Genetica e medicina di precisione nel diabete tipo 1

Mario Luca Morieri MD PhD

Department of Medicine - DIMED , Università di Padova, Padova, Italia

Conflitti di interesse

Il dr. Mario Luca Morieri dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Guidotti, Merck Sharp & Dohme, Novo Nordisk, Novartis, Servier. Nessuna in relazione a questa talk.

2nd International Consensus on Precision Medicine

nature medicine

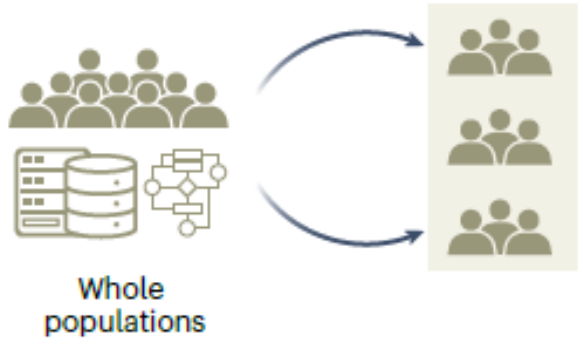
Consensus Statement https://doi.org/10.1038/s41591-023-02502-5

Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine

Tobias DK*, Merino J*, ..., Morieri ML* et al | Nat. Medicine | 2023

"***Personalized or Individualized Medicine: is the final step of in the process of translating knowledge into practice***"

"The use of a person's own data to objectively gauge the efficacy, safety, and tolerability of therapeutics, and, subjectively, to tailor health recommendations and/or medical decisions to the individual's preferences, circumstances, and capabilities".



"…Precision medicine emphasizes **tailoring diagnostics or therapeutics to subgroups of populations sharing similar characteristics" → minimizing error and risk while maximizing efficacy**"

2nd International Consensus on Precision Medicine

nature medicine

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Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine

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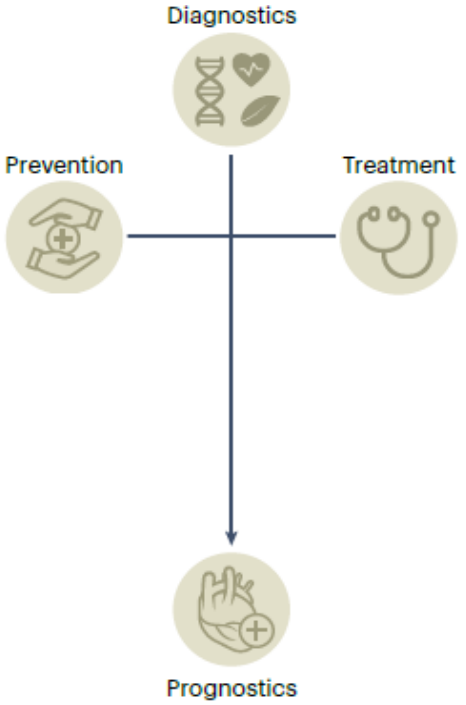
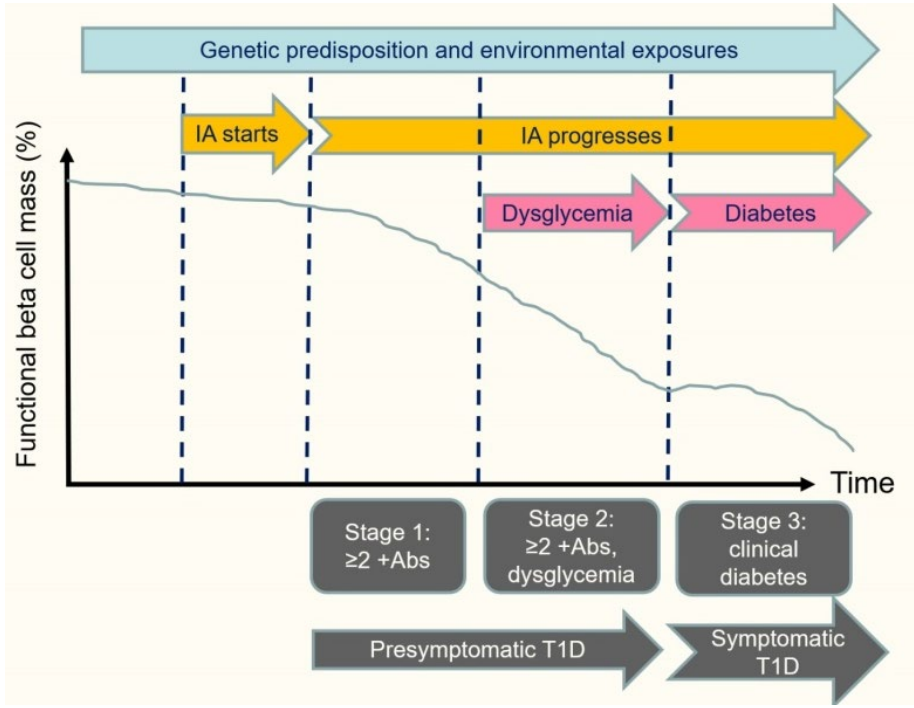
Pillars of precision medicine



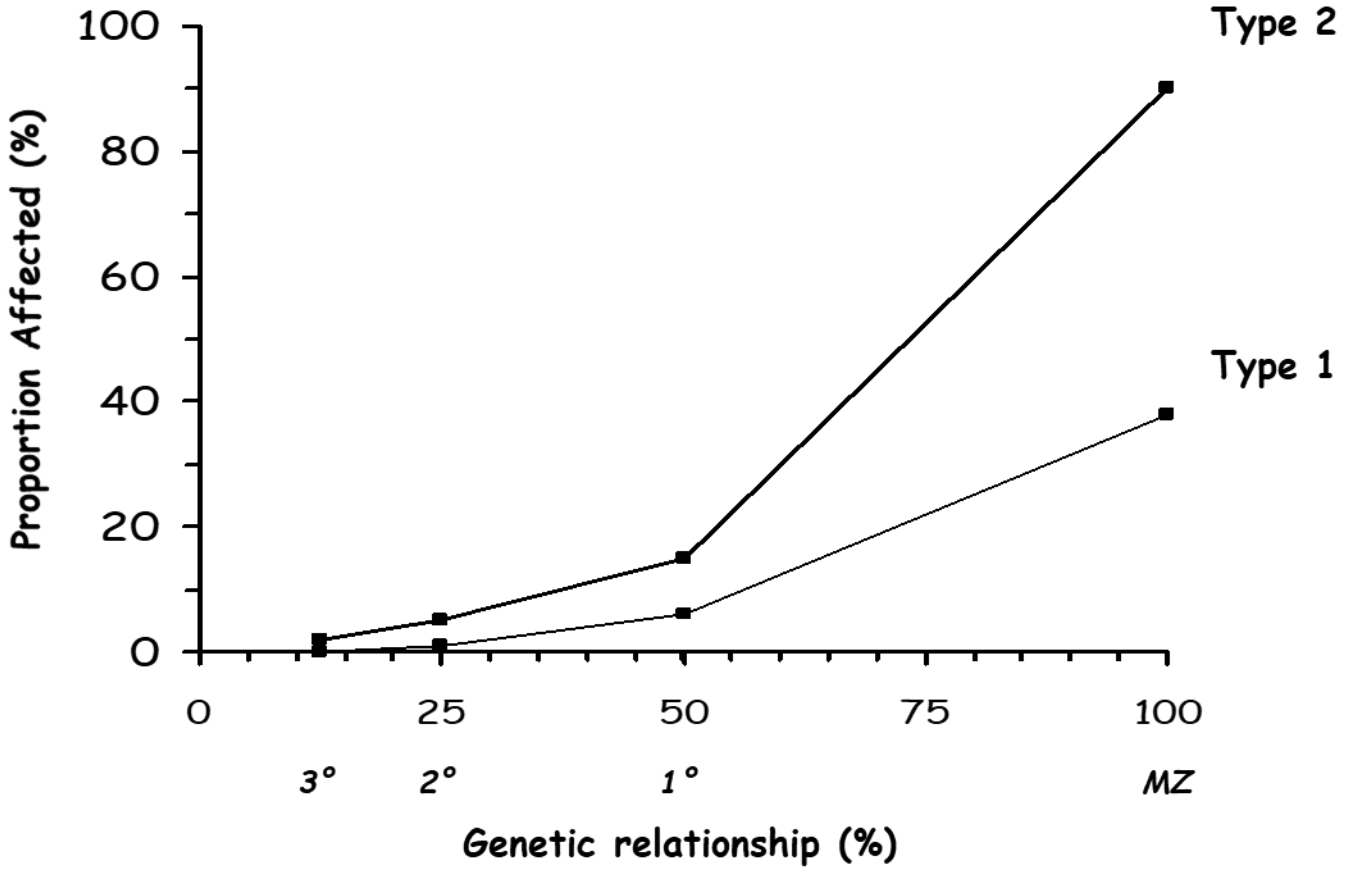
Genetic predisposition of T1D

T1D occurs in individuals with a genetic predisposition, in whom disease onset and progression is triggered by environmental or immunological events.



