

Polygenic Risk Score (PRS) Introduction 001

Overview and topic-stratified PRS reference list

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McLaughlin Centre PRS Team

- Critical mass of methodologists motivated by PRS-relevant data and implementation challenges
- Built on CIHR STAGE: over a decade of productive interdisciplinary research collaborations and capacity building

PRS Team Major Goal

Develop methodologies, platform and expertise for robust applications of PRS for precision health with a population impact



**McLAUGHLIN
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Statistical Sciences
UNIVERSITY OF TORONTO



Sinai Health | Lunenfeld-Tanenbaum Research Institute

Dalla Lana
School of Public Health

SickKids

Outline of the whole PRS workshop

1. Statistical fundamentals of PRS
2. Real-life users FAQ & solutions
3. Hands-on exercises (restricted)
4. Advanced topics
5. Clinical implications
6. Discussion

Outline of 1. Statistical Fundamentals of PRS

Lei Sun, Wei Deng and Yanyan Zhao

- ▶ PRS-intro001-overview: a topic-stratified PRS reference list
- ▶ PRS-intro101-foundation: GWAS, h^2 and prediction
- ▶ **PRS-intro201-basic:** PRS calculation and performance evaluation
- ▶ **PRS-intro301-basic-plus:** some obvious or not so obvious follow-up Qs
- ▶ **PRS-intro401-heterogeneity:** heterogeneity and transportability
- ▶ PRS-intro501-LD: linkage disequilibrium

Misc notes

- ▶ Deeper understanding of the **basic PRS**
- ▶ Step-by-step **R-assisted ‘hand calculation’** with (almost) **no black box**
- ▶ **Reproducible** examples and results

All .pdf and source .Rmd files will be made open resource soon after the IGES workshop at <https://github.com/LeiSunUofT>

- ▶ Workshop teaching: ≈ 2 hours, **covering only some of the notes.** Please go over the 001 and 101 slides distributed prior to the workshop carefully, so that more workshop time can be dedicated to other materials. Thank you!
- ▶ If interested: ∞ hours of self-study
- ▶ If interested: quizzes throughout the lecture notes

Goal of this lecture

- ▶ Overview of the topics to be covered in 1. statistical fundamentals of PRS of this workshop.
- ▶ PRS is intuitive with a simple expression:

$$PRS_i = \sum_{j=1}^J \hat{\beta}_j G_{ij}$$

- ▶ But, there are many (answered and open) complex (methodological and practical) questions.
- ▶ Provide a topic-stratified reference list for self-study.

If interested: PRS by NIH-National Human Genome Research Institute

A "polygenic risk score" is one way by which people can learn about their risk of developing a disease, based on the total number of changes related to the disease.

(environmental factors, populations)

If interested: PRS by Wiki (March 17, 2021)

*In genetics, a polygenic score, also called a polygenic risk score (PRS), genetic risk score, or genome-wide score, is a number that summarises the estimated effect of many genetic variants on an individual's phenotype, typically calculated as a **weighted sum of trait-associated alleles**.^{[1][2][3]}*

It reflects an individual's estimated genetic predisposition for a given trait and can be used as a predictor for that trait.^{[4][5][6][7][8]}

Polygenic scores are widely used in animal breeding and plant breeding (usually termed genomic prediction or genomic selection) due to their efficacy in improving livestock breeding and crops.^[9]

*They are also increasingly being used for **risk prediction** in humans for **complex diseases** [10] which are typically affected by many genetic variants that each confer a small effect on overall risk.^{[11][12]}*

