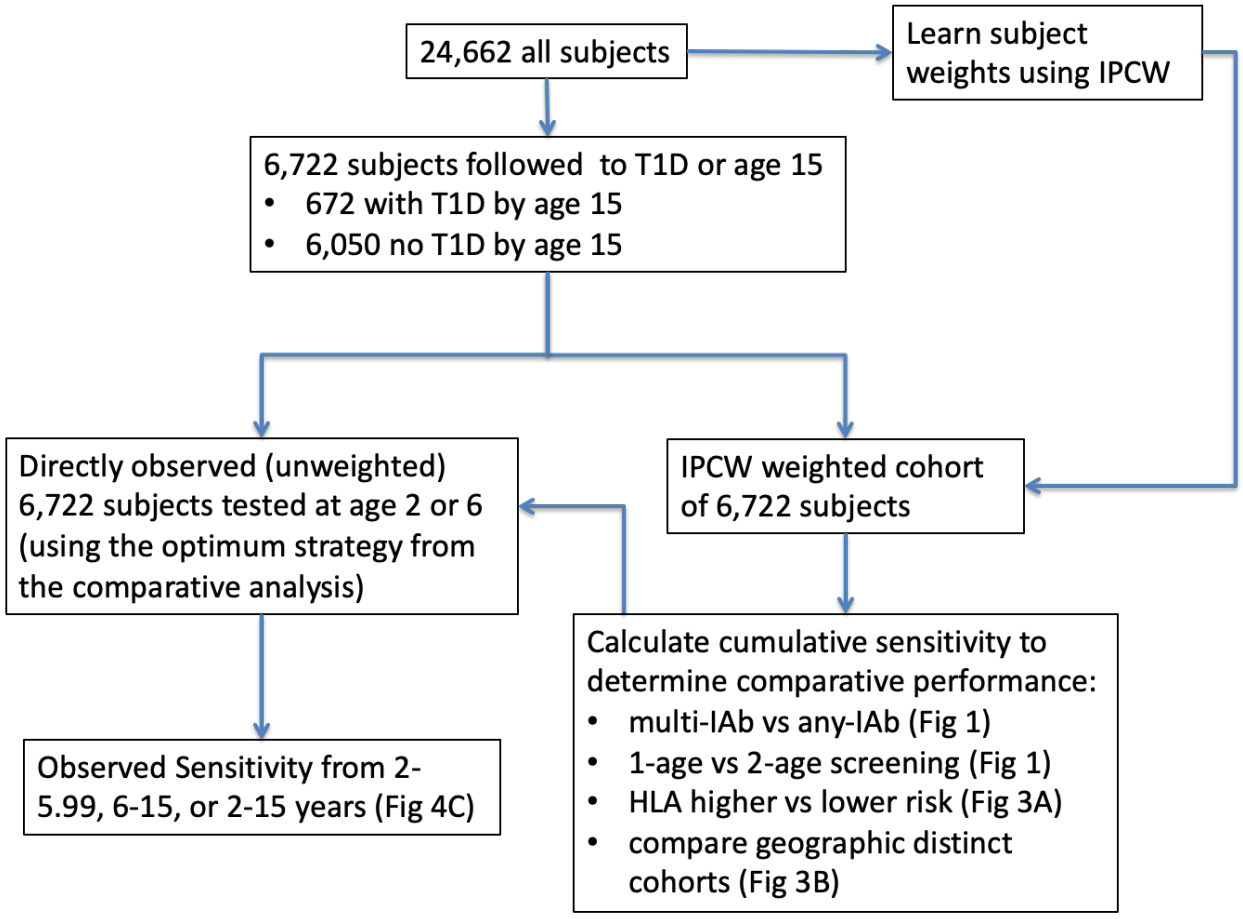
2. Each subject i is assigned a weight w_i as follows:

$$w_i = \begin{cases} \frac{1}{C(\theta)}, & diagnosed\ at\ time\ \theta < \tau \\ \frac{1}{C(\tau)}, & followed\ up\ until\ time\ \tau \\ 0, & otherwise \end{cases} \quad \text{..... (2)}$$

