Supplemental Figures and Tables

Variable name	Significant effect in TEDDY (ref)	Effect outside of TEDDY (ref)	ROC AUC (95%CI) to predict T1D	p-value for Cox model
Sex	53	54,55	0.50 (0.47-0.54)	0.88
Probiotic	53,56	57	0.51 (0.49-0.53)	0.66
Common cold days	26	58,59	0.50 (0.47-0.56)	0.098
Influenza episodes	60	58,59	0.51 (0.49-0.52)	0.69
Respiratory episodes	60	58,59	0.51 (0.47-0.55)	0.32
Fever episodes	60	58	0.51 (0.47-0.55)	0.80
Laryngitis tracheitis episodes	60	58,59	0.51 (0.48-0.53)	0.45
Acute sinusitis episodes	60	58,59	0.51 (0.49-0.53)	**0.03**
Caesarean section	61	62–66	0.52 (0.48-0.55)	0.27
Gestational respiratory infections	61	67,68	0.52 (0.49-0.56)	0.99
Mother T1D	26	27,55	0.51 (0.49-0.53)	**0.03**
Father T1D	26	27,55	0.53 (0.51-0.56)	**1.2e-05**
Siblings T1D	26	27,55	0.54 (0.52-0.56)	**1.7e-08**
Zscore weight 1y	26,69	70,71	0.54 (0.51-0.59)	**0.006**
Country	26,72	54,73,74	0.55 (0.51-0.59)	**0.03**
Any FH T1D	53	27,55	0.56 (0.53-0.59)	**1e-08**
IA2A	22	1,29,75	0.59 (0.56-0.62)	**7.9e-57**
GAD	22	1,29,75	0.65 (0.62-0.68)	**1.8e-81**
GRS2	-	24	0.73 (0.7-0.77)	**2.8e-36**
MIAA	53	1,28	0.73 (0.69-0.76)	**3.7e-119**
AB number	53	1,29,75	0.75 (0.71-0.78)	**5.5e-136**

Table S1- Variables previously shown or susceptible to be T1D- or T1D autoantibody associated now evaluated in univariate analysis. Time ROC AUC and p-value are computed at landmark 2 years old and horizon time of 8 years.

