Progress in complex phenotype prediction: the CAGI6 Polygenic Risk Score challenge

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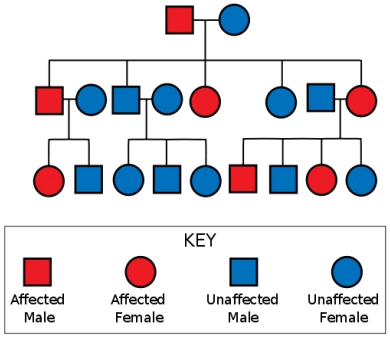
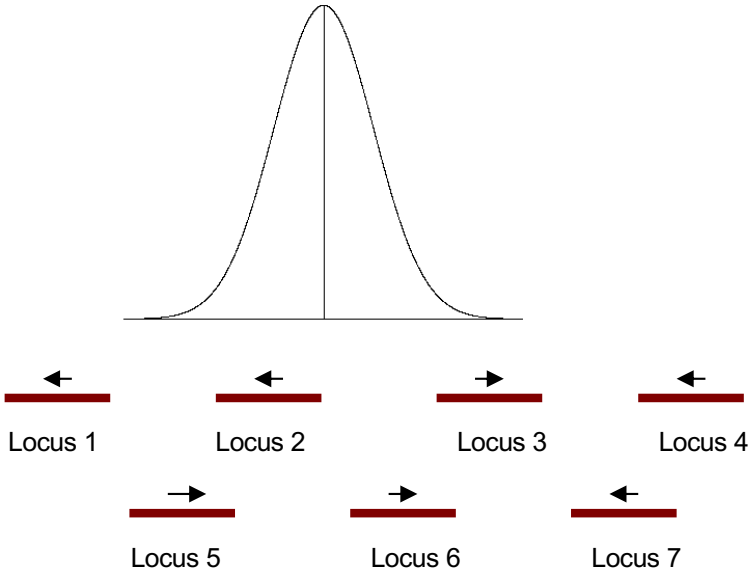
Complex phenotypes

Inheritance at each locus is Mendelian. Loci are independent



Phenotype is additive over locus effects -> normal distribution



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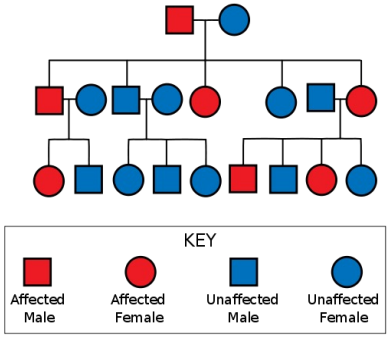

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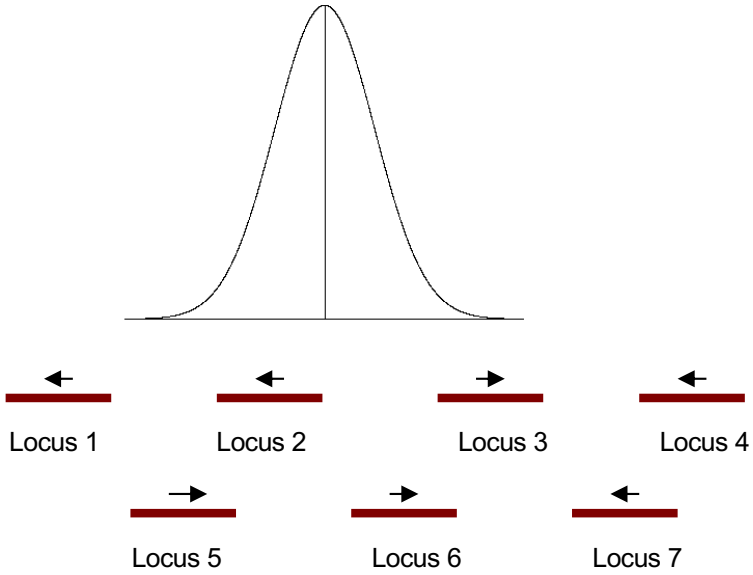
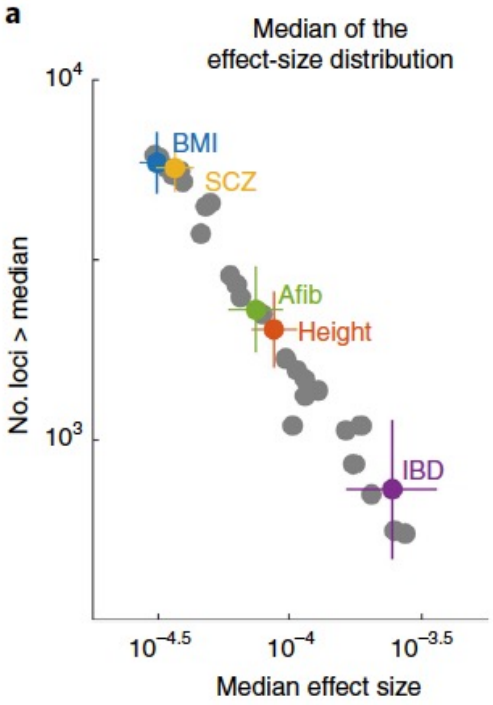
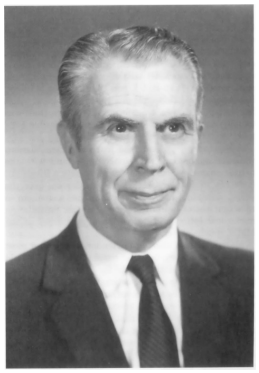