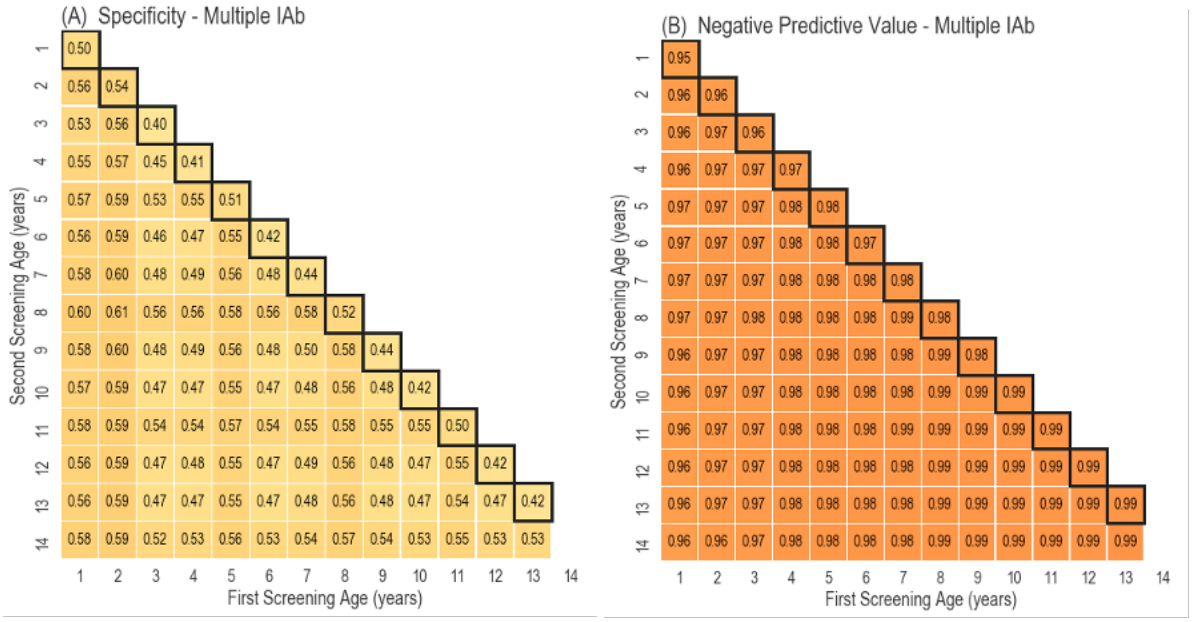
Subjects who are censored and not diagnosed before time τ will be assigned weight 0 and excluded from the analysis. However, their information is used in computing the probability of censoring and the corresponding weights assigned to other subjects. For example, if the probability of censoring after age 10 years is 0.2, this means that for any subject diagnosed at age 10, there are on average 4 other subjects censored before age 10 plus that one subject followed through age 10. In this example IPCW would assign a 5-times weight to the completely followed subject to account for 4 subjects censored before age 10 plus the followed subject (main manuscript reference #16).



