People with high T1D GRS

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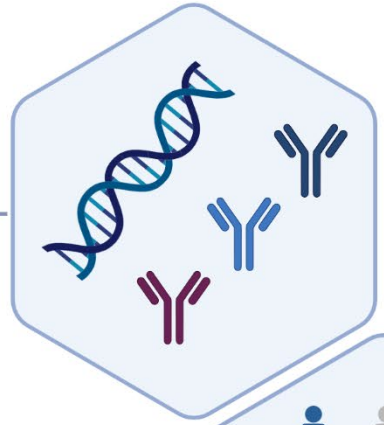
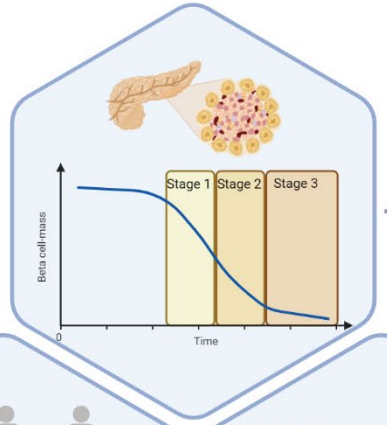
Presenter Disclosure

- No disclosure

Potential applications of genetic risk scores in the type 1 diabetes field

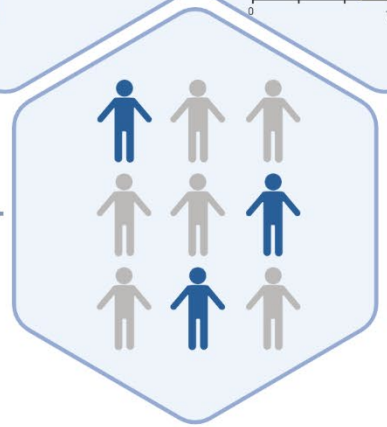
Personalized risk assessment

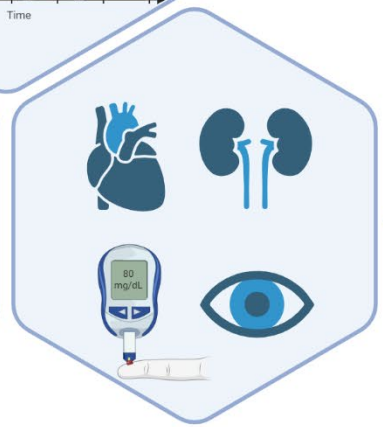




Early detection:
Delay onset and mitigate complications

Prioritization of individuals for immune interventions