- [1] Dudbridge (2013). *PLOS Genetics*. Power and predictive accuracy of polygenic risk scores.
- [2] Torkamani et al. (2018). *Nature Reviews Genetics*. The personal and clinical utility of polygenic risk scores.
- [3] Lambert et al. (2019). *Human Molecular Genetics*. Towards clinical utility of polygenic risk scores.
- [4] de Vlaming and Groenen (2015). *BioMed Research International*. The Current and Future Use of Ridge Regression for Prediction in Quantitative Genetics.
- [5] Lewis and Vassos E (2017). *Genome Medicine*. Prospects for using risk scores in polygenic medicine.
- [6] Khera et al. (2018). *Nature Genetics*. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations.
- [7] Yanes et al. (2020). *Clinical Genetics*. Uptake of polygenic risk information among women at increased risk of breast cancer.
- [8] Vilhjalmsson et al.(2015). *American Journal of Human Genetics*. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. (LDpred)
- [9] Spindel and McCouch (2016). *The New Phytologist*. When more is better: how data sharing would accelerate genomic selection of crop plants. (Caution: more is only better if you know how to deal with potential heterogeneity.)
- [10] Regalado (2019). *MIT Technology Review*. 23andMe thinks polygenic risk scores are ready for the masses, but experts aren't so sure.
- [11] Visscher et al. (2017) *American Journal of Human Genetics*. 10 Years of GWAS Discovery: Biology, Function, and Translation. (*The Utility of GWAS-Derived Genetic Predictors*)
- [12] Spiliopoulou et al. (2015). *Human Molecular Genetics*. Genomic prediction of complex human traits: relatedness, trait architecture and predictive meta-models.

PRS = a weighted sum of trait-associated alleles

a simple expression with many complex questions

$$PRS_i = \sum_{j=1}^J \hat{\beta}_j G_{ij}$$

- ▶ PRS_i : PRS for individual i
which population? environmental exposure?
- ▶ J : the total number of '**relevant**' bi-allelic (common) SNPs
rare variants? other types of genetic markers?
- ▶ $\hat{\beta}_j$: **estimated effect size** of SNP j
portability: which population? phenotype/pleiotropy? direction of effects?
- ▶ G_{ij} : the number of copies of the risk allele
counting a or A? the minor or major allele?
- ▶ Σ : how to deal with **dependency/linkage disequilibrium (LD)**?

Other Complications/Considerations (= Opportunities)

Autosomes → **the X-chromosome** (and Y-chromosome)

Dr. Wei Deng, McMaster University

Main → **Interaction effect**

Variance → Covariance, **genetic overlap**

Population → **Family data**

Cross-sectional → **Longitudinal data** Dr. Laurent Briollais,
Luenfeld-Tanenbaum

Association and prediction → **Causal inference**

Prof. Linbo Wang, UofT Stat

(dry) lab-environment method development and evaluation →
real-life implementation and clinical implication Dr. Delnaz

Roshandel, Sickkids, Dr. Jennifer Brooks, UofT Epi and Dr. Andrew Paterson,
Sickkids

PRS for risk prediction for complex diseases

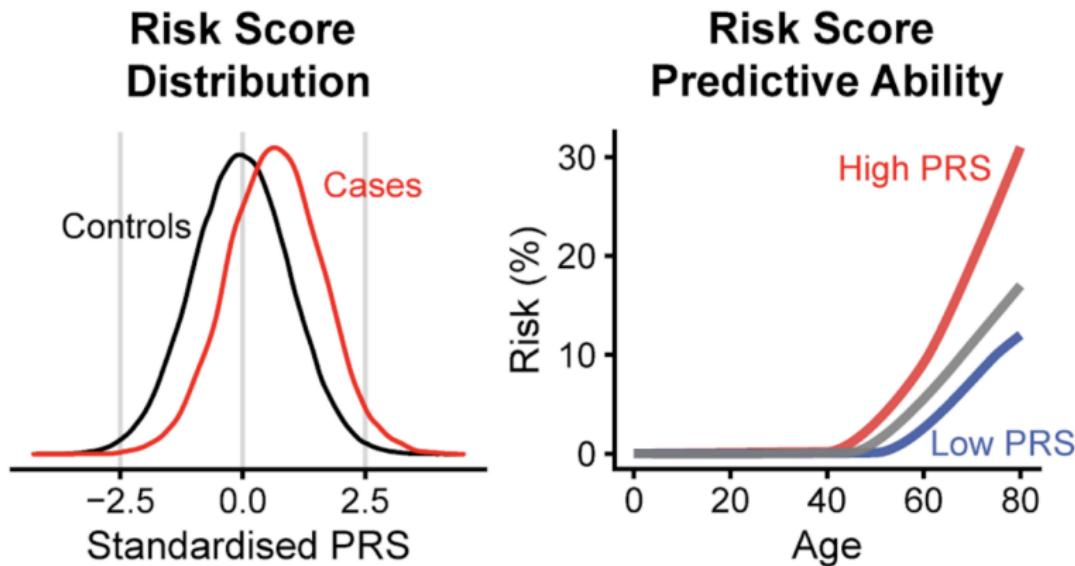


Figure 1 of Wand et al. (2021). *Nature*. Improving reporting standards for polygenic scores in risk prediction studies.