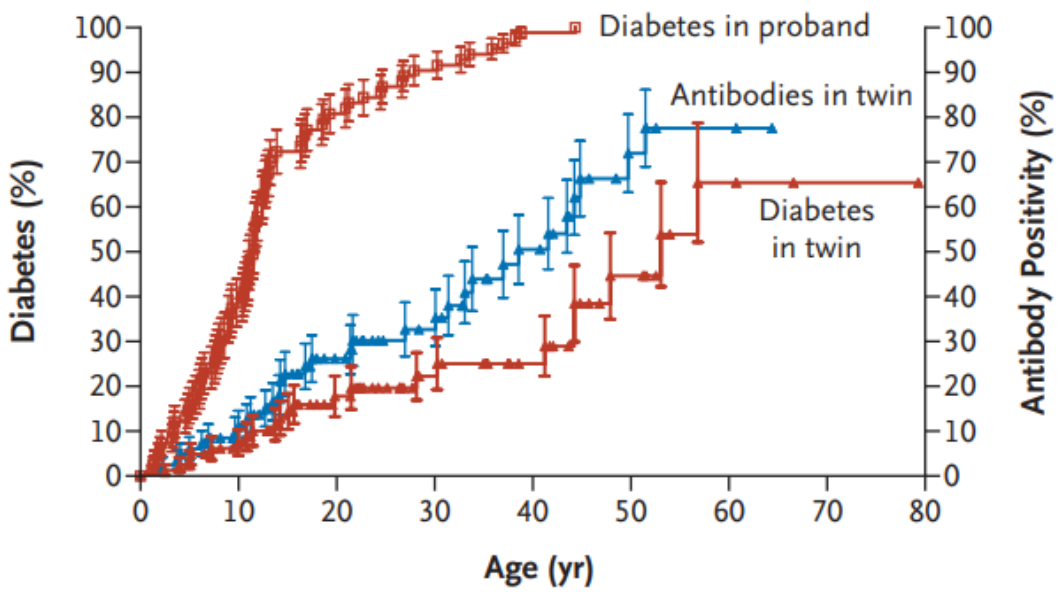
Risk of Type 1 or 2 diabetes in relatives of affected patients

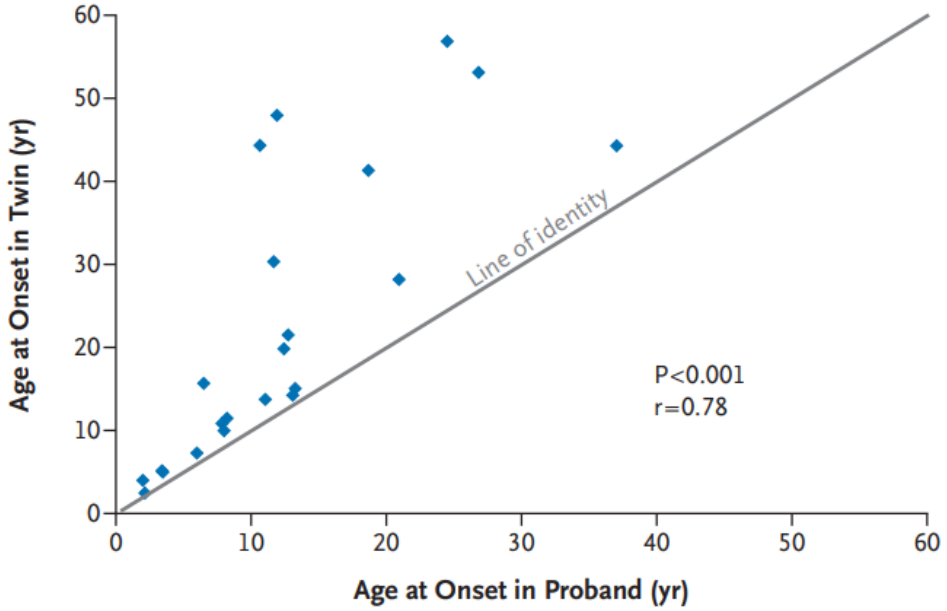
Substantial genetic contribution to the development of type 1 diabetes
→ 40–60% monozygotic twin concordance, around 6–10% sibling risk.



Rich, *Diabetes* 39:1315-19, 1990

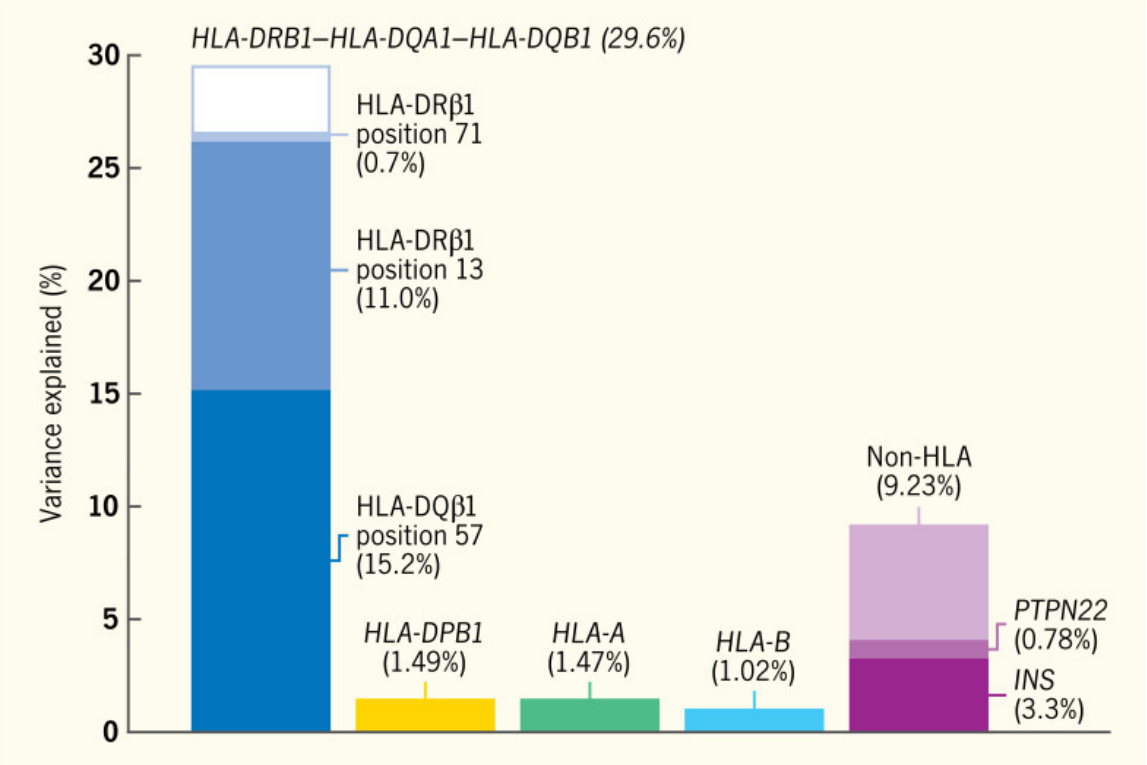
Progressive Development of Anti-Islet Autoimmunity and Diabetes among monozygotic twins





Redondo et al, *NEJM 2008*

Genetic of T1D → HLA



Phenotypic Variance in the HLA-DRB1 - HLA-DQA1 - HLA-DQB1 Locus

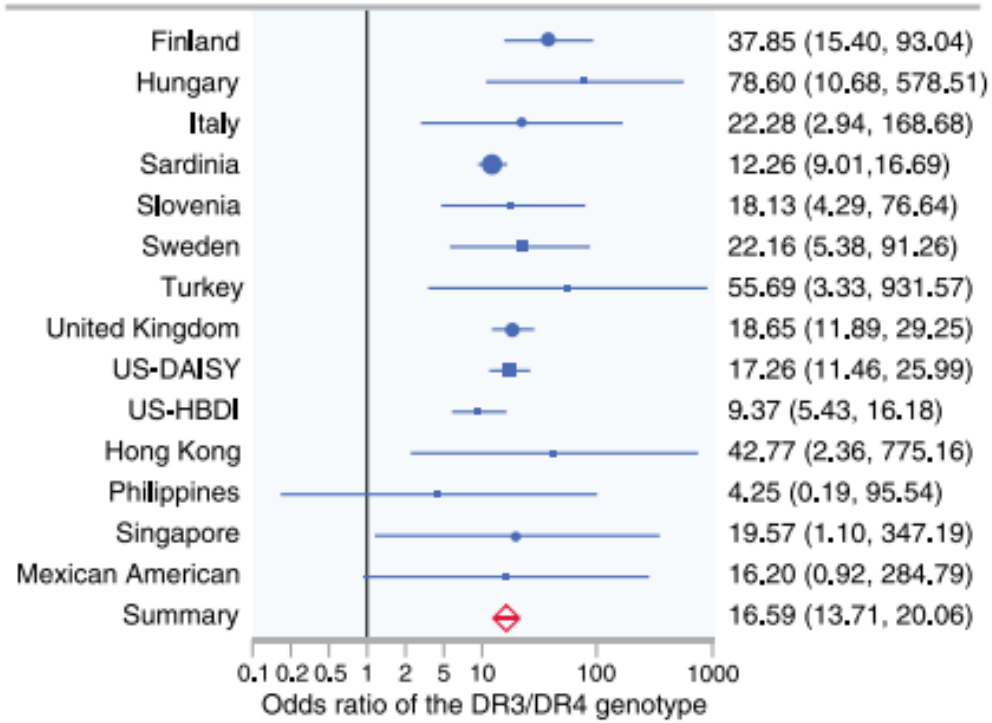
- Human leucocyte antigen (HLA) genes account for approximately 40–50% of familial predisposition
- Most frequent HLA haplotypes associated with T1D (DR3-DQ2 and DR4-DQ8) are present in up to 90% of T1D
- 30% of T1D have both this haplotype combined (DR4-DQ8/DR3-DQ2) vs 2 % of the general population.