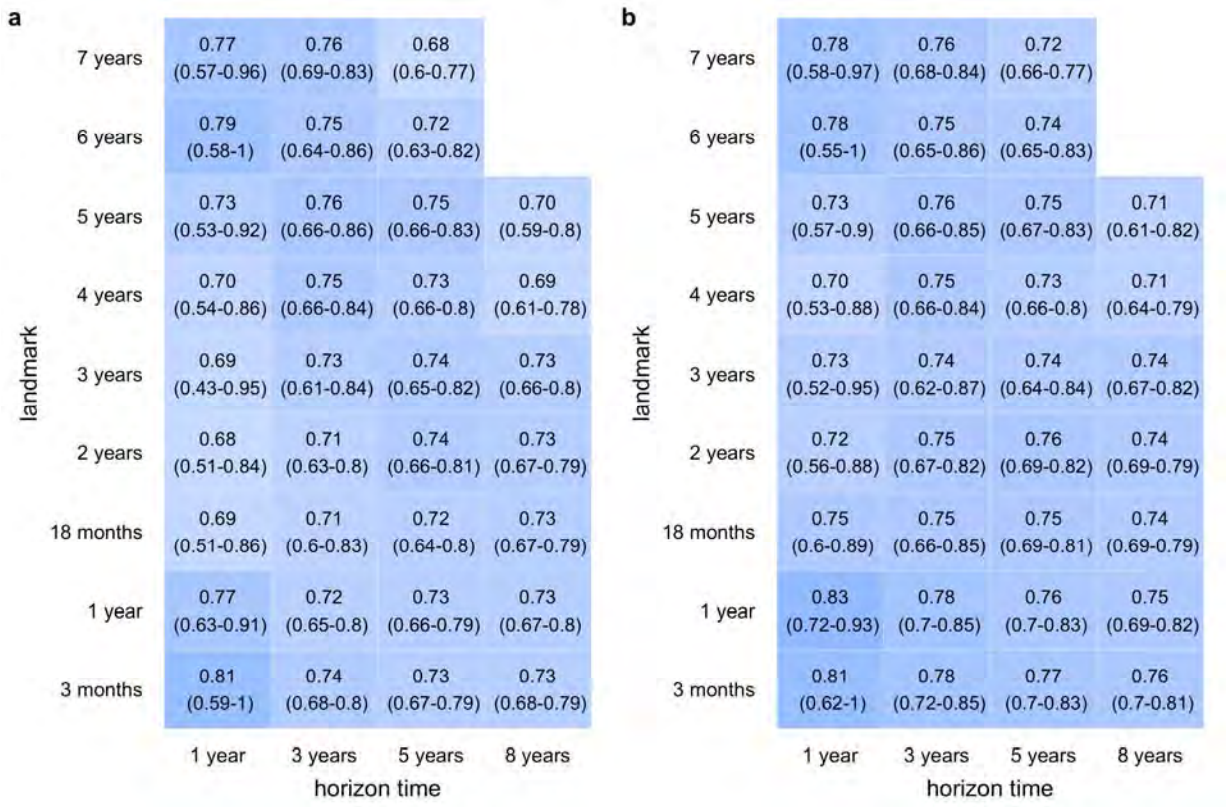

Table S2: Comparison of T1D GRS2 alone (Panel a) to T1D GRS2 + FH (Panel b) at 9 different landmark scoring ages and over 4 different horizon times. Although 95% confidence intervals always overlapped, among 34 total combinations, T1D GRS2+FH gave a larger AUC ROC in 24, results were similar in 9, and in only one was T1D GRS better. T1D GRS2 + FH superiority was greatest at landmarks ≤3 years of age.

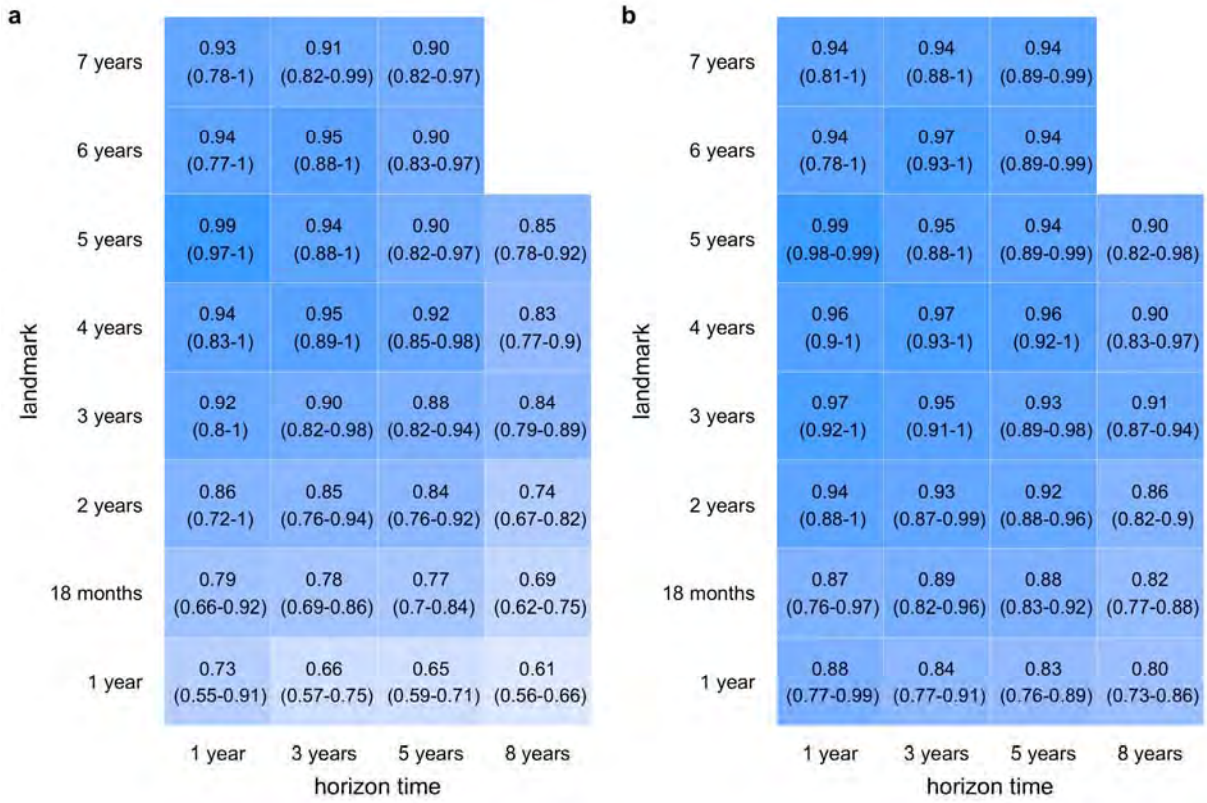

Table S3: Comparison of AB alone (Panel a) to the 3-variable model of AB, GRS2 and FH (Panel b) at 8 different landmark scoring ages and over 4 different horizon times. Although 95% confidence intervals overlapped, among 30 total combinations, the 3-variable model yielded larger AUC ROC in 28, and similar results in the remaining 2 combinations. The differences were often substantial, especially at landmarks ≤4 years of age.