O'Connor 2021

Complex phenotype prediction

BLUP: Best Linear Unbiased Predictor
(Random Effect Model)



Charles Handerson
(1911 – 1989)

- Infinitesimal model
- All SNPs are causal
- Genetic effects are random
- Predict the expected genetic effect

Complex phenotype prediction

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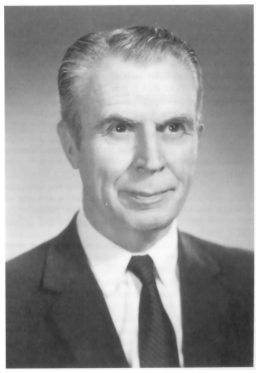
(Random Effect Model)



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- Infinitesimal model
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GENOME RESEARCH

Prediction of individual genetic risk to disease from genome-wide association studies

Naomi R. Wray, Michael E. Goddard and Peter M. Visscher

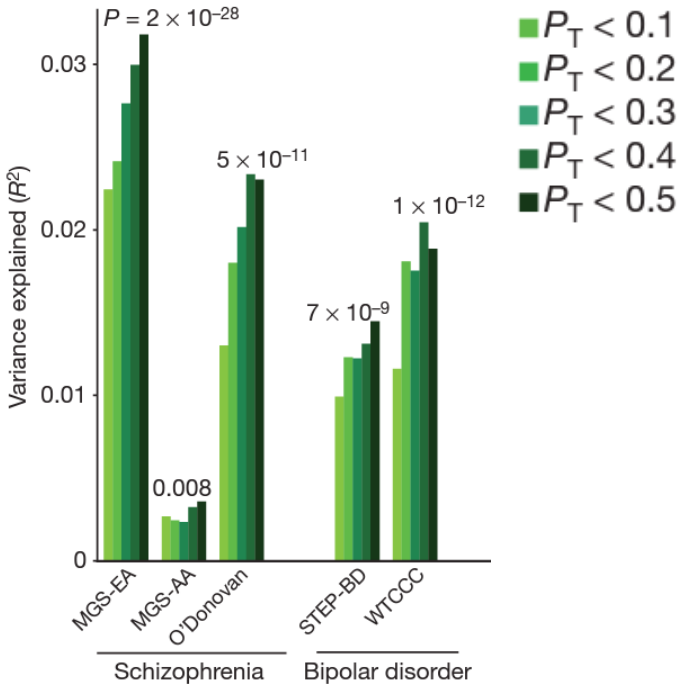
Genome Res. 2007 17: 1520-1528; originally published online Sep 4, 2007;
Access the most recent version at doi:10.1101/gr.6665407