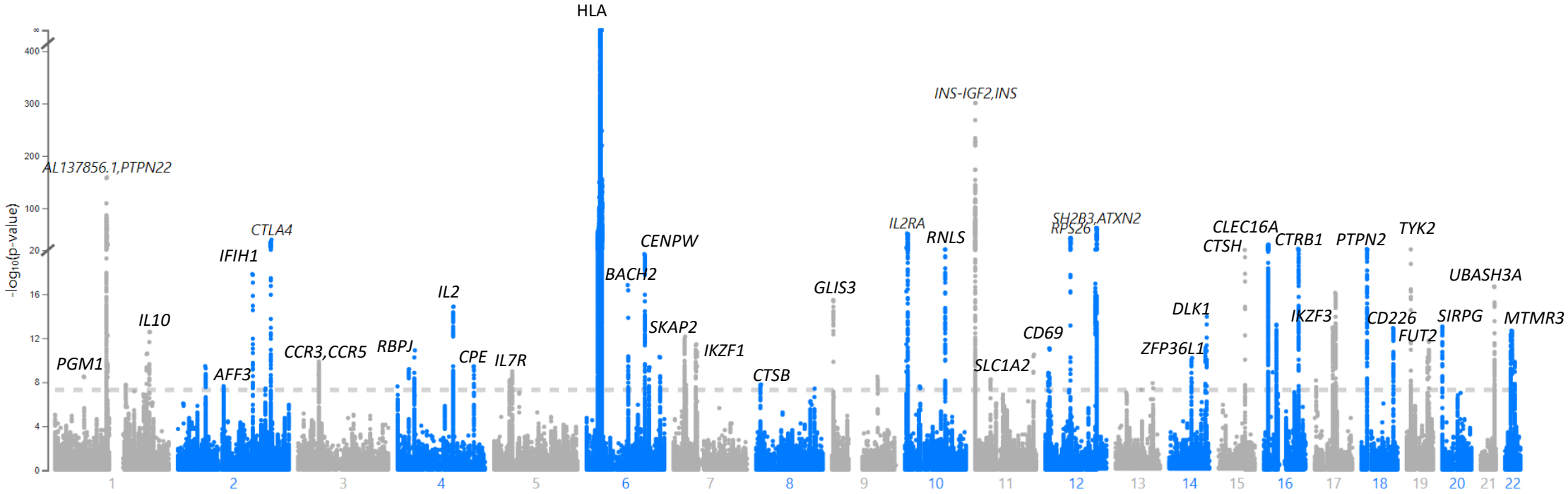




Personalized medicine:
Tailored approach to managing T1D and predisposition to complications

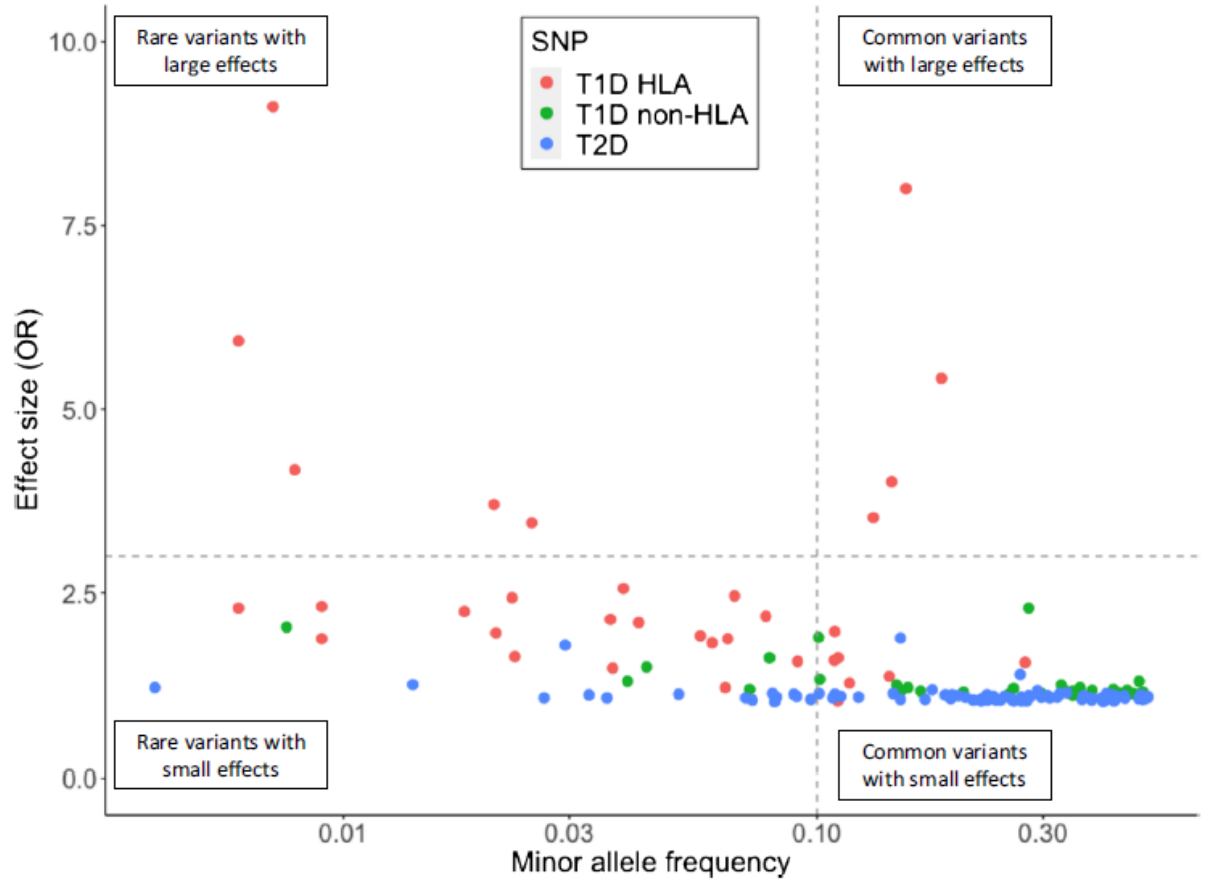
Adapted from Linda Kachuri, PhD, Stanford University

Genetic architecture of type 1 diabetes



Modified from Robertson et al. Nature Genetics, 2021

T1D associated HLA risk alleles have large effects on risk



Luckett et al (2023) Diabetologia

What is a Genetic Risk Score (GRS)?