Autoanti-body status	Genetic risk	Family history	1 year horizon		3 year horizon		5 year horizon	
			Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
0	++	No	100.0%	17.6%	100.0%	17.7%	100.0%	17.7%
0	++	Yes	97 .8%	57.3%	95.3%	57.4%	93.6%	57.7%
0	+++	No	97.8%	76.9 %	91.8%	77.3%	87.9%	77.5%
0	+++	Yes	87.0%	93.9%	85.1%	94.2%	78.6%	94.6%
1	++	No	80.3%	96.7%	80.5%	97.1%	75.5%	97.5%
1	++	Yes	76.0%	97.4%	73.6%	97.8%	69.3%	98.2%
1	+++	No	73.7%	97.8%	71.2%	98.2%	66.9%	98.6%
1	+++	Yes	58.6%	98.5%	58.9%	98.8%	58.7%	99.2%
2	++	No	73.7%	97.9%	71.2%	98.3%	66.9%	98.6%
2	++	Yes	54.1%	98.6%	51.9%	98.9%	54.1%	99.3%
2	+++	No	41.2%	99.0%	34.8%	99.2%	40.4%	99.6%
2	+++	Yes	13.3%	99.6%	9.0%	99.7%	11.8%	99.8%
3	++	No	58.6%	98.5%	58.9%	98.8%	58.7%	99.2%
3	++	Yes	36.8%	99.2%	31.4%	99.3%	36.5%	99.6%
3	+++	No	21.9%	99.5%	18.0%	99.6%	20.2%	99.7%
3	+++	Yes	4.5%	100.0%	2.3%	99.9%	2.3%	100.0%

Table S4 Sensitivity and specificity given future T1D risk probabilities for 16 different scenarios combining a GRS and FH background risk level with different AB status for two-year-old children. "++" represents a genetic risk score at 90th percentile of the general (UK) population. "+++" represents a genetic risk score at 99th percentile of the general (UK) population.

landmark/ horizon	T1D children caught	T1D children missed	% of T1D caught per period	% of people in the cohort	cumulative caught	cumulative missed	cumulative evaluations
0/1	10	0	100%	100%	10	0	7798
1/1	36	0	100%	100%	46	0	38050
2/1	31	0	100%	100%	77	0	65270
3/1	20	0	100%	100%	97	0	77902
4/1	34	0	100%	100%	131	0	89848
5/1	24	0	100%	100%	155	0	101260
6/1	20	0	100%	100%	175	0	106777
7/1	27	0	100%	100%	202	0	112100
8/2	46	0	100%	100%	248	0	117234

Table S5A: Visit number calculations for the "Classic" design. Infants initially selected for high GRS2 genetic risk were all followed quarterly until age 3, and every 6 months until age 6, then annually thereafter. Simulation made on the TEDDY dataset.

Landmark/ horizon	T1D children caught	T1D children missed	% of T1D caught per year	% of people in the cohort	cumulative caught	cumulative missed	cumulative evaluations
0/1	10	0	100%	100%	10	0	7798
1/1	36	0	100%	95.7%	46	0	36742
2/1	31	0	100%	94.9%	77	0	62630
3/1	20	1	95.%	78.2%	97	1	72552
4/1	34	6	85%	46.6%	131	7	78140
5/1	24	2	92.3%	23.6%	155	9	80838
6/1	20	3	87.0%	8.5%	175	12	81305
7/1	22	2	91.7%	6.7%	197	14	81640
8/2	36	1	97.3%	6.5%	233	15	81937

Table S5B: Visit number calculations for the "Simple Adaptive" design. Infants selected for high genetic risk were initially followed as in the Classic strategy, but the T1D CRS was recalculated at annual landmarks, at which time any child whose T1D probability by age 10 had decreased to <0.008 was eliminated from further follow-up. Of new cases, 94% had high risk detected before onset. Simulation made on the TEDDY dataset.

landmark/ horizon	T1D children caught	T1D children missed	% of T1D caught per period	% of people in the cohort	cumulative caught	cumulative missed	cumulative evaluations
0/1	8	2	80.0%	25.8%	8	2	7798
1/1	32	4	88.9%	28.4%	40	6	21811
2/1	28	3	90.3%	6.7%	68	9	29993
3/1	18	2	90.0%	5.5%	86	11	36656
4/2	56	2	96.6%	6.4%	142	13	43772
6/2	44	3	93.6%	7.7%	186	16	49714
8/2	42	4	91.3%	8.5%	228	20	54848

Table S5C: Visit number calculations for the "Advanced Adaptive" design. Infants selected for high genetic risk were initially followed as in the Classic strategy, but at birth and annually thereafter, a T1D CRS calculation was used to reallocate children among the quarterly or annual surveillance groups based on T1D probability in 2 years of ≥0.006 or <0.006, respectively. Of new cases, 92% had high risk detected before onset. Simulation made on the TEDDY dataset.