LETTERS

Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

The International Schizophrenia Consortium*

Phenotype prediction by thresholding on p-values of GWAS association statistics



Pruning and Thresholding

Fixed Effect Model

$$y_i = \sum_j \beta_j \times x_{ij}$$

Genetic risk of individual i

Genotype of SNP j and individual i

Effect size of SNP j

LETTERS

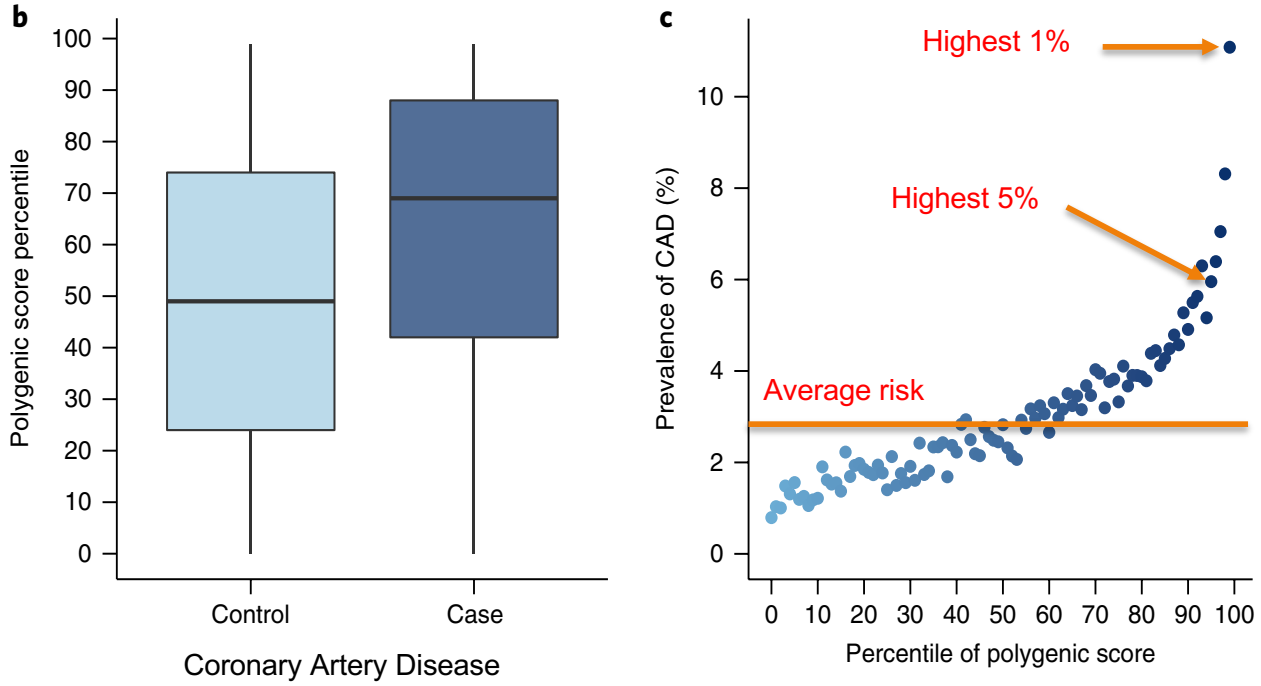
Common polygenic variation contributes to risk of schizophrenia and bipolar disorder

The International Schizophrenia Consortium*

Polygenic Risk Scores (PRS)

- Summary statistics are easily available
- Many methods require a separate small individual level dataset to tune parameters
- Methods: BSLMM, LDPred, lassosum, PRScs, BayesR, MegaPRS, AnnoPred, NPS, etc

Extreme tails of PRS are highly predictive



Khera et al. 2018

CAGI6 Polygenic Risk Prediction challenge

- Evaluates the accuracy of statistical methods
- New area for CAGI
- Massive protected patient data for training/validation cohort
- Receive software submission
- Synthetic data to augment real data challenge