An illustration of the distribution of a polygenic risk score in both cases (individuals with a disease/trait) and controls (those without) [left], and

the predictive ability where individuals with a high polygenic risk score have an increased risk of disease/trait over time [right].

PRS for risk prediction, cont'd

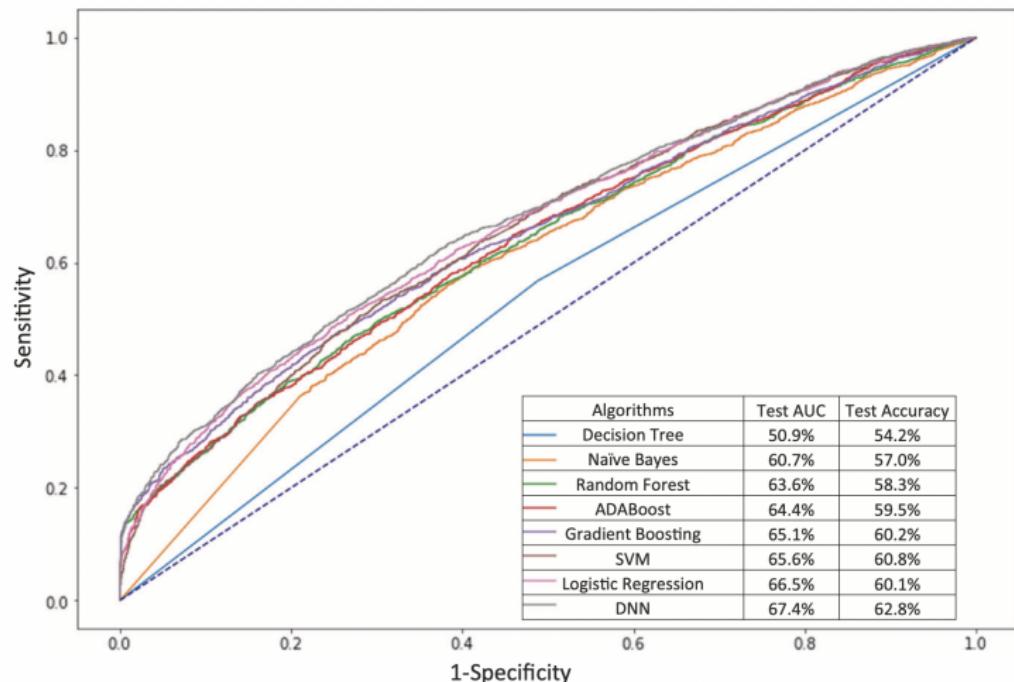


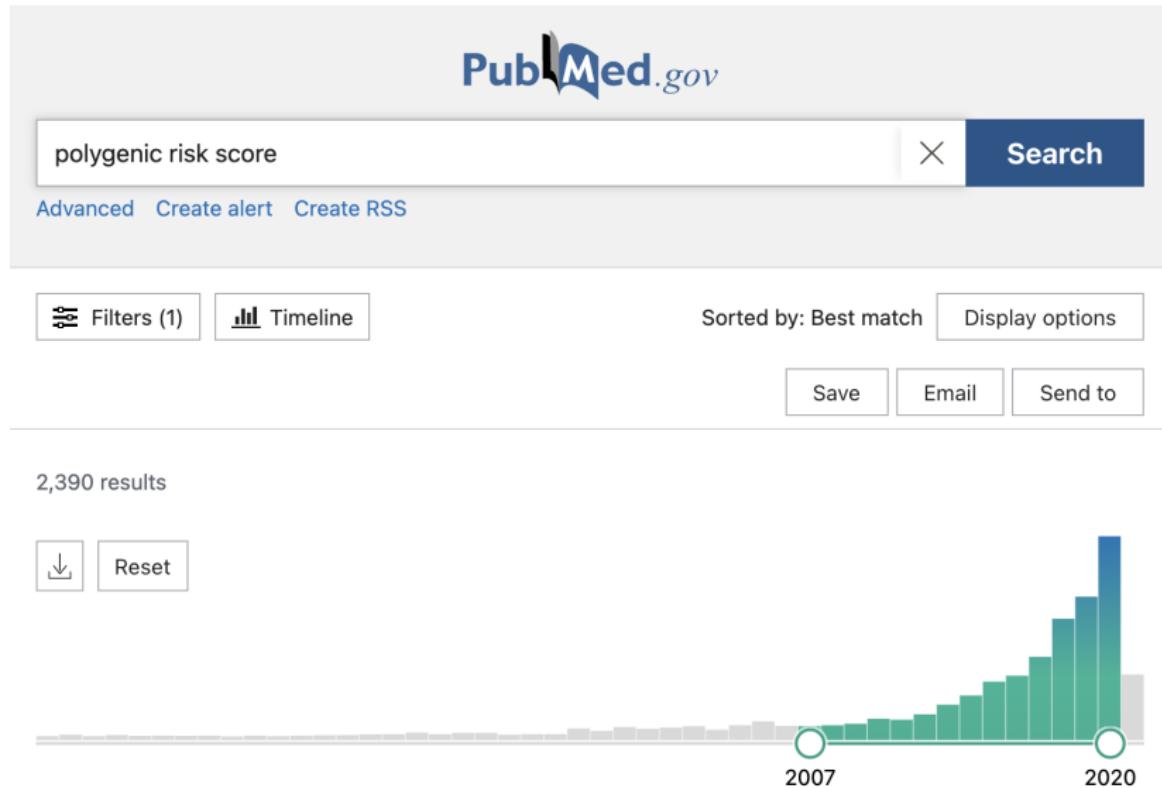
Figure 3 of Badre et al. (2021). *Journal of Human Genetics*. Deep neural network improves the estimation of polygenic risk scores for breast cancer.