Variable		non T1D (7493)	T1D (305)
Country	USA	3143	103
	Finland	1612	89
	Germany	507	28
	Sweden	2231	85
First degree relative with T1D	no	6691	221
	yes	802	84
Mother T1D	no	7214	283
	yes	279	22
Father T1D	no	7131	260
	yes	362	45
Siblings T1D	no	7381	280
	yes	112	25
HLA genotype	other	340	17
	DR4/DR3	2835	166
	DR4/DR4	1464	55
	DR4/DR8	1277	42
	DR3/DR3	1577	25
Sex	Female	3684	148
	Male	3809	157
Caesarean section	no	5542	223
	yes	1951	82

Table S6: Numbers of diabetic and non-diabetic children in the cohort by model variable.

Chromosome	SNP	MAF	Minor allele	Major allele	r^2
1	rs2476601	0.1083	A	G	Genotyped
1	rs3024505	0.1509	A	G	Genotyped
2	rs2111485	0.4118	A	G	Genotyped
2	rs3087243	0.3982	A	G	Genotyped
4	rs17388568	0.3064	A	G	Genotyped
6	rs9500974	0.0060	T	G	Genotyped
6	rs72848653	0.0686	T	C	0.915
6	rs76569729	0.1268	T	C	0.944
6	rs144530872	0.0160	A	G	0.959
6	rs12153924	0.3001	A	G	0.979
6	rs12189871	0.0330	T	C	Genotyped
6	6:31274793_G_GC	0.0073	GC	G	0.808
6	rs371250843	0.0463	T	TG	0.996
6	rs16899379	0.0025	A	G	0.933
6	rs149663102	0.0100	T	TG	0.994
6	rs2524277	0.0104	A	G	Genotyped
6	rs116522341	0.0610	G	C	0.791
6	rs75658393	0.0318	C	T	0.992
6	rs9269173	0.0528	A	T	0.977
6	rs9271346	0.0011	C	T	0.892
6	rs1281934	0.0039	G	A	0.544
6	rs9405117	0.0073	A	C	0.358
6	rs111485156	0.0003	C	T	0.889
6	rs9273369	0.4008	C	T	Genotyped
6	rs10947332	0.0109	A	G	Genotyped
6	rs12527228	0.0814	T	C	0.981
6	rs7454108	0.4878	G	A	Genotyped
6	rs6934289	0.1117	C	T	0.998
6	rs17214657	0.1346	C	T	Genotyped
6	rs2567287	0.0086	A	G	0.998
6	rs9378176	0.0154	G	A	0.999
6	6:33071027_C_CTA	0.1583	CTA	C	0.944
6	rs72928038	0.1573	A	G	Genotyped
6	rs9388489	0.4641	G	A	Genotyped
6	rs1738074	0.4308	T	C	Genotyped
7	rs4948088	0.0457	A	C	Genotyped
9	rs6476839	0.4213	A	T	Genotyped
10	rs61839660	0.0745	T	C	Genotyped
10	rs41295121	0.0092	T	C	Genotyped

10	rs60888743	0.2500	G	A	0.998
11	rs3842753	0.2540	T	G	0.968
12	rs10492166	0.4889	A	G	Genotyped
12	rs11170466	0.0635	T	C	0.466
12	rs4759229	0.3286	A	G	Genotyped
12	rs653178	0.4486	C	T	Genotyped
13	rs9585056	0.2507	C	T	Genotyped
14	rs56994090	0.4421	C	T	Genotyped
15	rs72727394	0.2064	T	C	Genotyped
15	rs2289702	0.1026	T	C	0.988
16	rs12708716	0.3349	G	A	Genotyped
16	rs9924471	0.1450	A	G	Genotyped
18	rs1893217	0.1612	G	A	Genotyped
18	rs1615504	0.4821	T	C	Genotyped
19	rs144309607	0.0070	T	C	0.514
19	rs425105	0.1585	C	T	Genotyped
20	rs2281808	0.3306	T	C	0.996
21	rs9981624	0.3277	G	C	Genotyped
22	rs5763779	0.3403	A	G	Genotyped
22	rs229541	0.4207	A	G	Genotyped

Table S7 The 59 SNPs used in the T1D GRS2 with the Minor allele frequency and when needed the imputation score r^2. A total of 8 SNPs from the published GRS2 are not used because they mark HLA-DQ haplotypes not included in the TEDDY cohort.