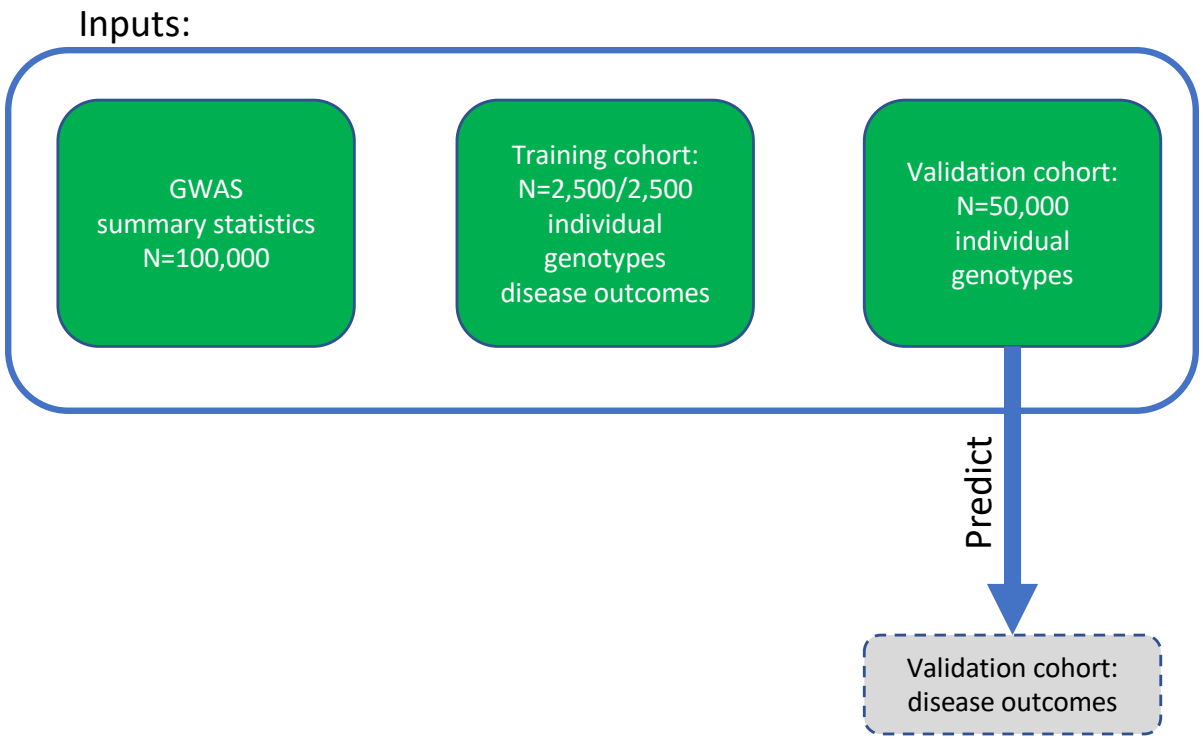
Phenotypes: Real and simulated traits

- Four Real phenotypes:
  - Breast Cancer
  - Early-onset Coronary Artery Disease
  - Inflammatory Bowel Disease (IBD)
  - Type 2 Diabetes

- 30 Simulated phenotypes (optional challenge)

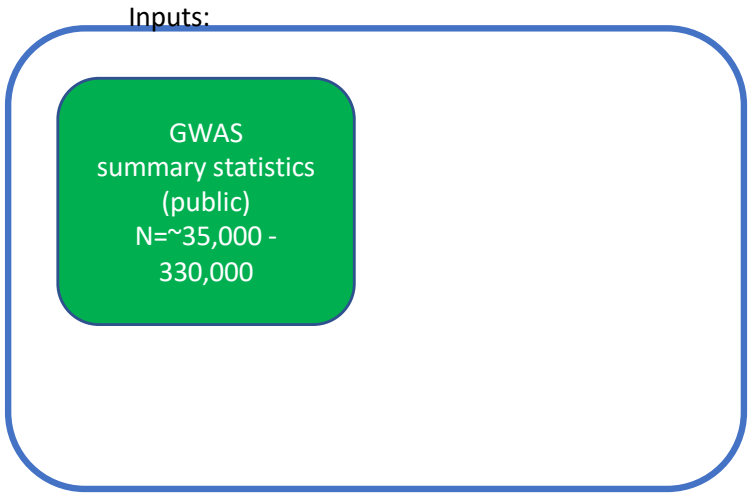
Source: Chun and Imakaev et al. AJHG 2020