Redondo MJ, et al. Diabetes in America 2023 and Pediatric Diabetes. 2018

Genetic of T1D - HLA

The highest-risk HLA genotype (*DR3/DR4-DQB1*03:02*)

has an odds ratio of greater than 16 for the diagnosis of T1D by the age 15 years.



DR3/DR3 OR=6.32 (95% CI,5.12–7.80)
DR4/DR4 OR=5.68 (95% CI, 3.91–8.23)

Noble et al ; Curr Diab Rep (2011) 11:533–542

Genetic of T1D - HLA

DRB1-DQA1-DQB1 haplotypes most strongly associated with T1D in European descent populations

DRB1	*DQA1*	*DQB1*	Controls (%)	T1D (%)	OR	95% CI[a]
Predisposing haplotypes						
04:05	03:01	03:02	0.2	2.5	11.37	2.71-47.68
04:01	03:01	03:02	4.5	28.1	8.39	5.97-11.80
03:01	05:01	02:01	12.5	34.1	3.64	2.89-4.58
04:02	03:01	03:02	1.0	3.5	3.63	1.76-7.49
Protective haplotypes						
13:03	05:01	03:01	1.0	0.1	0.08	0.01-0.64
11:04	05:01	03:01	2.3	0.2	0.07	0.02-0.30
15:01	01:02	06:02	12.0	0.4	0.03	0.01-0.07
07:01	02:01	03:03	4.3	0.1	0.02	0.00-0.13
14:01	01:01	05:03	2.1	0.0	0.02	0.00-0.32

Prevalence T1D globally → 4/1000

Incidence from 0.1/100,000/year (China) to >20/100,000/year (Sardinia,Finland,Sweden,UK…)

(onset 18% < 20 yrs; 64% 20–59 years, 18%> 60 yrs)

Noble et al ; Curr Diab Rep (2011) -- Redondo et al LDE 2022 -- Erlich et al Diabetes 2008

Genetics use for prediction of auto-Ab development and T1D onset

T1D screening studies take advantage of the major genetic risk factors
→ genotyping for HLA-DR and HLA-DQ loci (combined with family history) and screening for autoantibodies.

- **Diabetest Trial Net**: ***First-degree relatives of T1D patients and includes autoantibody testing and (limited) genetic screen*** → invited to participate in the trial (various interventions and followed up for development of multiple Ab and progression to T1D)

→ Antibody-positive individuals are included only if not carring the highly T1D-protective DR2 haplotype - DQB1*06:02 allele).

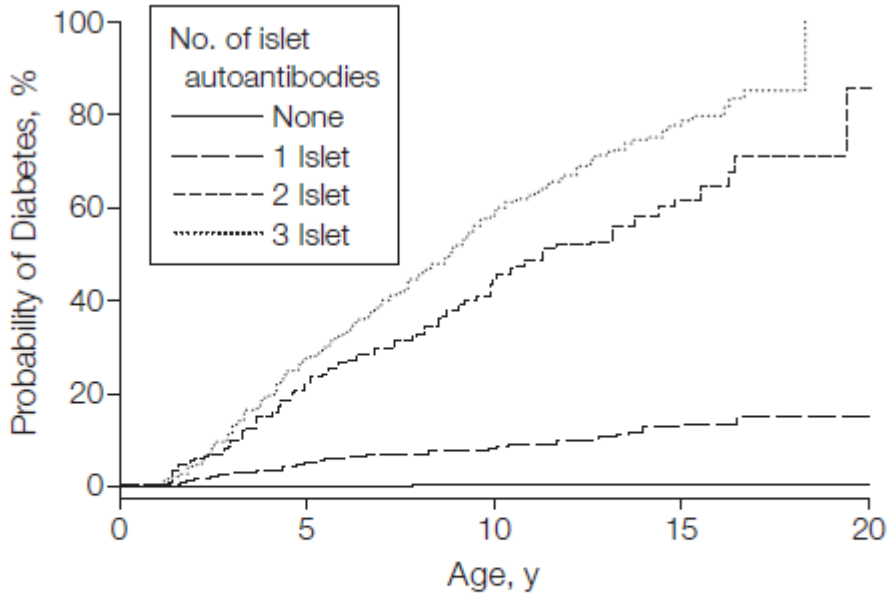
- **The Colorado Diabetes Autoimmunity Study in the Young (DAISY) study**
- **Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study**
- **German BABYDIAB and BABYDIET**
- **Teddy - The Environmental Determinants of Diabetes in the Young**

Example: Children considered to be at high genetic risk → those with HLA genotypes DR3/4-DQ8, DR4-DQ8/DR4-DQ8, or DR3/3 and children who had 2 or more first-degree relatives with type 1 diabetes.

Salonen Lancet 2008 – Ziegler Diabetes 1999 – Ziegler JAMA 2013

Precision prediction of T1D – autoantibodies role

Development of Diabetes in ***Children at high genetic risk*** Stratified for Islet Autoantibody Outcome



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

Studies: (N= Colorado, 1962; Finland, 8597; Germany, 2818). The Colorado Diabetes Autoimmunity Study in the Young (DAISY) study, the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, and the German BABYDIAB and BABYDIET studies.

DR3/DR4 prediction T1D onset among children with multiple Islet Autoantibodies

Progression to Diabetes From the Time of Seroconversion in Children With Multiple Islet Autoantibodies

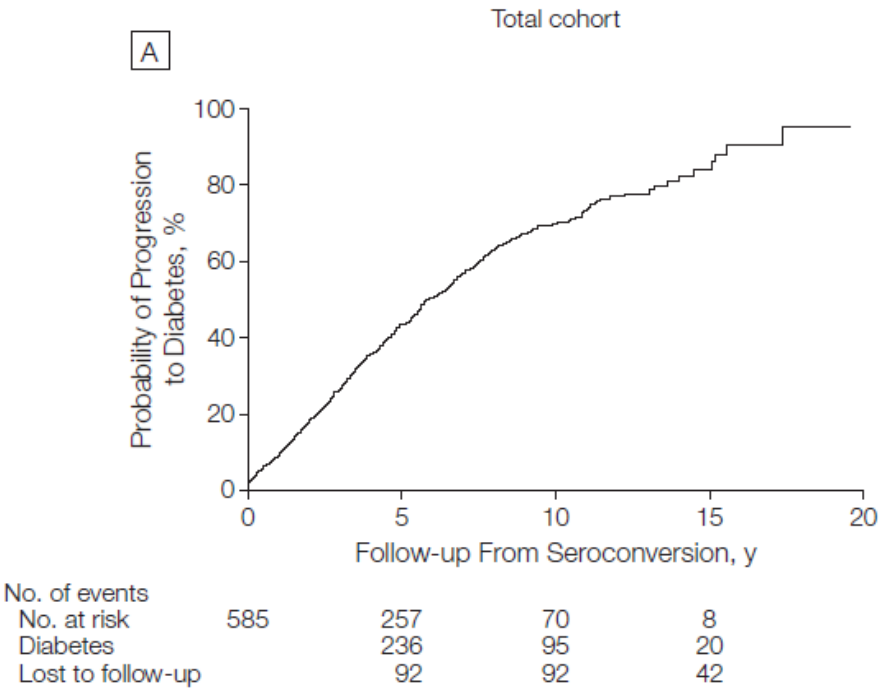


Table 2. Predictors of Type 1 Diabetes After Seroconversion in Children With Multiple Islet Autoantibodies

Variable	10-Year Risk, % (95% CI)	Bivariable Hazard Ratio (95% CI)	*P* Value	Multivariable Hazard Ratio (95% CI)[a]	*P* Value
Serocoversion age, y					
<3	74.9 (69.7-80.1)	1.72 (1.36-2.17)	<.001	1.65 (1.30-2.09)	<.001
≥3	60.9 (51.5-70.3)	1 [Reference]		1 [Reference]	
HLA genotype					
DR3/DR4-DQ8	76.6 (69.2-84.0)	1.40 (1.12-1.73)	.003	1.35 (1.09-1.68)	.007
Other	66.2 (60.2-72.2)	1 [Reference]		1 [Reference]	
Sex					
Girls	74.8 (68.0-81.6)	1.30 (1.05-1.60)	.02	1.28 (1.04-1.58)	.02
Boys	65.7 (59.3-72.1)	1 [Reference]		1 [Reference]	
No. of autoantibodies					
3	72.1 (66.5-77.7)	1.27 (1.02-1.59)	.04	1.19 (0.95-1.49)	.14
2	65.1 (56.3-73.9)	1 [Reference]		1 [Reference]	

[a] Multivariable hazard ratio includes all listed variables (seroconversion age, human leukocyte antigen genotype, sex, number of autoantibodies).

Studies: (N= Colorado, 1962; Finland, 8597; Germany, 2818). The Colorado Diabetes Autoimmunity Study in the Young (DAISY) study, the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, and the German BABYDIAB and BABYDIET studies.