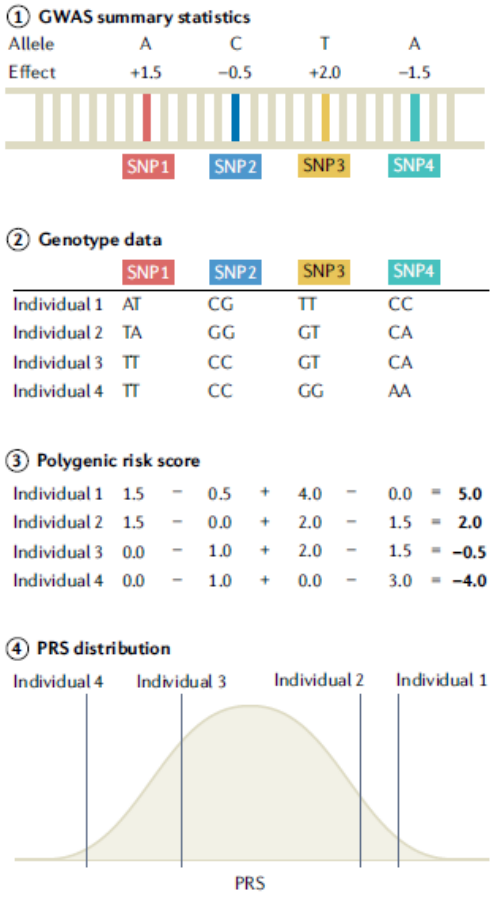
- Polygenic risk score (PRS) or GRS estimates an individual's genetic predisposition to a certain phenotype (trait or disease).
- A GRS is calculated as weighted sum scores of risk alleles, with weights based on the effect sizes from GWAS:

$$PRS = \sum_{i=1}^{n} \beta_i \, x \, G_i$$

β_i: Effect size of the ith variant (Usually derived from GWAS)

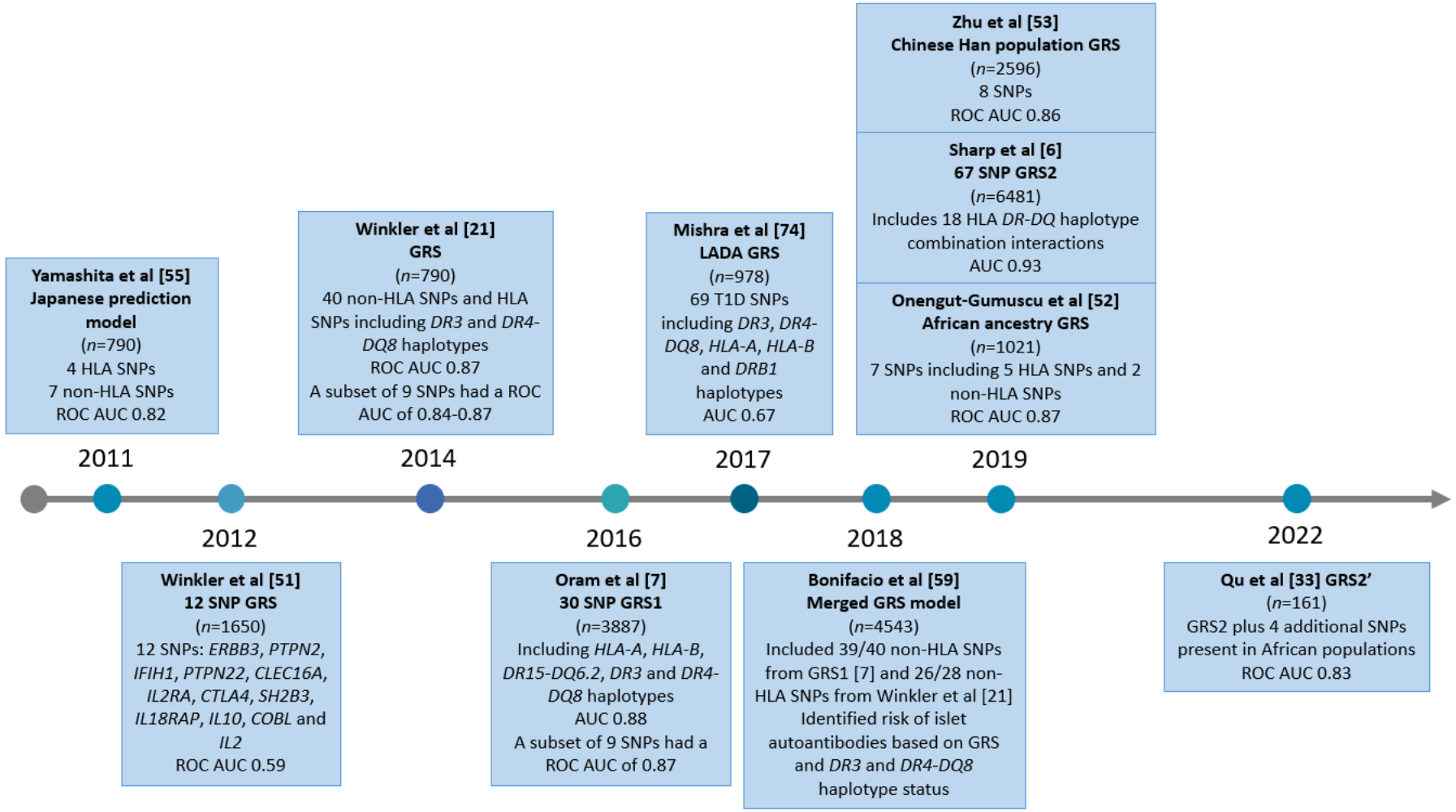
G_i: Genotype at the ith variant for the individual