Datasets: Simulated phenotypes

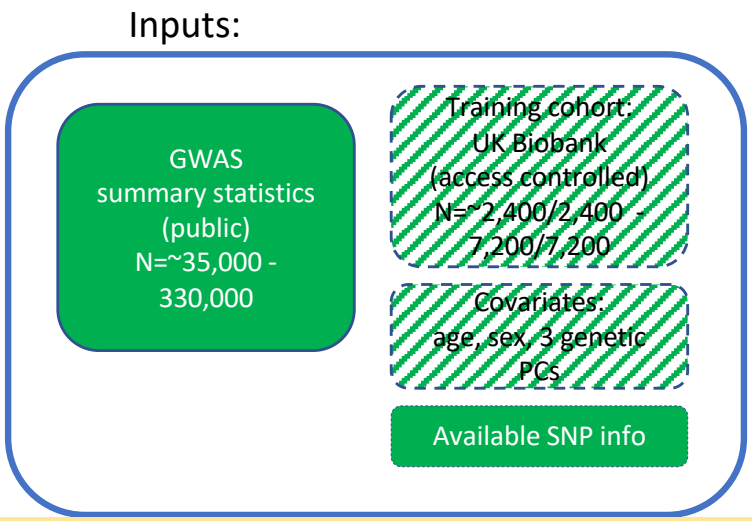


Source: Chun and Imakaev et al. AJHG 2020

Datasets: Real phenotypes



Datasets: Real phenotypes

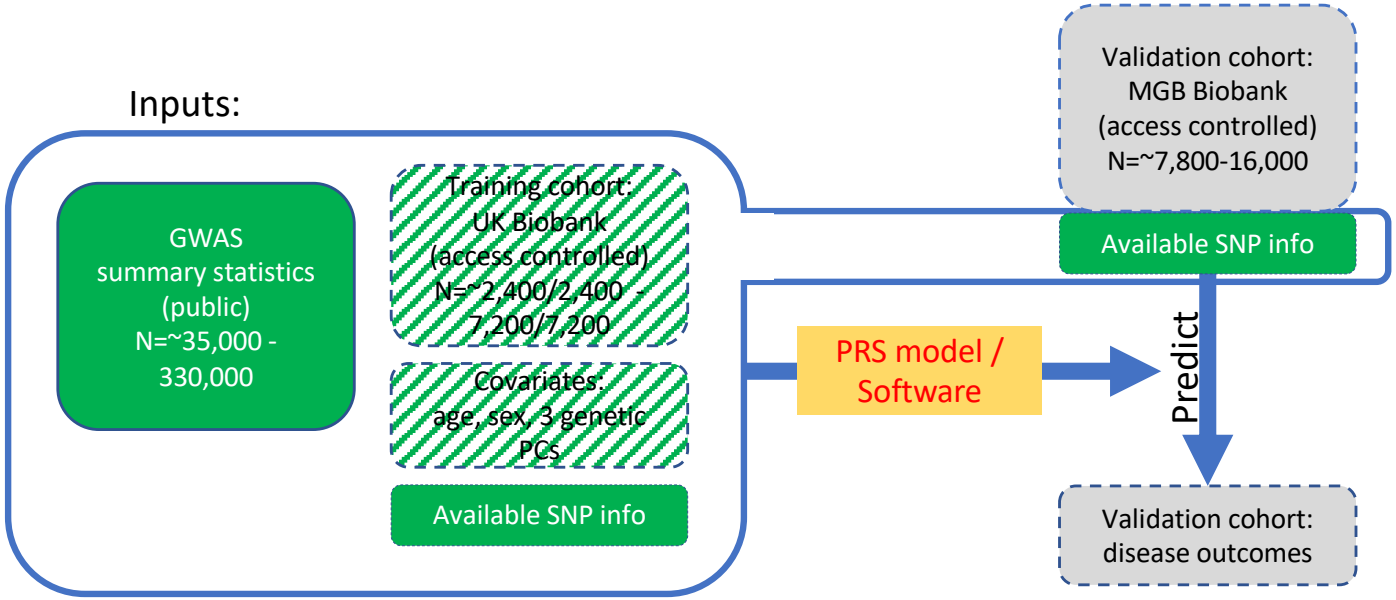


Training cohort from UK Biobank (N)

	Case	Control
Breast cancer	3,956	3,956
IBD	2,483	2,483
CAD	2,000	2,000
Type 2 Diabetes	7,298	7,298

Training on UK Biobank data was handled centrally via software submission. UK Biobank data are not directly shared with participants.

Datasets: Real phenotypes



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Validation Cohort: MGB Biobank

Journal of *Personalized Medicine*

MDPI

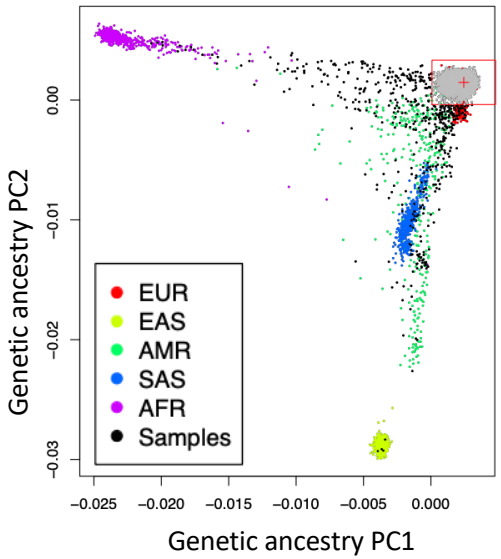
Article

Building the Partners HealthCare Biobank at Partners Personalized Medicine: Informed Consent, Return of Research Results, Recruitment Lessons and Operational Considerations

Elizabeth W. Karlson [1,*], Natalie T. Boutin [2], Alison G. Hoffnagle [3] and Nicole L. Allen [1]

Sample sizes:

- 16,839 Whites
- 1,100 African Americans
- 403 Asians



Overview of submissions

Team 1	• Applied an AI technique • Incorporate covariates directly into the model	Software submission (Pre-trained)
Team 2	• Applied MegaPRS	Per-SNP effect sizes
Team 3	• Aggressively using variant annotations • Based on LD Pruning + Thresholding technique	Software submission (Training requested)
Team 4	• A sparse lasso regression technique	Software submission (Pre-trained)
Team 5	• Multiple published PRS methods	Per-SNP effect sizes

Evaluation metrics

Logistic regression of:

$$y \sim age + sex + PC1 + PC2 + PC3 + \cdots + PC10 + PRS$$

- AUC of the full model including PRS and covariates

Primary metric

- $R^2_{nagelkerke}$: the likelihood of data under the full model compared to the likelihood under the null model

- 5% Tail Odds Ratio (OR): The odd at top 5% of the score relative to the odd of the rest of distribution (covariates included)

$$\frac{\#\{y = 1 \wedge \hat{y} > q_{0.95}\}}{\#\{y = 0 \wedge \hat{y} > q_{0.95}\}} / \frac{\#\{y = 1 \wedge \hat{y} < q_{0.95}\}}{\#\{y = 0 \wedge \hat{y} < q_{0.95}\}}$$

Methods for baseline comparison

- Negative control:
  - Logistic regression with only covariates (no PRS)

$$y \sim age + sex + PC1 + PC2 + PC3 + \cdots + PC10$$

- 4 widely used or current state-of-the-art methods:
  - LD Pruning + Thresholding (P+T)
  - LDPred v1
  - PRS-cs
  - NPS

Prediction accuracy ($R^2_{nagelkerke}$)

Breast Cancer

Model	$R^2_{nagelkerke}$	Rank
NPS	0.111	-
PRScs	0.109	-
MegaPRS	**0.101**	**1**
Team 2-1	0.100	2
Team 5-C	0.093	3
Team 5-L1	0.091	4
Team 3-4	0.091	5
Team 5-A	0.090	6
P+T	0.090	-
Team 5-T	0.089	7
LDPred 1	0.088	-
Team 4-3	0.087	8
Team 3-3	0.085	9
Team 5-L2i	0.085	10
Team 4-1	0.084	11
Team 3-2	0.082	12
Team 5-L2	0.074	13
Team 4-2	0.073	14
Cov only	**0.073**	**-**
Team 3-5	0.072	15
Team 3-6	0.072	16
Team 3-1	0.072	17
Team 1	n/a	-

IBD

Model	$R^2_{nagelkerke}$	Rank
MegaPRS	**0.173**	**1**
NPS	0.157	-
PRScs	0.157	-
Team 2-1	0.156	2
Team 5-A	0.148	3
Team 5-L1	0.141	4
Team 5-L2	0.141	5
P+T	0.140	-
Team 5-C	0.139	6
LDPred 1	0.134	-
Team 5-T	0.125	7
Team 5-L2i	0.124	8
Team 4-1	0.103	9
Team 4-3	0.103	10
Team 1	0.102	11
Team 4-2	0.099	12
Cov only	**0.099**	**-**
Team 3-5	0.098	13
Team 3-4	0.098	14
Team 3-2	0.098	15
Team 3-1	0.098	16
Team 3-3	0.098	17
Team 3-6	0.098	18