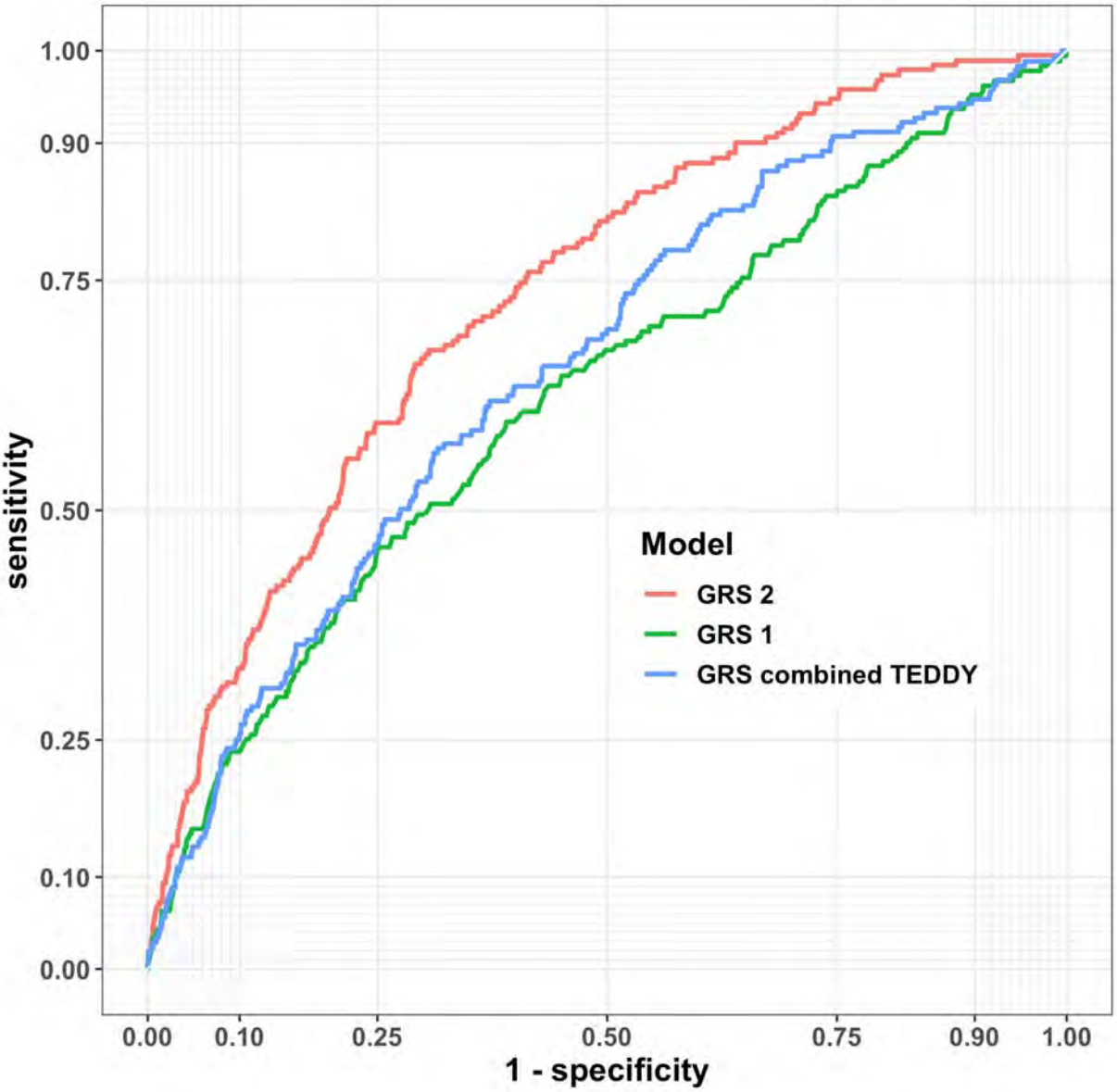

Figure S1: ROC curves comparing GRS1[33], GRS2[24] and the combined TEDDY GRS[19] to predict T1D from a landmark age of birth, horizon of 8 years.