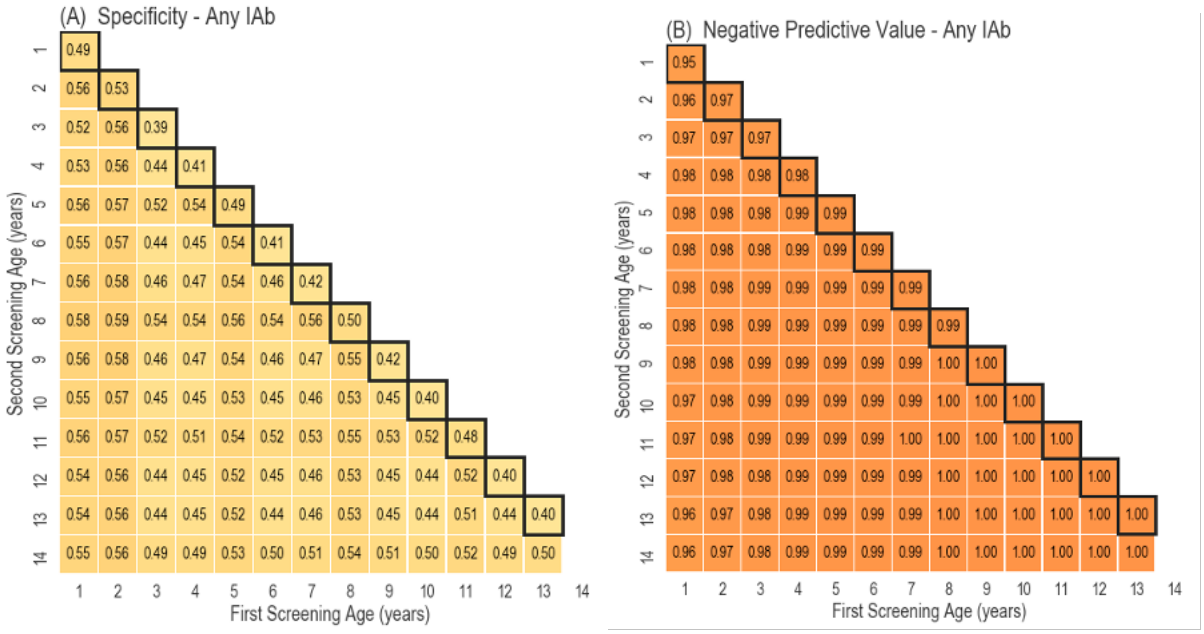
Supplemental Figure S1: STROBE diagram for the analysis cohort.



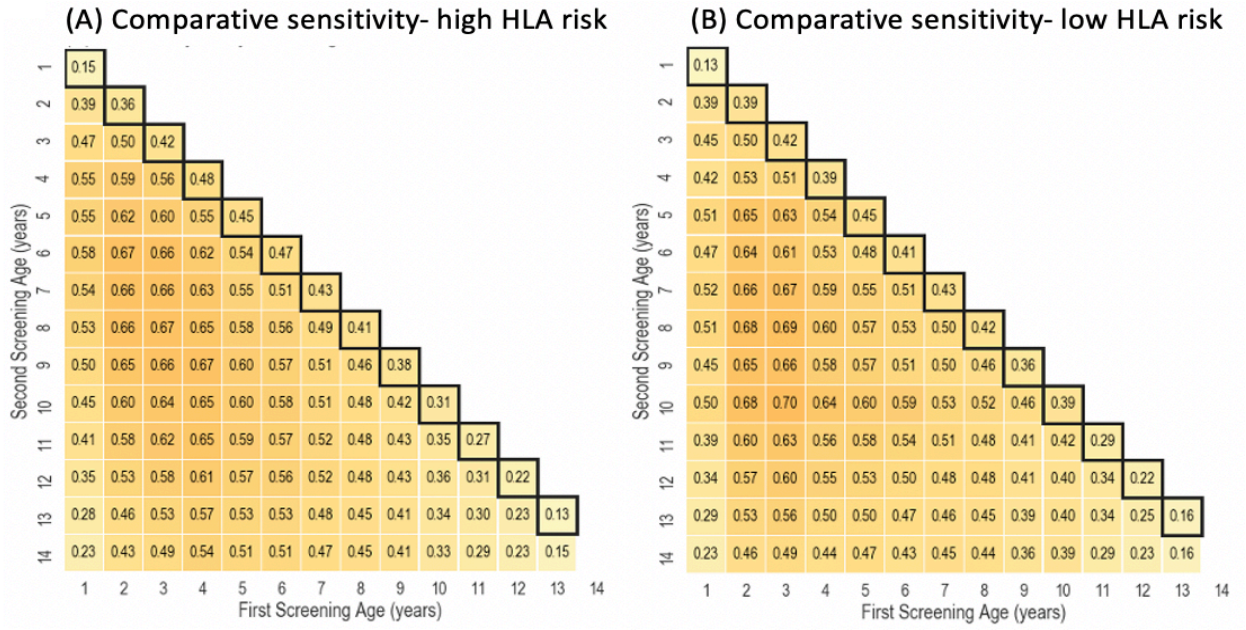
Supplemental Figure S2: Analysis flow diagram. All 24,662 subjects were used for IPCW to account for right censored subjects. 6,722 subjects followed to type 1 diabetes or followed to and without diabetes at age 15, were weighted using IPCW and then used in cumulative (comparative) sensitivity calculations to assess comparative performance. Directly observed subjects tested at age 2 or 6 were used to calculate the observed sensitivities.