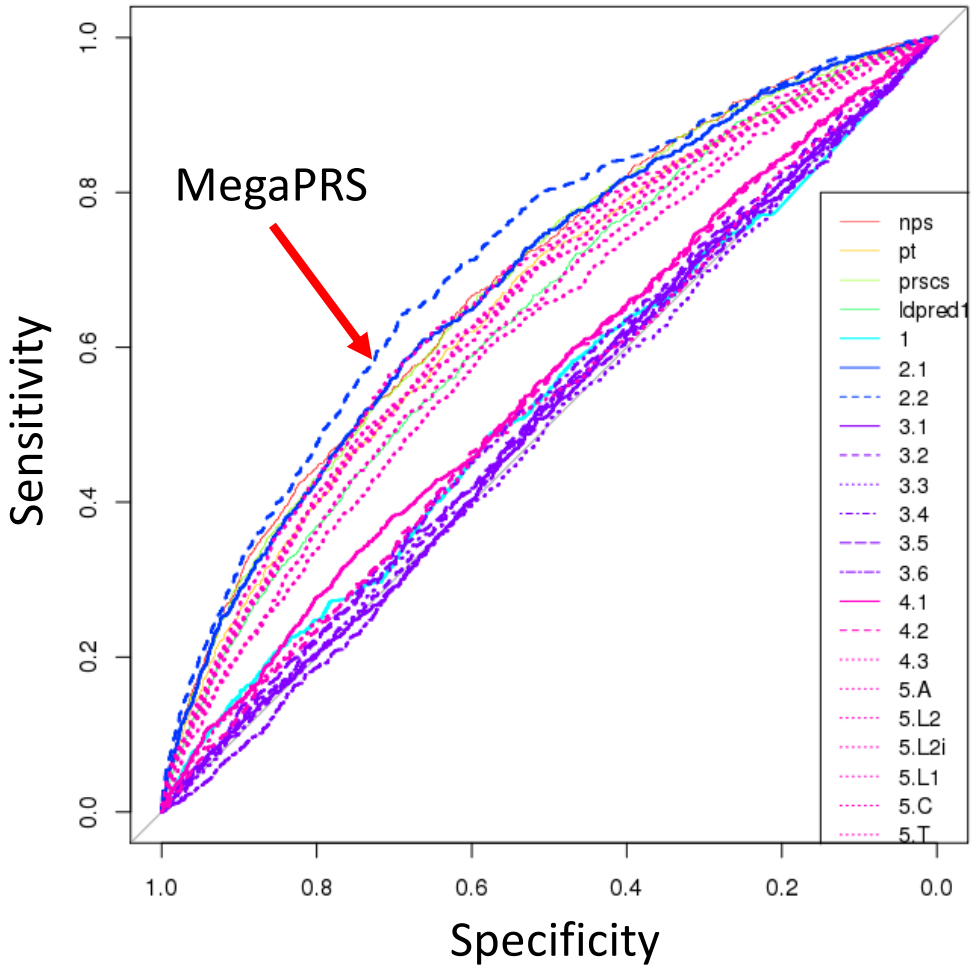
Coronary Artery Disease

Model	$R^2_{nagelkerke}$	Rank
PRScs	0.160	-
NPS	0.160	-
P+T	0.155	-
MegaPRS	**0.155**	**1**
Team 3-4	0.154	2
Team 5-L2	0.153	3
Team 5-C	0.153	4
Team 5-L2i	0.153	5
Team 5-A	0.153	6
LDPred 1	0.151	-
Team 3-3	0.150	7
Team 3-2	0.148	8
Team 5-T	0.147	9
Team 3-1	0.146	10
Team 3-6	0.146	11
Team 3-5	0.146	12
Team 4-1	0.143	13
Team 5-L1	0.143	14
Team 4-2	0.142	15
Team 4-3	0.142	16
Team 1	0.142	17
Cov only	**0.142**	**-**

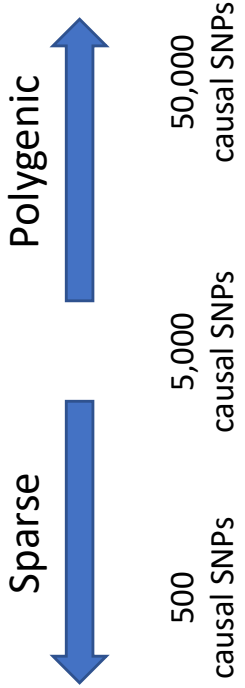
Type 2 Diabetes

Model	$R^2_{nagelkerke}$	Rank
NPS	0.130	-
PRScs	0.130	-
MegaPRS	**0.127**	**1**
Team 5-A	0.118	2
LDPred 1	0.117	-
Team 5-C	0.117	3
Team 4-3	0.112	4
Team 5-L2	0.111	5
Team 5-L2i	0.107	6
P+T	0.107	-
Team 1	0.105	7
Team 5-T	0.099	8
Team 4-1	0.099	9
Team 3-4	0.098	10
Team 3-3	0.095	11
Team 5-L1	0.095	12
Team 3-2	0.095	13
Team 3-1	0.094	14
Team 3-5	0.093	15
Team 3-6	0.093	16
Team 4-2	0.092	17
Cov only	**0.092**	**-**