Genetic variants predicts development of the first autoantibody

Individual and combined ability of genetic and enviromental factor to predict Ab

	At age of 6 years								
	Any IA			IAA-first			GADA-first		
Risk factor	*Se*	*Sp*	*J*	*Se*	*Sp*	*J*	*Se*	*Sp*	*J*
Family history (FDR vs. GP)	0.214	0.886	0.100	0.226	0.886	0.112	0.193	0.886	0.079
Sex (female vs. male)	0.547	0.491	0.038	0.564	0.491	0.055	0.532	0.491	0.023
HLA genotype (DR3/4 vs. others)	0.498	0.619	0.117	0.485	0.619	0.104	0.484	0.619	0.103
Probiotics introduction age (<28 days vs. ≥28 days)	0.943	0.078	0.020	0.945	0.078	0.023	0.959	0.078	0.036
Weight *z* score at 12 months (≥median vs. <median)	0.550	0.509	0.059	0.511	0.509	0.020	0.605	0.509	0.114
First infant formula type during the first 7 days of life (extensively hydrolyzed vs. other)	0.045	0.972	0.017	0.056	0.972	0.028	0.037	0.972	0.009
First infant formula type during the first 3 months of life (extensively hydrolyzed vs. other)	0.050	0.966	0.015	0.060	0.966	0.025	0.041	0.966	0.006
Age at multiple persistent confirmed autoantibodies (months) (≥median vs. <median)									
Type of first autoantibody (≥2 autoantibodies vs. 1 autoantibody)									
rs1004446 (*INS*)	0.463	0.606	0.069	0.488	0.606	0.093	0.416	0.606	0.022
rs10517086	0.511	0.514	0.025	0.511	0.514	0.025	0.508	0.486	−0.006
rs1534422									
rs2327832 (*TNFAIP3*)									
rs1143678 (*ITGAM*)	0.746	0.268	0.014	0.726	0.268	−0.006	0.762	0.268	0.030
rs12708716 (*CLEC16A*)	0.475	0.561	0.036	0.442	0.561	0.003	0.480	0.561	0.042
rs2292239 (*ERBB3*)	0.624	0.472	0.096	0.621	0.472	0.093	0.640	0.472	0.112
rs2476601 (*PTPN22*)	0.309	0.802	0.111	0.321	0.802	0.123	0.294	0.802	0.095
rs2816316 (*RGS1*)	0.344	0.673	0.016	0.328	0.673	0.000	0.337	0.673	0.010
rs3184504 (*SH2B3*)	0.755	0.315	0.069	0.725	0.315	0.040	0.791	0.315	0.105
rs4597342 (*ITGAM*)	0.582	0.436	0.018	0.456	0.564	0.020	0.595	0.436	0.031
rs4948088 (*COBL*)	0.936	0.086	0.022	0.951	0.086	0.037	0.921	0.086	0.008

TEDDY

8,677 children enrolled from birth who carry HLA-susceptibility genotypes for development of islet autoantibodies (IA) and type 1 diabetes (T1D)

HLA genotype (DR3/4 vs. others) was the best predictor for Any IA (Youden's index J = 0.117).

SNP rs2476601, in PTPN22, → best predictor for insulin autoantibodies (IAA) appearing first (IAA-first) (J = 0.123).

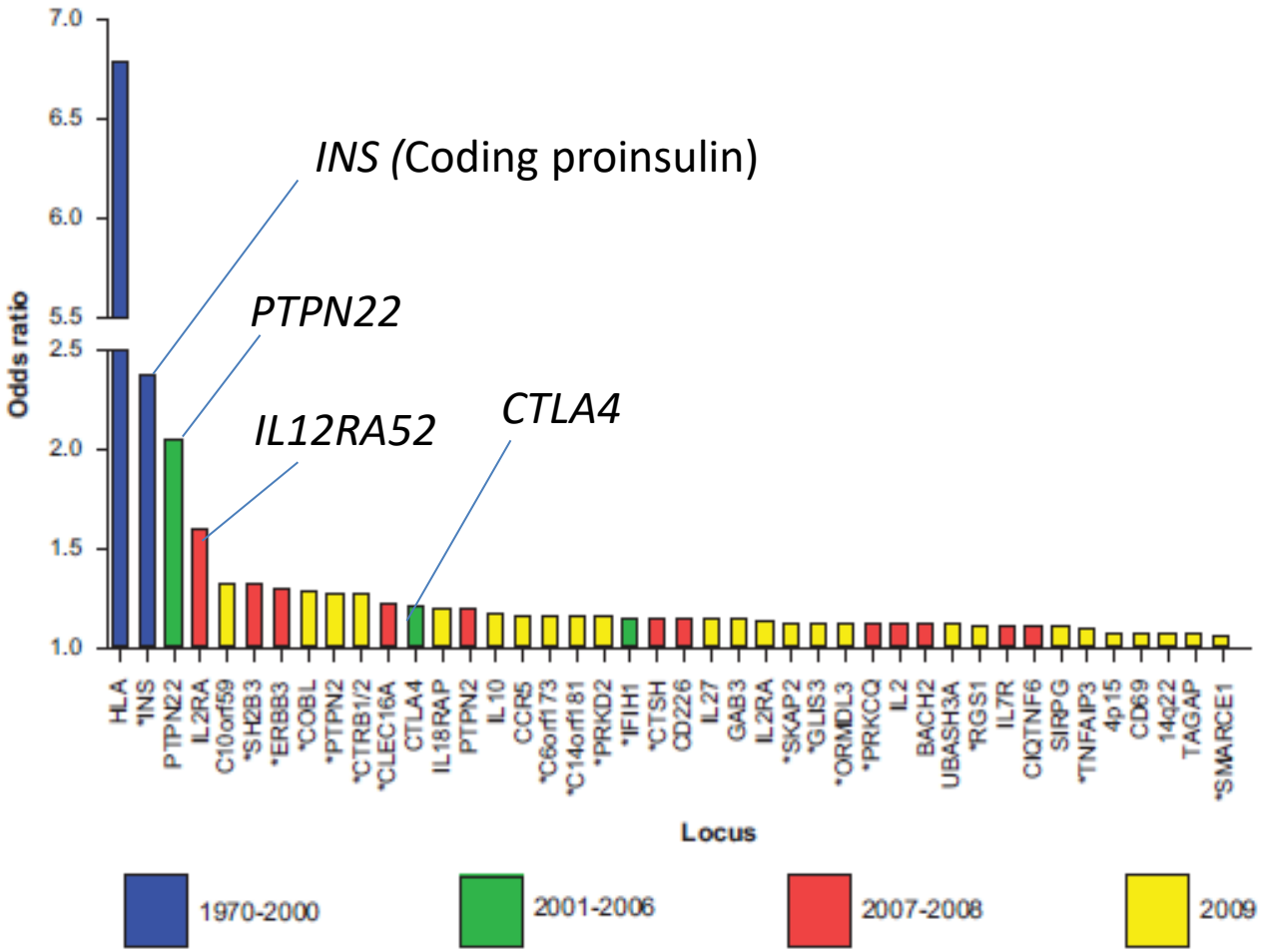
weight at 1 year → best predictor for GAD autoantibodies (GADA)-first (J = 0.114).

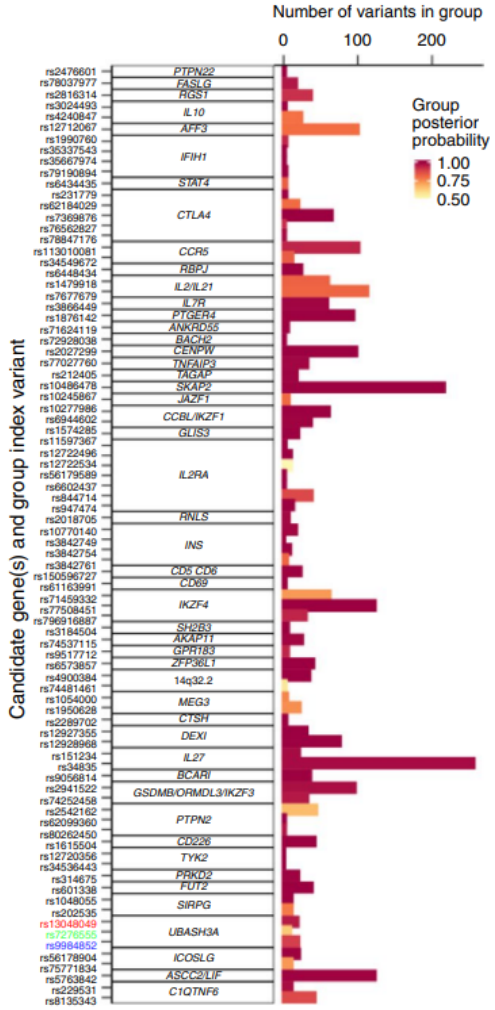
MVA model for Ab presence at 6 years
AUC= 0.678 (95%CI 0.655, 0.701) for IA
AUC = 0.707 (95% CI 0.676, 0.739) for IAA-first
AUC= 0.686 (95% CI 0.651, 0.722) for GADA-first

TEDDY study - Kischer Diabetes Care 2019

Multiple loci (>75) are associated with risk of T1D

Genetic studies identified ca. 143 regions associated with susceptibility for T1D, comprising nearly 60-75 independent candidate genes.