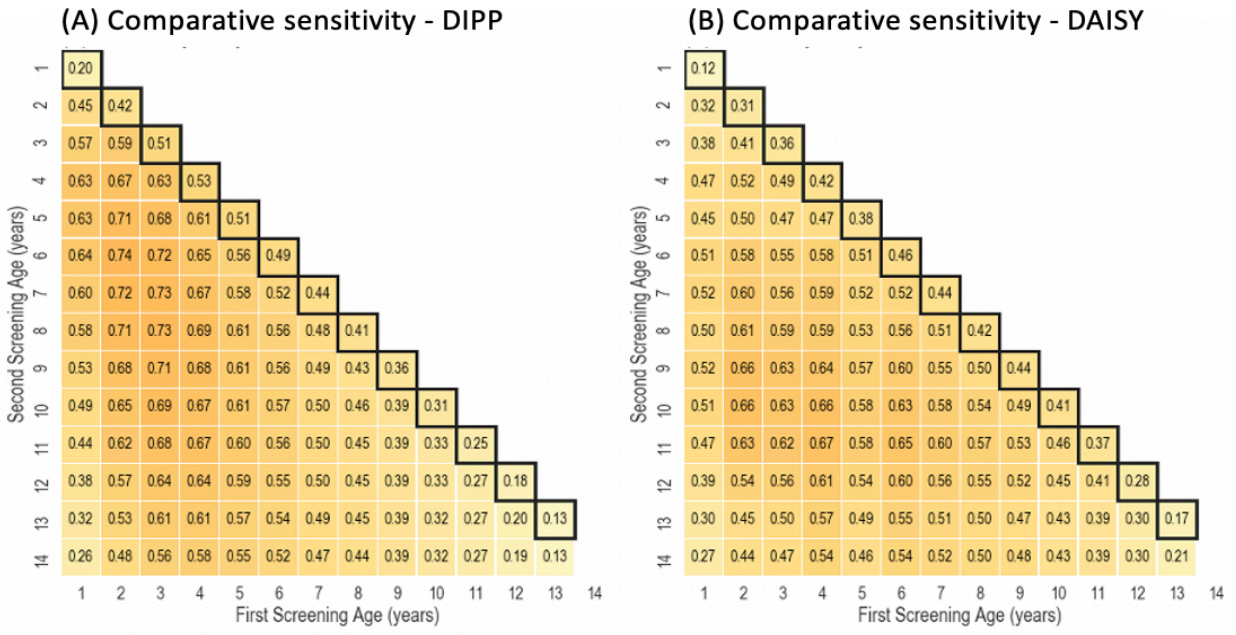
Supplemental Figure S3: Panels (a) specificity and (b) negative predictive value of "Multiple IAb" screening strategy at two ages for type 1 diabetes risk by age 15 on the entire T1DI cohort.