ROC of IBD PRS models

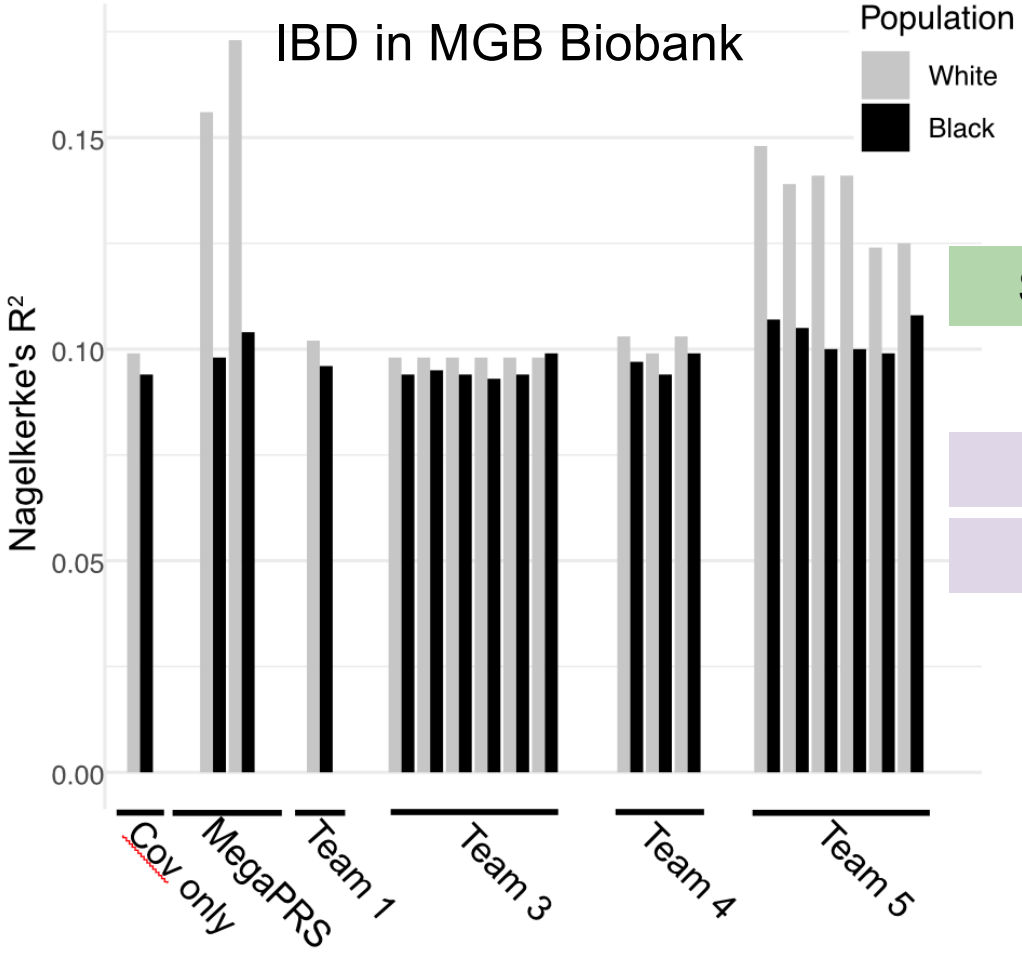


Prediction accuracy in simulated datasets



		Validation	
% causal SNPs	Method	$R^2_{Liability}$	95% CI
1%	P+T	0.074	
	LDPred 1	0.103	
	PRS-CS	0.110	
	NPS	0.123	
	MegaPRS	**0.145***	**[0.143 - 0.147]**
0.1%	P+T	0.199	
	LDPred 1	0.115	
	PRS-CS	0.224	
	NPS	0.256	
	MegaPRS	**0.297***	**[0.292 - 0.302]**
0.01%	P+T	0.307	
	LDPred 1	0.219	
	PRS-CS	0.327	
	NPS	0.463	
	MegaPRS	**0.460**	**[0.453 - 0.467]**

Poor transferability across populations



Sample size in MGB Biobank		
	Case	Control
White	820	16,335
Black	26	1,100

Conclusions

- We would not have an improvement over the existing state-of-the-art methods for any of the phenotypes.
    - Looks like we do!

- Investment in the statistics does not pay off any longer.
    - Looks like it still does!

CAGI6 PRS challenge: Limitations

- Technically difficult challenge – 22 groups signed up initially; only 5 groups made submission
- Bringing experts into CAGI – need to demonstrate a clear benefit of participating
- Bringing new computational biology groups into the field – help getting over the hurdle of training data access

CAGI6 PRS challenge: Limitations

- A machine learning-based prediction model did not perform well – not designed to evaluate the full potential
- Need a mechanism to share training cohorts more easily and make more covariates available
- Need to include more diverse ancestry

Acknowledgements

- Co-assessor/data provider: Shamil Sunyaev (Harvard/BWH)
- Data provider: Nikolaos Patsopoulos (Harvard/BWH)
- Data provider: Benjamin Neale (Broad Institute)
- CAGI organizer: Constantina Bakolitsa (UC Berkeley)
- CAGI organizer: Predrag Radivojac (Northeastern University)

We would like thank all CAGI6 PRS challenge participants.

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We are looking for postdocs.