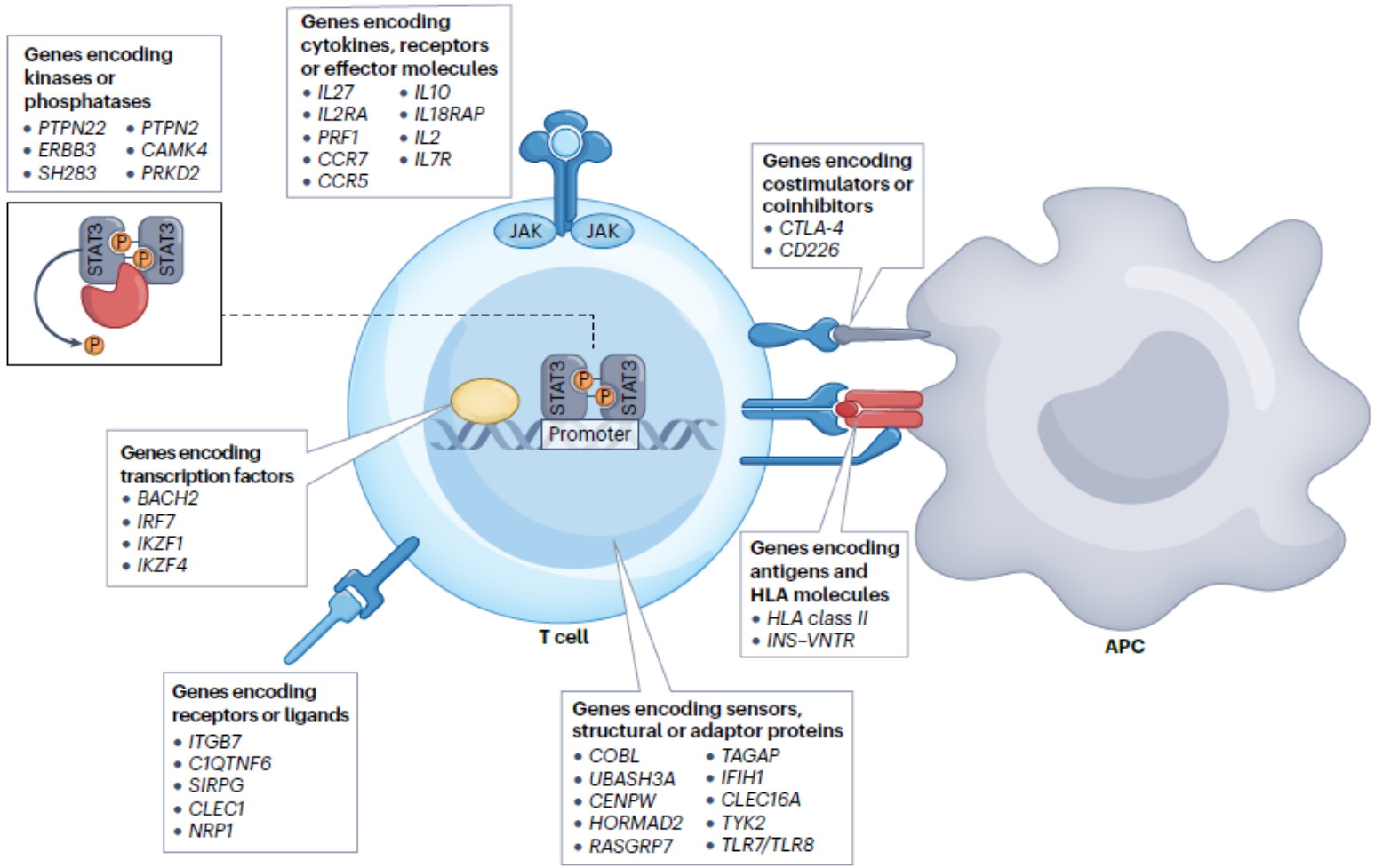




Pochiot et al. Diabetes 2010

Robertson et al. Nat Gen 2021

Risk genes for type 1 diabetes mostly encode proteins that impact immune system

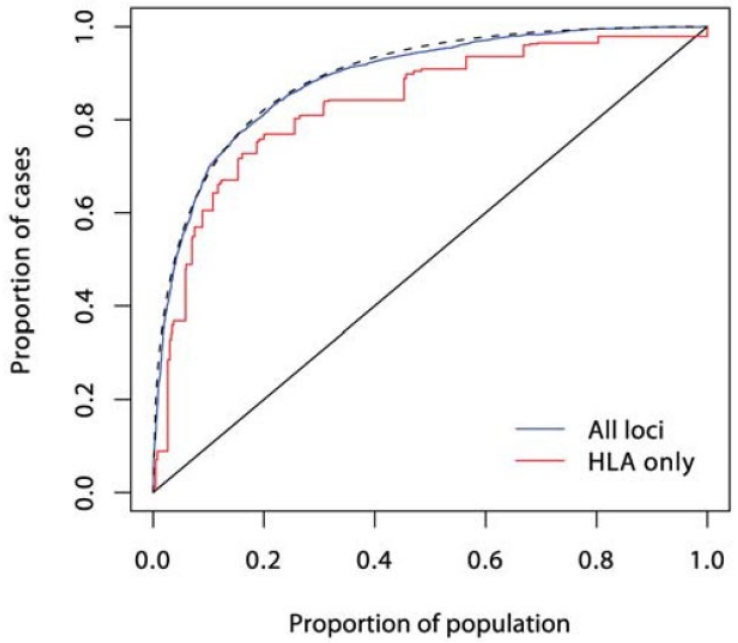


Herold et al Nat Rev Immunol 2024

Gene – gene interactions (HLA – non-HLA variants)

Table 1. T1D risk by HLA and rs2476601 (*PTPN22*) genotype.

HLA Risk	rs2476601 Genotype			
	GG	AG	AA	
Low	*1.0*	2.56	6.76	Ratios (RR)
	1.7	4.4	11.6	Absolute Risk
Medium	*1.0*	2.29	3.24	Ratios (RR)
	6.9	15.8	22.4	Absolute Risk
High	*1.0*	1.67	2.37	Ratios (RR)
	53.6	89.3	127.0	Absolute Risk



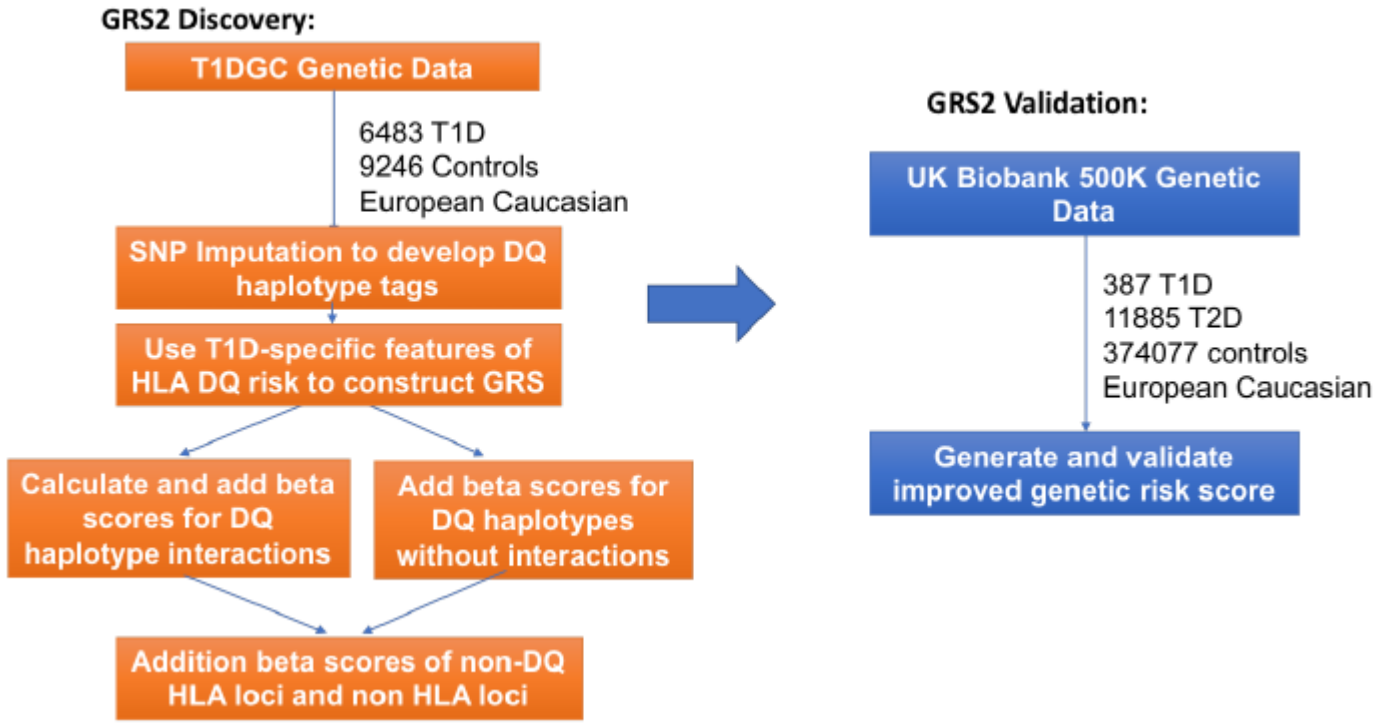
Non-HLA by HLA interactions

***Absolute Risk per 1,000 in a population with with cumulative incidence of 1%**

Modified from Clayton Plos Medicine 2009

Improve precise T1D prediction with GRS

Building of more precise T1D genetic risk scores



Interaction exists (Table S3)

$$GRS2 = \begin{cases} beta_{interaction} \\ \sum(beta_{haplotype} * n_{ra}) \end{cases} + \sum(beta_{other-HLA} * n_{ra}) + \sum(beta_{non-HLA} * n_{ra})$$