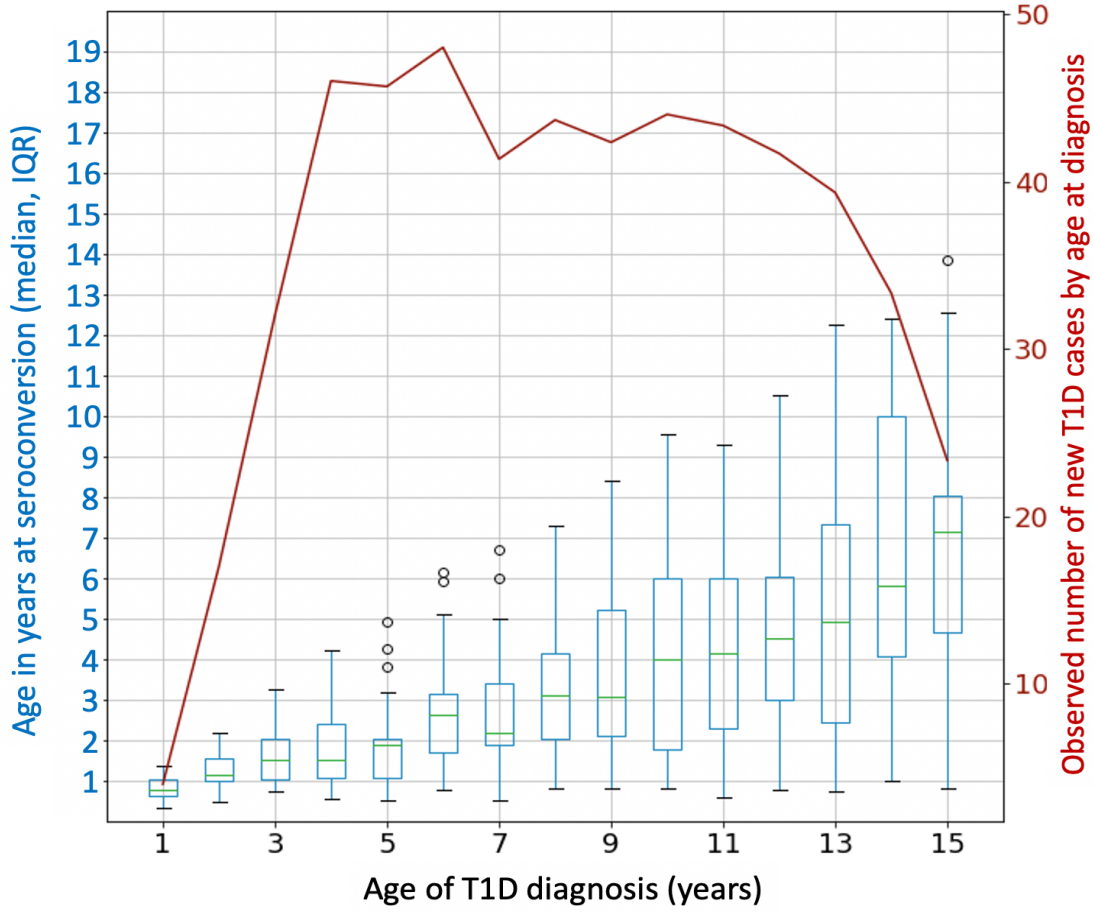
Supplemental Figure S4: Panels (a) specificity and (b) negative predictive value of "Any IAb" screening strategy at two ages for type 1 diabetes risk by age 15 on the entire T1DI cohort.



Supplemental Figure S5: Comparative sensitivity for screening of "Any IAb" at ages 2 and 6 for type 1 diabetes risk by age of 15 years on (A) Combined HLA groups A+B (very high risk + high risk) and (B) Combined HLA groups C+D (moderate risk + low risk).



Supplemental Figure S6: Comparative sensitivity for "Any IAb" screening at two ages for T1D risk by age of 15 years on the Finnish DIPP Study (A) versus the US DAISY Study (B).



Supplemental Figure S7: Median (IQR, range) age at seroconversion (blue symbols). Overlayed is the smoothed annual incidence, expressed as number of cases observed by age in the T1DI cohort (maroon line). Both are displayed by age of T1D onset in years. The Pearson correlation (r) between the age at seroconversion to onset is 0.80 (P-value <0.001).

Suppl.Table S1A HLA DR-DQ haplotype groups (based on Type 1 Diabetes Genetics Consortium odds ratios (ref S1,S2).