n: The total number of variants included in the score



Uffelmann et al., Nature Reviews, Methods Primers, (2021)1:59

Timeline of type 1 diabetes genetic risk score development



Luckett et al (2023) Diabetologia DOI 10.1007/s00125-023-05955-y

Implementation of GRS in T1D screening programs

Program	Population screened	Location	Screening material	DNA based Screening assay(s)
DIPP	Age 0.25–15 years	Finland	Serum	HLA genotyping
BABY- SCREEN	Newborns to 3 years	Helsinki, Finland	Serum	HLA genotyping
GPPAD	Infants <1 month of age	Germany, U.K., Poland, Belgium, and Sweden	Capillary blood spots	47-SNP GRS to identify those with >10% risk of ≥2 AA+ by age 6 years
PLEDGE	Age <6 years	North and South Dakota and Minnesota, U.S.	Capillary blood spot for GRS, serum for AA	GRS2
CASCADE	Age ≥1 year	Northwest U.S.	Serum	GRS
PRiMeD	Age 2–16 years	Virginia, U.S.	Saliva for GRS, serum for AA	82-SNP GRS
eMerge Network	Age 3-75 years	10 Clinical Sites in U.S.	Saliva	GRS2 with additional optimization to improve prediction power in African American and East Asian ancestry
EarlyCheck	Newborns	North Carolina, U.S.	Blood spots	GRS2

Modified from Sims et al., Diabetes, 2022, vol. 71.

Risk alleles and effect sizes can vary across populations

HLA-			African Ancestry			European Ancestry		
DRB1*	DQA1*	DQB1*	Control Allele freq	Case Allele freq	OR	Control Allele freq	Case Allele freq	OR
03:01	05:01	02:01	0.08	0.27	3.91	0.13	0.34	3.64
04:01	03:01	03:02	0.01	0.07	5.36	0.05	0.28	8.39
04:04	03:01	03:02	0.01	0.03	2.6	0.03	0.05	1.59
04:05	03:01	03:02	0.01	0.08	6.75	0.00	0.03	11.37
07:01	03:01	02:01	0.01	0.04	4.41	-	-	-
09:01	03:01	02:01	0.02	0.09	4.87	0	0.002	-

Onengut-Gumuscu et al, 2019, Diabetes Care
Erlich et al., 2008, Diabetes

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09:01	03:01	02:01	0.02	0.09	4.87	0	0.002	-