No interaction exists

Sharp Diabetes Care 2019

Tag/markers for HLA haplotypes

DQA1	DQB1	Freq*	Marker**	r^2	Odds Ratio	Beta
03:0X	03:02	0.154	rs9275490	0.987	7.99	2.08
01:02	06:02	0.1437	rs17843689	0.968	4.02	1.39
05:01	02:01	0.1314	rs9273369	0.998	3.54	1.26
02:01	02:02	0.1108	rs17211699	0.985	1.62	0.48
05:05	03:01	0.1106	rs9469200	0.975	0.97	-0.03
01:0X	05:01	0.1088	rs10947332	0.994	0.63	-0.46
03:0X	03:01	0.0648	rs1281935	0.882	0.53	-0.63
01:03	06:03	0.0567	rs62406889	0.968	0.52	-0.65
02:01	03:03	0.0366	rs28746898	0.955	0.47	-0.76
04:01	04:02	0.0227	rs12527228	0.956	0.41	-0.89
01:0X	05:03	0.0208	rs1794265	0.990	0.27	-1.31
03:02	03:03	0.0079	rs9405117	0.956	0.24	-1.43
01:02	06:09	0.0071	rs16822632	0.954	0.11	-2.21
01:03	06:01	0.0066	rs117806464	0.986	0.09	-2.41

*Frequency of HLA haplotypes in European-Americans (Klitz et al 2003 Tissue Antigens)
**Minor allele corresponds to the presence of the indicated haplotype

Role of gene-gene interactions on T1D risk

Haplotype	DQA1*03:0X-DQB1*03:02	DQA1*05:01-DQB1*02:01	DQA1*04:01-DQB1*04:02	DQA1*01:0X-DQB1*05:01	DQA1*03:02-DQB1*03:03	OTHER	DQA1*02:01-DQB1*02:02	DQA1*03:0X-DQB1*03:01	DQA1*05:05-DQB1*03:01	DQA1*01:03-DQB1*06:03	DQA1*01:02-DQB1*06:09	DQA1*01:03-DQB1*06:01	DQA1*02:01-DQB1*03:03	DQA1*01:0X-DQB1*05:03	DQA1*01:02-DQB1*06:02
DQA1*03:0X-DQB1*03:02	32.30	63.17	24.68	16.14	11.20	14.89	8.25	5.26	4.50	5.53	3.94		0.53	0.70	0.73
DQA1*05:01-DQB1*02:01	63.17	20.92	8.63	6.96	19.69	10.16	3.24	3.18	1.31	1.14	3.94	1.17	0.47		0.08
DQA1*04:01-DQB1*04:02	24.68	8.63	1.17	5.29	2.33	3.27	9.33	2.71	0.42	0.54					0.29
DQA1*01:0X-DQB1*05:01	16.14	6.96	5.29	2.41	6.36	3.33	0.86	5.88	0.29	0.10	0.41		0.30	0.32	0.06
DQA1*03:02-DQB1*03:03	11.20	19.69	2.33	6.36		3.00	3.37	2.50	1.22					3.50	
OTHER	14.89	10.16	3.27	3.33	3.00	1.00	1.19	3.88	0.56	0.56	1.42	1.56	0.58	0.32	0.05
DQA1*02:01-DQB1*02:02	8.25	3.24	9.33	0.86	3.37	1.19	0.06	2.88	0.79		0.58		0.27		0.08
DQA1*03:0X-DQB1*03:01	5.26	3.18	2.71	5.88	2.50	3.88	2.88	3.80	1.22	0.46	0.70		0.38	0.29	0.15
DQA1*05:05-DQB1*03:01	4.50	1.31	0.42	0.29	1.22	0.56	0.79	1.22	0.27		0.70		0.10		0.13
DQA1*01:03-DQB1*06:03	5.53	1.14	0.54	0.10		0.56		0.46							0.12
DQA1*01:02-DQB1*06:09	3.94	3.94		0.41		1.42	0.58	0.70	0.70						
DQA1*01:03-DQB1*06:01		1.17				1.56									1.75
DQA1*02:01-DQB1*03:03	0.53	0.47		0.30		0.58	0.27	0.38	0.10						0.07
DQA1*01:0X-DQB1*05:03	0.70			0.32	3.50	0.32		0.29							
DQA1*01:02-DQB1*06:02	0.73	0.08	0.29	0.06		0.05	0.08	0.15	0.13	0.12		1.75	0.07		0.11

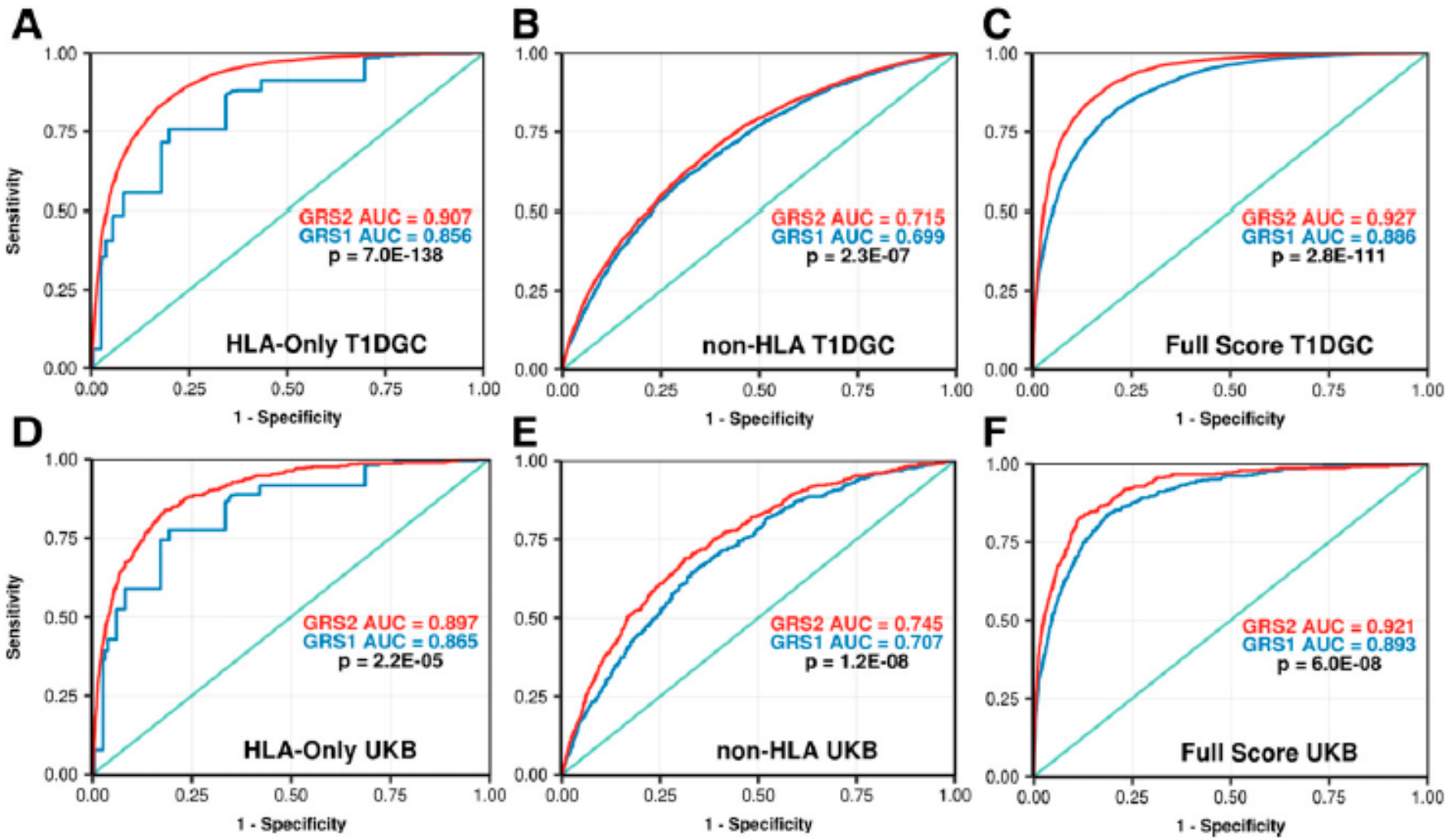
Interaction exists (Table S3)

$$GRS2 = \begin{cases} beta_{interaction} \\ \sum(beta_{haplotype} * n_{ra}) \end{cases} + \sum(beta_{other-HLA} * n_{ra}) + \sum(beta_{non-HLA} * n_{ra})$$