DR3-DQ2.5 includes	**DR4-DQ8.1 includes**	
(DR3)-DQA1*05-DQB1*02	DRB1*04:01-DQA1*03-DQB1*03:02	
(DR3)-DQA1*05:01-DQB1*02:01	DRB1*04:02-DQA1*03-DQB1*03:02	
DQ2 (Finland)	DRB1*04:03-DQA1*03-DQB1*03:02	
	DRB1*04:04-DQA1*03-DQB1*03:02	
	DRB1*04:05-DQA1*03-DQB1*03:02	
	DRB1*04:08-DQA1*03-DQB1*0304	
	DRB1*04:08-DQA1*03-DQB1*03:02	
	DRB1*04:13-DQA1*03-DQB1*03:02	
	(DR4)-DQA1*03:01-DQB1*03:02/4	
	(DR4)-DQA1*03-DQB1*03:02	
	(DR4/9)-DQA1*03:01-DQB1*03:02/3/4	
	DRB1*04:01-DQA1*03:01-DQB1*03:02	
	DRB1*04:04-DQA1*03:01-DQB1*03:02	
	DQA1*03:01-DQB1*03:02/3/4	
	(DR4)-DQA1*03:01-DQB1*03:02	
	(DR4)-DQA1*03:01-DQB1*03:02/4	
	(DR4)-DQA1*03-DQB1*03:02	
X (Neutral) includes	**Y (Protective) includes**	**Z (Highly Protective) includes**
(DR1)-DQA1*01:01-DQB1*05:01	(DR11/12/13)-DQA1*05-DQB1*03:01	(DR13/14/15/16)-DQA1*01-DQB1*06
(DR10)-DQA1*01-DQB1*05:01	(DR4)-DQA1*03-DQB1*03:01	(DR13)-DQA1*01:02-DQB1*06:09
(DR4)-DQA1*030x-DQB1*04:01	DRB1*0407-DQA1*03-DQB1*03:02	(DR13)-DQA1*01-DQB1*06:09
(DR4)-DQA1*03:01-DQB1*04:01	DRB1*04:01-DQA1*03-DQB1*03:01	(DR14)-DQA1*01:03-DQB1*0503
(DR4)-DQA1*03:02-DQB1*02:02	DRB1*0408-DQA1*03-DQB1*03:01	(DR14)-DQA1*01:04-DQB1*0503
(DR9)-DQA1*03-DQB1*02:02	(DR11/13)-DQA1*05-DQB1*03:01/9	(DR7)-DQA1*0201-DQB1*03:03
(DR9)-DQA1*03:02-DQB1*03:03	(DR11/13)-DQA1*05:01-DQB1*03:01	(DR15)-DQB1*06:02
(DR9)-DQA1*03:01-DQB1*03:02	(DR11/13) -DQA1*05-DQB1*03:01/9	(DR13)-DQB1*06:03
(DR9)-DQA1*03-DQB1*03:03	(DR11/13)-DQA1*05-DQB1*03:01	(DR13)-DQB1*06:03
(DR9)-DQA1*03:01-DQB1*03:04	(DR15)- DQA1*01:03-DQB1*06:01	(DR13)-DQB1*06:09
(DR9)-DQA1*03:01-DQB1*03:03	(DR7)-DQA1*02:01-DQB1*02:02	(DR14)-DQB1*05:03
(DR13)-DQA1*01:02-DQB1*06:04	(DR7)-DQA1*02:01-DQB1*02:01	(DR7)-DQA1*02:01-DQB1*03:03
(DR13)-DQB1*06:04	(DR7)-DQA1*02:01-DQB1*02	(DR15)-DQA1*01-DQB1*06:03
(DR16)-DQA1*01:02-DQB1*05:02	(DR7)-DQA1*02:01-DQB1*03:01?	(DR15)-DQA1*01-DQB1*06:02/3
(DR16)-DQB1*05:02	(DR4)-DQA1*03-DQB1*03:01	(DR15)-DQA1*01:03-DQB1*06:03
(DR8)-DQA1*04:01-DQB1*04:02	(DR3)-DQA1*05:01-DQB1*03:01?	(DR15)-DQA1*01:03-DQB1*06:02/3
(DR8)-DQB1*04	DRB1*0403-DQA1*03-DQB1*03:02	(DR15)-DQA1*01:02-DQB1*06:02
(DR13,14,15,16)-DQA1*01-DQB1*05/06	(DR4)-DQA1*03-DQB1*03:01	DRB1*0407-DQA1*03-DQB1*03:01