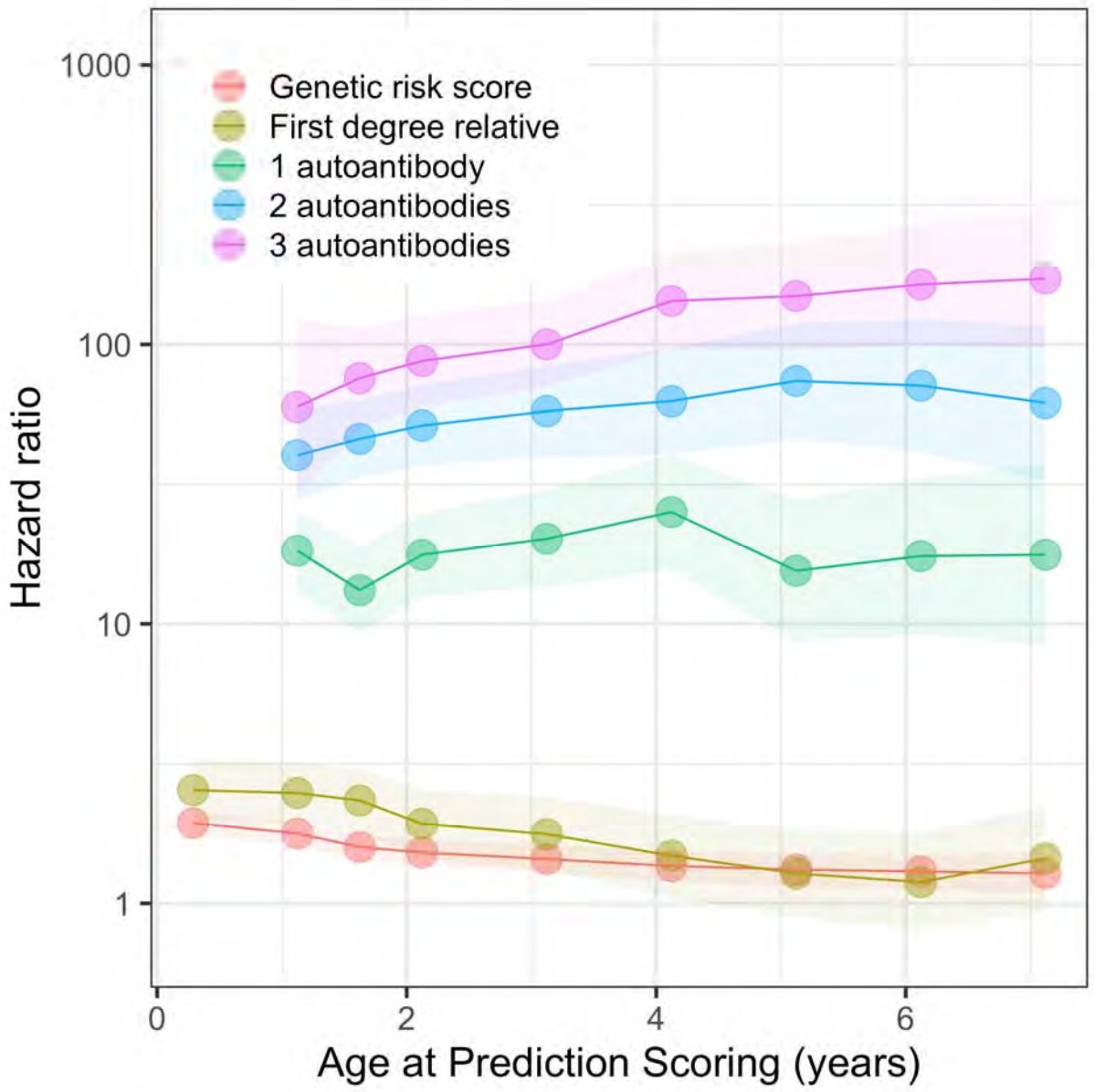

Figure S2: Hazard ratio for each variable at different ages at prediction scoring (landmarks).