No interaction exists

Sharp Diabetes Care 2019

Improved prediction performance in test and validation dataset



Sharp Diabetes Care 2019

Precision diagnostic in T1D with T1D GRS

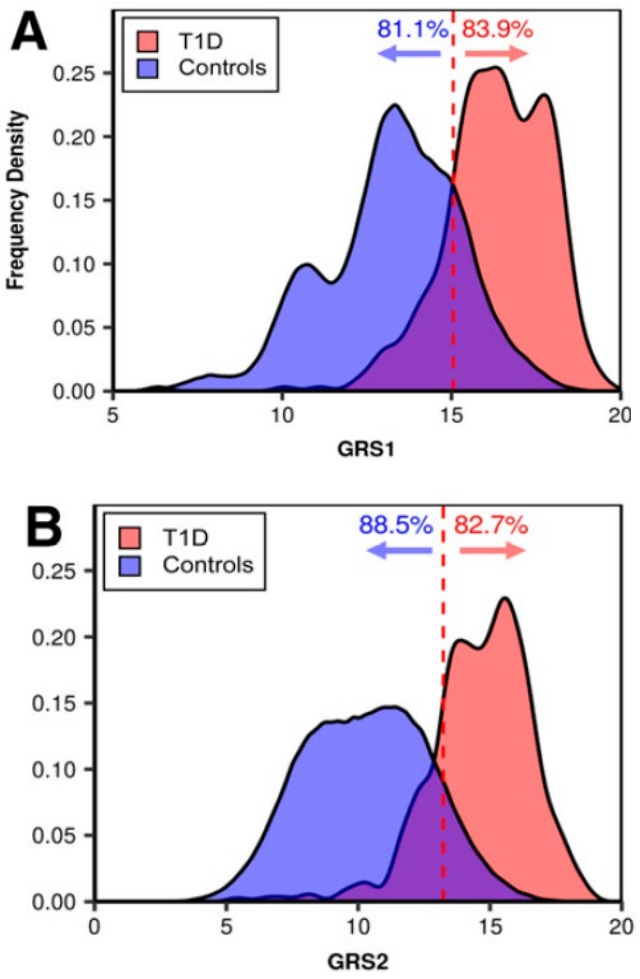


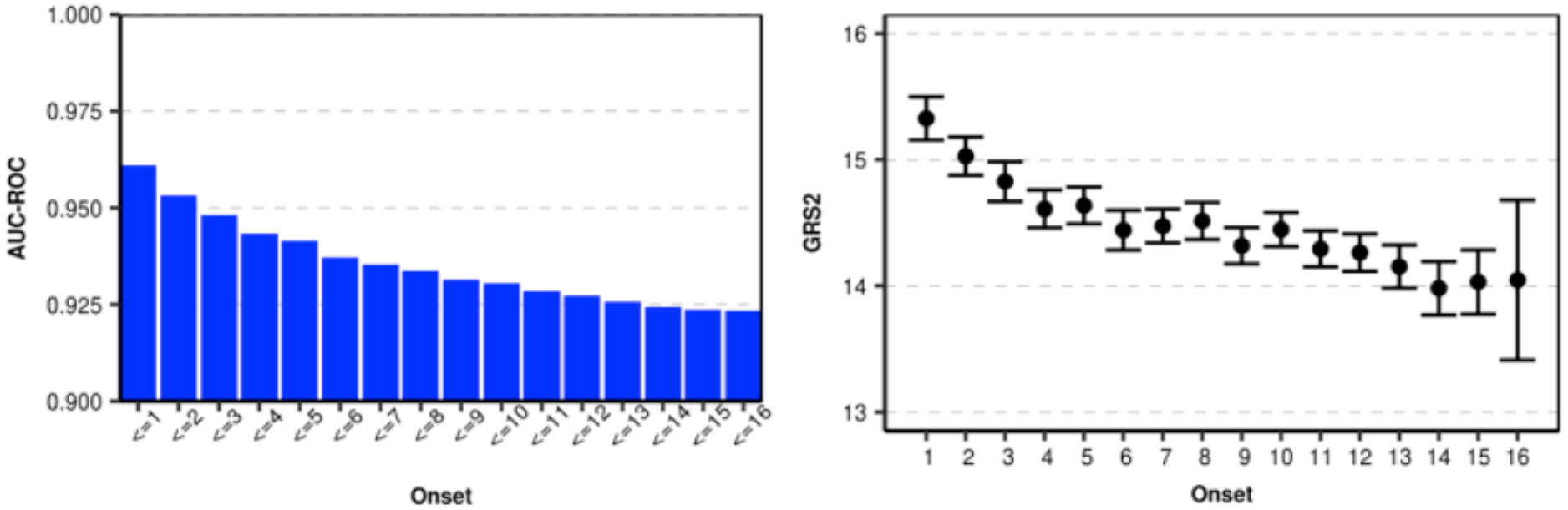
Table 1—Simulated population-based prediction of T1D using HLA screening, the original T1D GRS, and the T1D GRS2

T1D centile*	Population centile**	GRS2	Specificity (%)	Sensitivity (%)	1-Specificity (%)	Youden index (*j*)	T1D risk (%)***
5	70.2	11.68	69.5	94.8	30.5	0.643	0.9
10	79.4	12.36	78.9	89.4	21.1	0.683	1.3
25	90.6	13.45	90.4	77.5	9.6	0.679	2.4
50	96.8	14.60	96.7	53.7	3.3	0.505	4.7
75	99.1	15.65	99.1	30.2	0.9	0.293	9.1
90	99.8	16.54	99.8	13.2	0.2	0.130	15.7
95	99.9	17.06	99.9	7.2	0.1	0.072	22.8
T1D centile*	Population centile**	GRS1	Specificity (%)	Sensitivity (%)	1-Specificity (%)	Youden index (*j*)	T1D risk (%)***
5	53.3	13.48	51.9	95.9	48.1	0.478	0.6
10	60.7	14.06	63.9	92.5	36.1	0.564	0.8
25	73.8	15.07	81.7	82.9	18.3	0.646	1.3
50	86.1	16.16	94.0	56.3	6.0	0.503	2.7
75	93.3	17.17	98.3	32.6	1.7	0.308	5.4
90	96.5	17.83	99.5	18.3	0.5	0.178	9.9
95	97.8	18.19	99.8	9.0	0.2	0.088	11.8
T1D centile*	Risk category	HLA type	Specificity (%)	Sensitivity (%)	1-Specificity (%)	Youden index (*j*)	T1D risk (%)***
—	Background	Other	0.0	100.0	0.0	0.000	0.3
57.0	Moderate	DR3/3, DR4/X	79.1	77.0	23.0	0.561	0.6
81.1	High	DR4/4	96.3	41.3	58.7	0.376	2.5
84.5	Very High	DR3/4	97.2	37.0	63.1	0.342	3.8

Risk of T1D is calculated assuming a 0.3% population prevalence of T1D. *T1D cases in T1DGC. **Centile in UK Biobank European population. ***Risk of T1D is calculated assuming a 0.3% population prevalence of T1D.

Sharp Diabetes Care 2019

GRS performance is higher for early onset of T1D

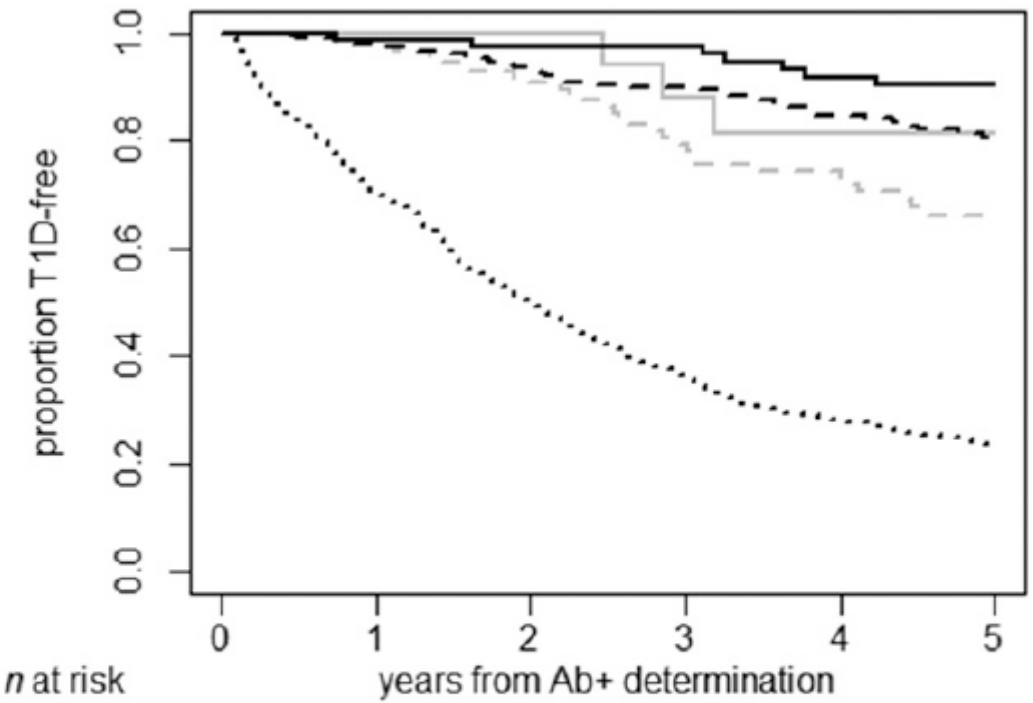


Age at Diagnosis

Sharp Diabetes Care 2019

Combined genetic and clinical information improve prediction of T1D risk

<u>Time to T1D</u> in multiple islet autoantibody–positive (Ab+) relatives of patients



n at risk					
DPTRS >7 ····401	239	156	104	71	50
DPTRS ≤7, <10 yrs, GRS <0.25 —— 34	23	18	14	11	10
DPTRS ≤7, <10 yrs, GRS ≥0.25 – –145	113	88	65	56	42
DPTRS ≤7, ≥10 yrs, GRS <0.25 —— 90	84	78	74	61	52
DPTRS ≤7, ≥10 yrs, GRS ≥0.25 – –341	294	249	208	175	141