Supplemental Table S1B - HLA harmonization to 4 Risk Groups

Group A	**Group B**	**Group C**	**Group D**
DR3-DQ2.5/DR4-DQ8.1	DR4-DQ8.1/DR4-DQ8.1	DR4-DQ8.1/Y	DR3-DQ2.5/Y
	DR4-DQ8.1/X	DR3-DQ2.5/X	DR3-DQ2.5/Z
	DR3-DQ2.5/DR3-DQ2.5		DR4-DQ8.1/Z
			X/Y,Y/Y,X/X,X/Z,Y/Z,Z/Z

Supplemental references

S1. Emery L, Babu S, Bugawan T, et al. Newborn HLA-DR,DQ genotype screening: age- and ethnicity-specific type 1 diabetes risk estimates. Pediatr Diabetes 2005 6:136-44.

S2. Erlich H, Valdes A, Noble J et al. HLA DR-DQ haplotypes, genotypes and T1D risk. Diabetes 2008 57:1084-92

		DIPP	DiPiS	DAISY	DEW-IT	BABYDIAB
Proportion of FDR	Yes	-	12 (0.2%)	550 (8%)	111 (2%)	1052 (16%)
	No	-	63 (1%)	478 (7%)	546 (8%)	-
	Not Available	3910 (58%)	-	-	-	-
# Subjects in HLA groups	A	675 (10%)	36 (0.5%)	222 (3%)	152 (2%)	78 (1%)
	B	2699 (40%)	9 (0.1%)	443 (7%)	259 (4%)	268 (4%)
	C	341 (5%)	4 (0.1%)	198 (3%)	200 (3%)	208 (3%)
	D	191 (3%)	26 (0.4%)	165 (3%)	42 (1%)	487 (7%)
	Undetermined	4 (0.1%)	-	-	4 (0.1%)	11(0.2%)

Supplemental Table S2: Number of subjects with family history (FDR) and proportion with respect to the entire T1DI cohort (6722 subjects). Number and proportion of subjects in each HLA risk group for each study in the T1DI cohort.

Condition	Metric	Value %	95% CI
screening ages 2 and 6, any islet autoantibody	comparative sensitivity	66%	63-69%
	positive predictive value	54%	51-58%
screening ages 2 and 6, multiple islet autoantibodies	comparative sensitivity	51%	47-54%
	positive predictive value	74%	69-78%
screening ages 2 and 6, any islet autoantibody, HLA A+B	comparative sensitivity	67%	64-70%
	positive predictive value	59%	54-63%
screening ages 2 and 6, any islet autoantibody, HLA C+D	comparative sensitivity	64%	57-71%
	positive predictive value	45%	38-53%
screening ages 2 and 6, any islet autoantibody, DIPP	comparative sensitivity	74%	71-78%
	positive predictive value	57%	54-61%
screening ages 2 and 6, any islet autoantibody, DAISY	comparative sensitivity	58%	50-67%
	positive predictive value	58%	49-67%
screening ages 2 and 9, any islet autoantibody, DAISY	comparative sensitivity	66%	58-74%
	positive predictive value	54%	45-62%
a single islet autoantibody, age 2	4 yr risk from age 2-5.99	31%	23-39%
multiple islet autoantibodies, age 2	4 yr risk from age 2-5.99	55%	50-62%
a single islet autoantibody at age 6, after age 2 test neg or missing	9 yr risk from age 6-15	39%	29-48%
a single islet autoantibody at age 6, after age 2 test pos any islet ab	9 yr risk from age 6-15	70%	67-76%
multiple islet autoantibodies age 6	9 yr risk from age 6-15	83%	78-88%
screening ages 2 and 6, any islet autoantibody	observed sensitivity	82%	79–86%
	observed PPV	79%	75–80%

Supplemental Table S3: Comparative or observed sensitivities, their positive predictive values (PPV) and their 95% Confidence Intervals, as cited in the text.