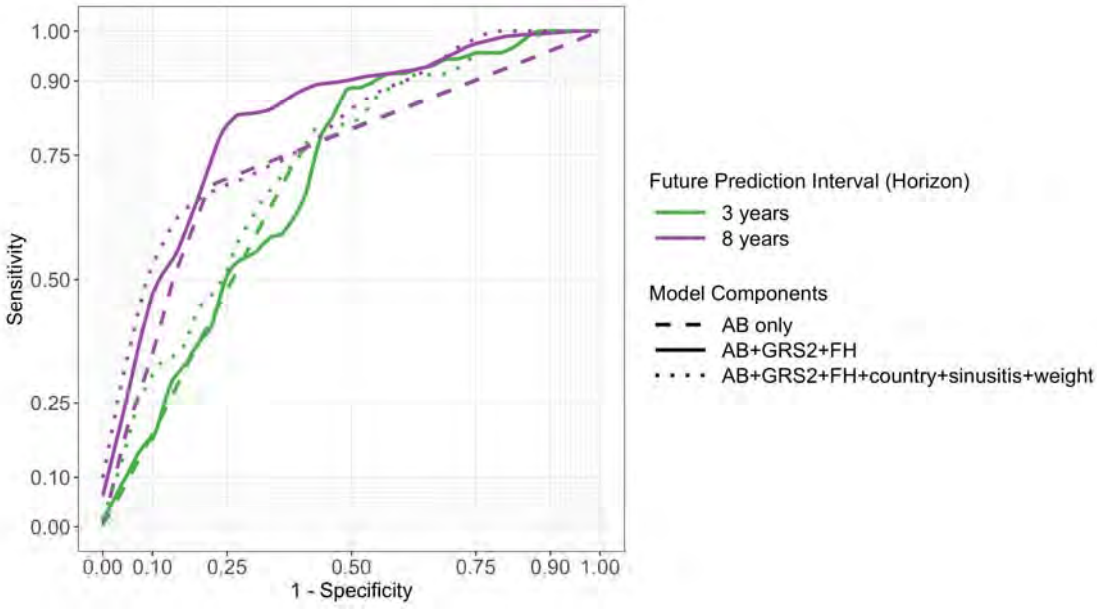

Figure S3- Time dependent ROC of the different models now including only children positive for at least one AB. The landmark age is two years. At a 3 year horizon the CRS (AB+GRS2+FH) performs similarly to AB only, but at an 8 year horizon the CRS is more predictive.

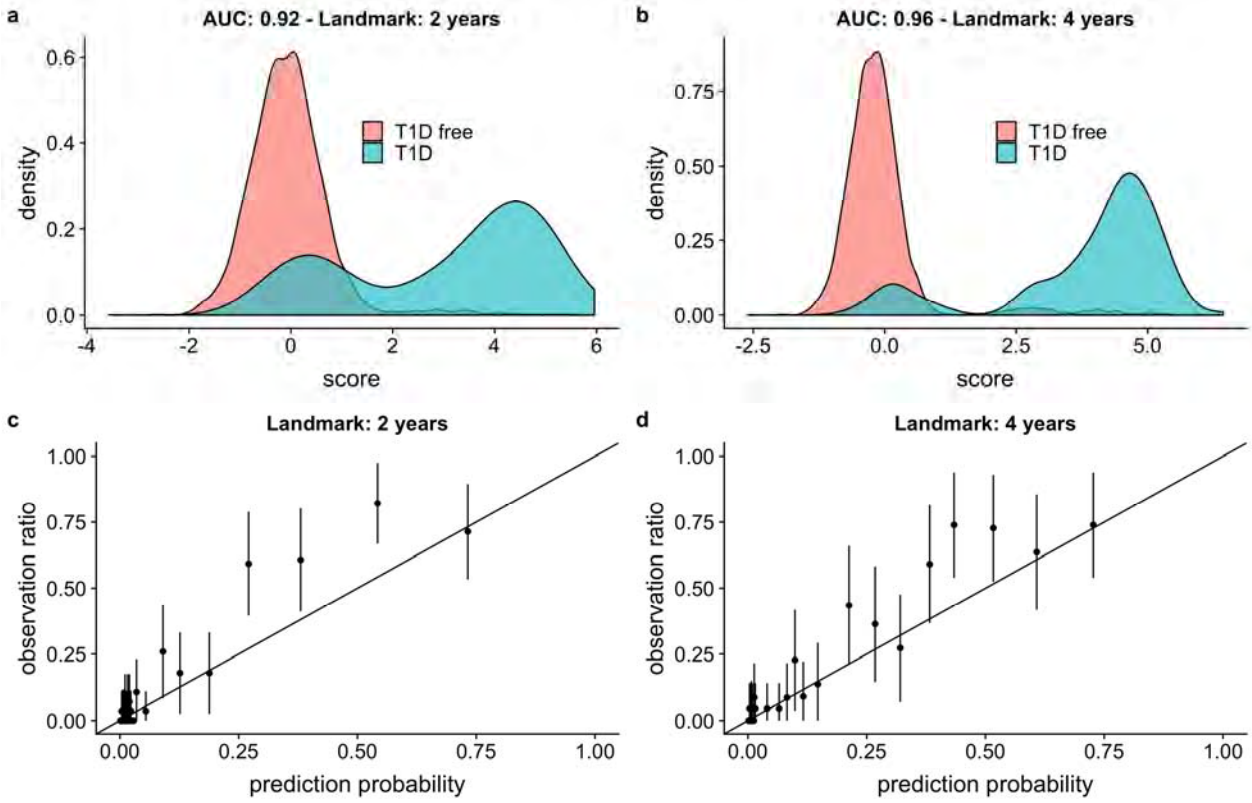

Figure S4, Panels a and b: score distribution for 3-variable model at a horizon time of 5 years for a) landmark at 2 year, b) landmark at 4 years with increases in AUC ROC as noted on the figure. The T1D CRS was generated by the linear predictor of the parametric part of the hazard function of the Cox model.