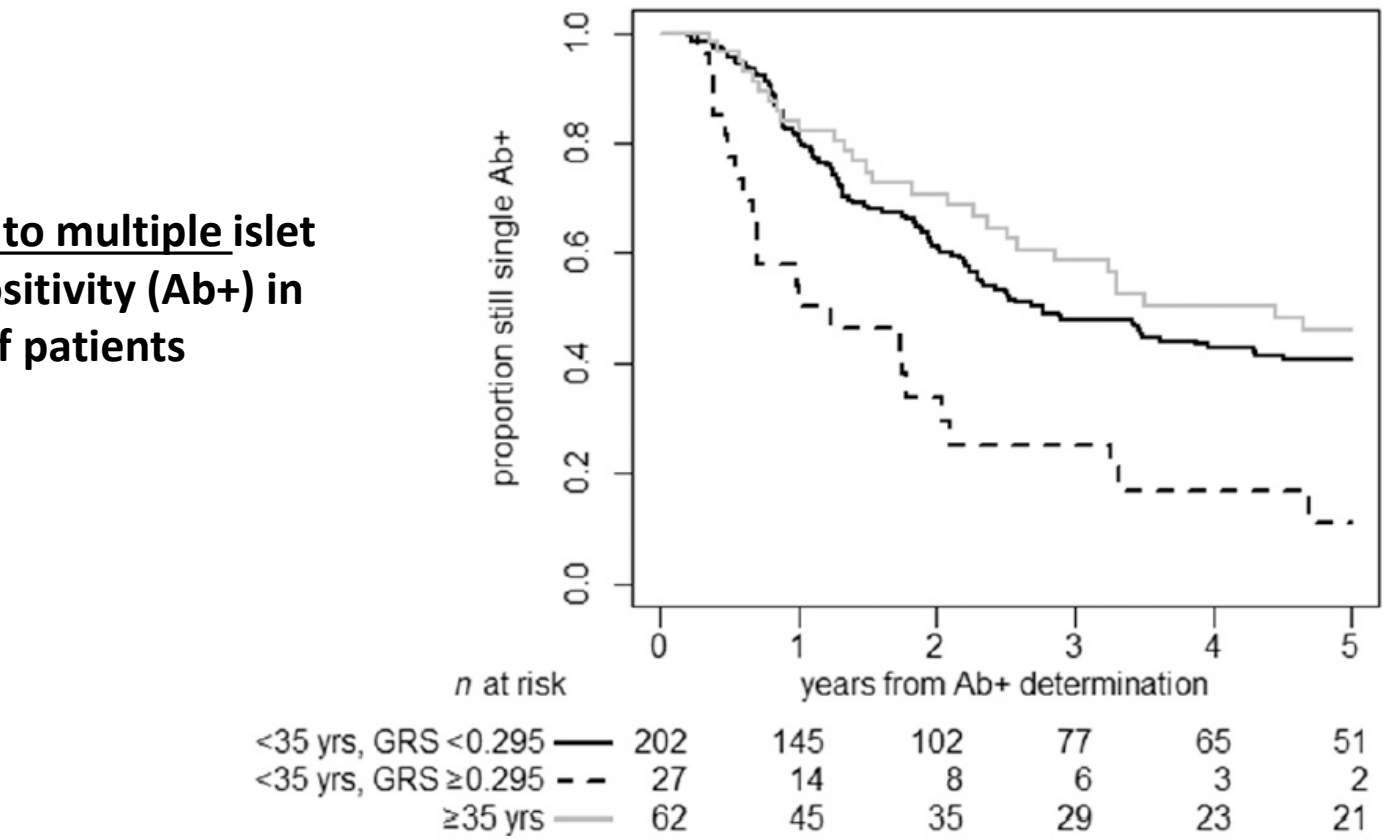
1,244 TrialNet participants genotyped with Illumina ImmunoChip (median [range] age at initial autoantibody determination 11.1 years [1.2–51.8], 48% male, 80.5% non-Hispanic white, median follow-up 5.4 years).

DPT-1 Risk score= 1.569 x [**log-BMI** (kg/m_2)] - 0.056 x [**age** (years)] + 0.813 x [**total glucose** (mg/dl)/100] + 0.476 x [**log–fasting C-peptide** (ng/ml)] - 0.848 x [**total C-peptide** (ng/ml)/10] - Total glucose and total C-peptide, defined as the totals of OGTT postchallenge glucose and C-peptide values, were utilized – they correlated very well with the respective AUC (trapezoidal rule) (*r* 0.99 for both).

Redondo Diabetes care 2018

Combined genetic and clinical information improve prediction of T1D risk

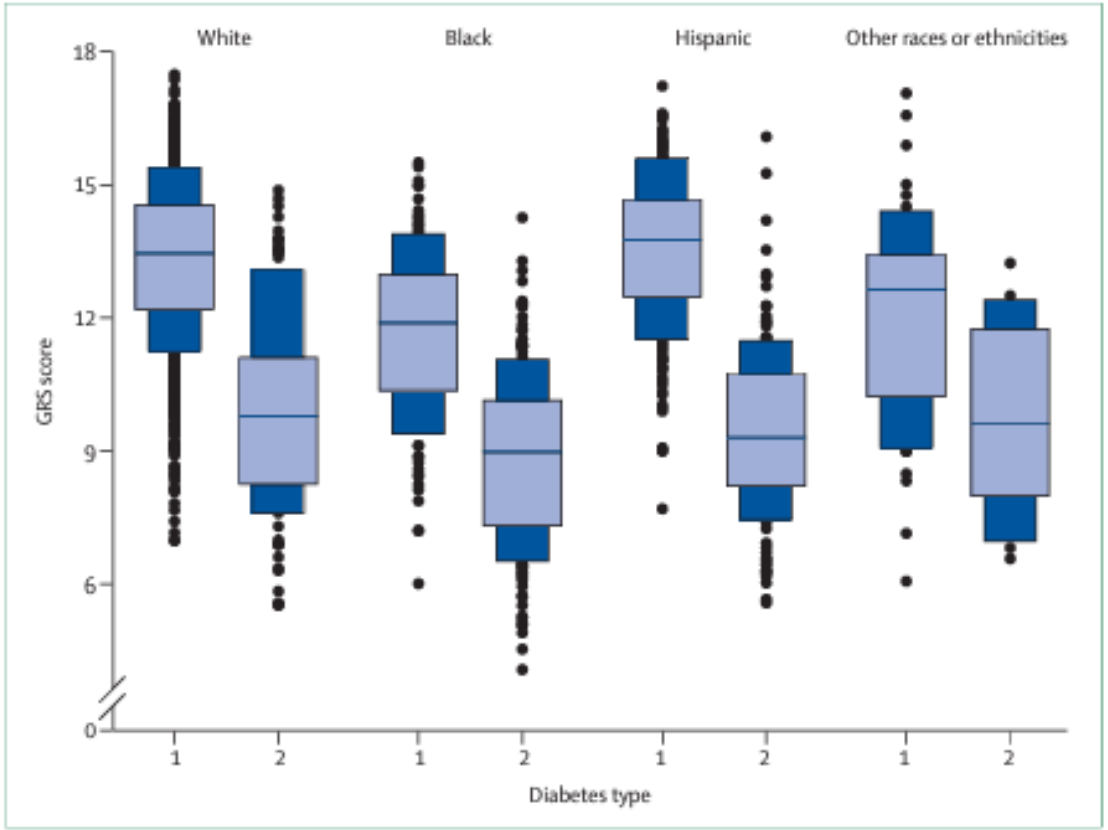
Time <u>from single to multiple</u> islet autoantibody positivity (Ab+) in relatives of patients



Time from single to multiple islet autoantibody positivity (Ab+) in relatives of patients, by age (,35 vs. $35 years) and T1D GRS group (,0.295 vs. $0.295) (P = 0.0001). While the T1D GRS did not further increase the predictive ability in participants aged $35 years, it was able to stratify risk in individuals aged ,35 years.

Redondo Diabetes care 2018

Performance of GRS-2 in different ancestries



Precision medicine and equity of T1D

	Prevalence			Remaining life expectancy if diagnosed at age 10 years in 2021	
	Total*	Age <20 years	Age ≥20 years	Type 1 diabetes, years	Non type 1 diabetes, years†
Global	8 423 530 (8 103 139–8 749 702)	1 476 030 (1 412 988–1 542 713)	6 947 403 (6 670 019–7 228 108)	40 (37–43)	64
High-income countries	4 584 200 (4 435 431–4 742 083)	525 174 (504 759–547 223)	4 059 734 (3 920 799–4 203 710)	61 (57–65)	72
Upper-middle income countries	2 049 417 (1 968 012–2 128 509)	375 345 (356 088–394 971)	1 673 363 (1 606 286–1 740 203)	43 (40–46)	67
Lower-middle income countries	1 574 314 (1 500 333–1 647 053)	499 991 (481 241–519 961)	1 074 211 (1 015 460–1 132 039)	26 (23–28)	62
Low-income countries	215 599 (199 363–232 056)	75 521 (70 901–80 558)	140 096 (127 473–152 156)	13 (12–15)	60

Remaining life expectancy for a 10-year-old individual diagnosed in a high-income country was reduced by approximately 11 years and in a low-income country by 49 years
[Modelling using random-forest regression of published T1D mortality data]

Gregory, Lancet Diabetes Endocrinology 2022

Conclusions

- **Genetic plays a major role in precision T1D (prediction and maybe prevention)**
- **Beyond HLA genotypes, polygenic-scores improve prediction of T1D.**
- **Prediction performances increase with our ability to better understand genetic background (gene-gene interaction).**

→ Genetic data should inform and improve screening strategies.

- **“Equity” is a main gaps in precision medicine needing to be addressed**
- **Large room for improvement for the use of genetics after T1D diagnosis**