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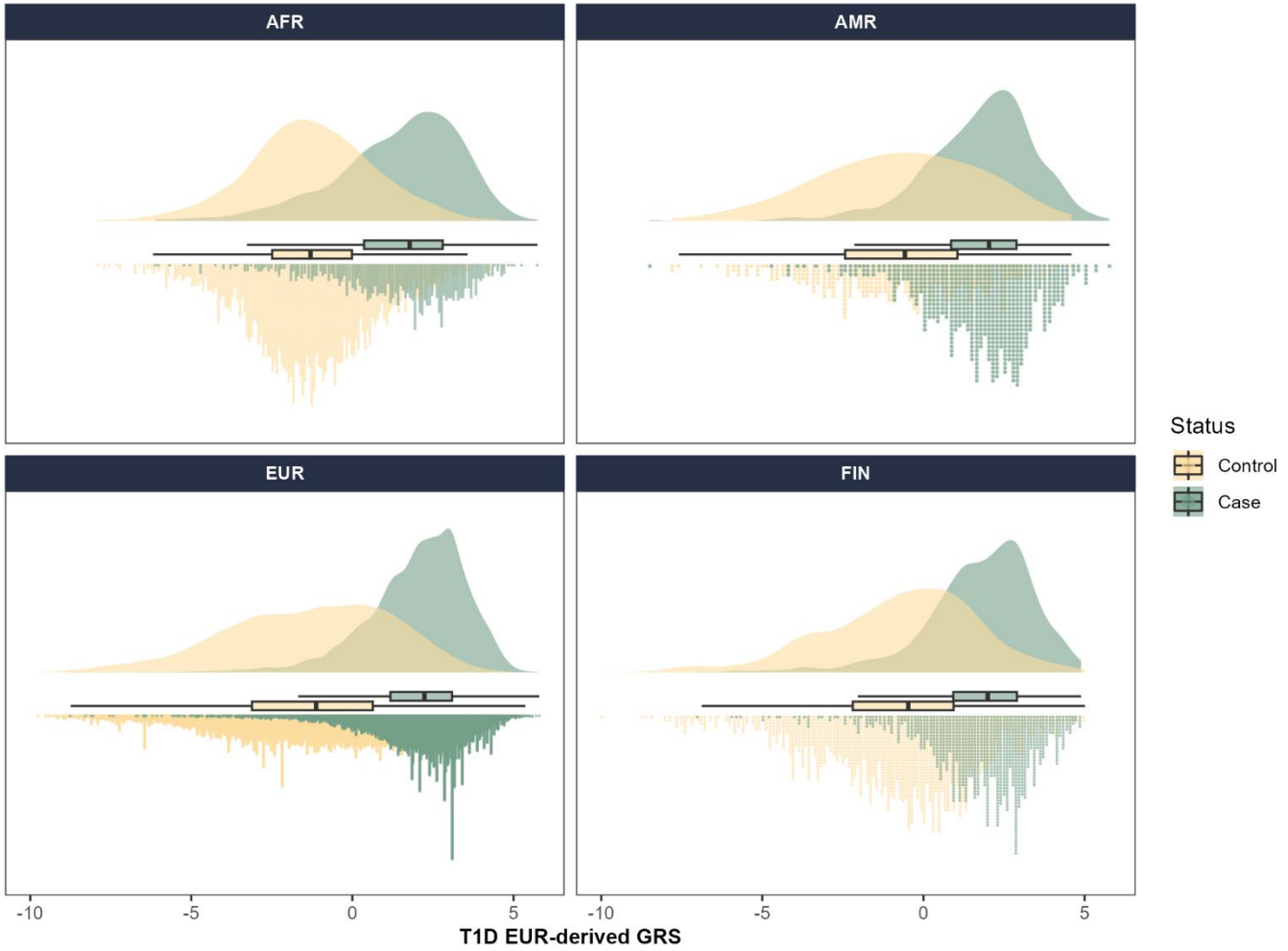
Distribution of type 1 diabetes GRS_{HLA} across ancestry groups



Dominika Michalek

Conclusion

Key Takeaways

- **Genetic Risk Scores (GRS)** offer a powerful tool for early identification of individuals at risk for **type 1 diabetes**.
- **Early screening** using GRS can enable targeted **preventative strategies** and more personalized healthcare interventions.
- The application of **genetic screening** programs is rapidly advancing, providing new opportunities to reduce the disease burden.

Future Directions

- **Diverse populations** require tailored GRS models to ensure accurate risk predictions and equitable access to genetic testing.
- **Current GRS models** in type 1 diabetes are predominantly based on **GWAS data from European ancestry** populations. There is a critical need to **recruit study participants from diverse ancestries** to develop GRSs that can help better capture risk across all populations.
- Collaboration is needed between **healthcare providers, public health institutions,** and **policymakers** to scale and implement screening programs.

Study participants and families

Type 1 Diabetes Genetics Consortium:

Beena Akolkar
Patrick Concannon
Henry Erlich
Cécile Julier
Flemming Pociot
Stephen S. Rich
Jørn Nerup
Concepcion Nierras
Grant Morahan
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Questions

HLA-focused type 1 diabetes genetic risk prediction in populations of diverse ancestry