Panels c and d: calibration plot for 3-variable model at a horizon time of 5 years and c) landmark at 2 years and d) landmark at 4 years. The predictions are grouped into centiles based on their predicted values, and then the bin prevalence (the ratio of plots in this bin with observed values of present verses the total number of plots in this bin) is calculated for each bin.

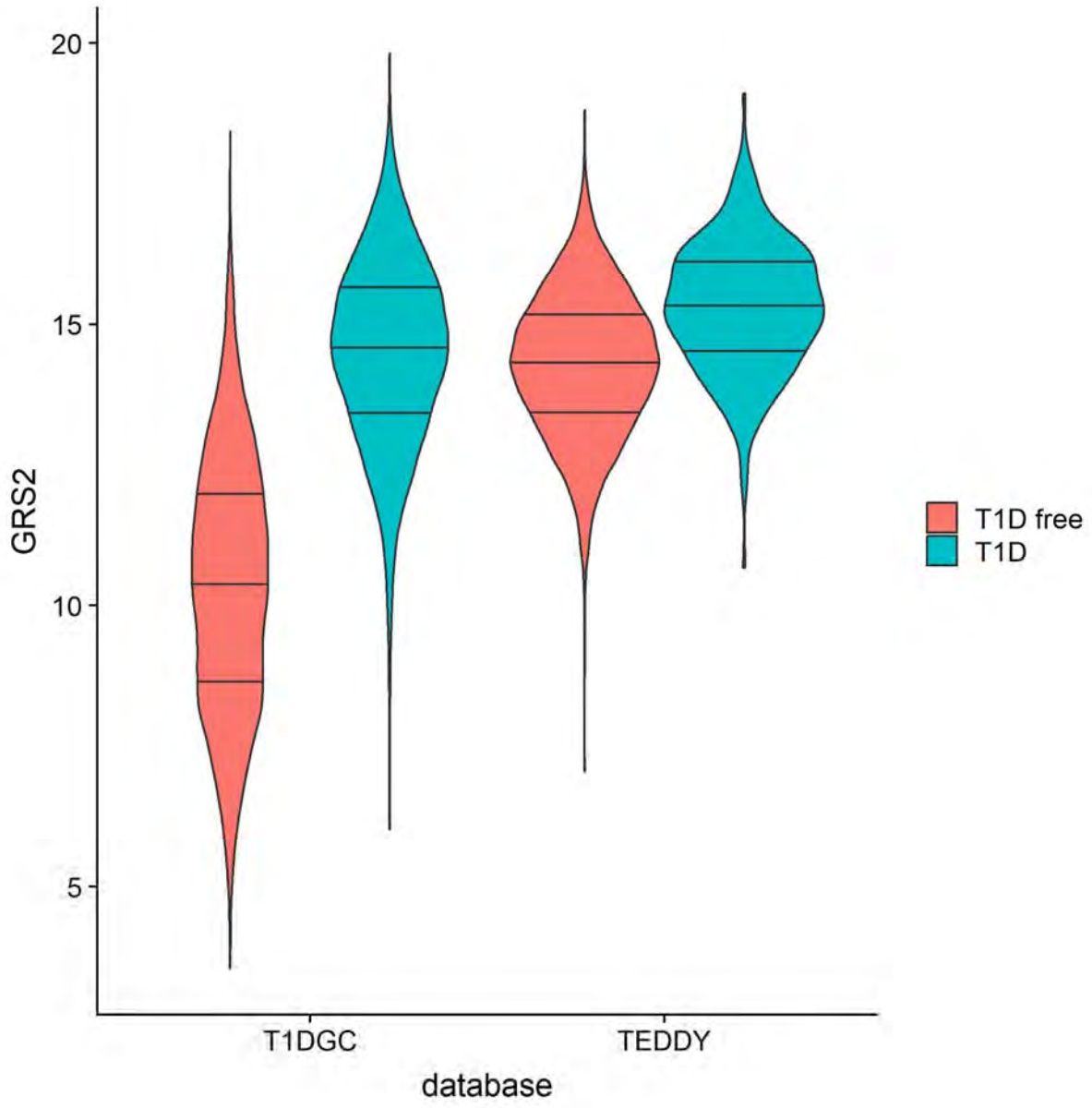

Figure S5. GRS2 violin plot in the Type 1 Diabetes Genetics Consortium (T1DGC) and TEDDY datasets. T1DGC is more representative of the general background population. The genetic pre-selection in TEDDY based on the major T1D risk locus HLA-DR-DQ, renders the T1D GRS2 higher in TEDDY, even in T1D free subjects. Further, the separation between T1D and non-T1D subjects in TEDDY is much less.