N.B. The classical logistic regression is competitive!

Reference – PRS Paper ‘0’

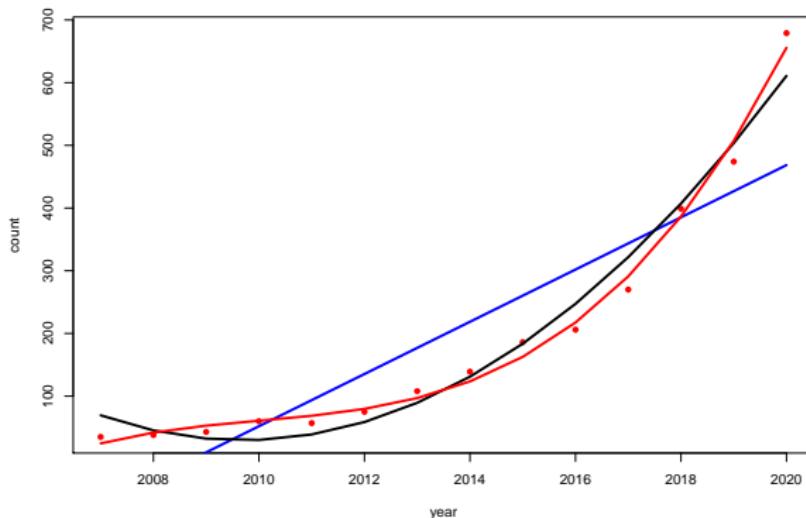
- ▶ Wray, Goddard, Visscher PM (2007). *Genome Research*. Prediction of individual genetic risk to disease from genome-wide association studies. (514 citation in PMC; March 17, 2021)
- ▶ International Schizophrenia Consortium; Purcell et al. (2009). *Nature*. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder (4123 citations in PMC; March 17, 2021)

If interested: Growth of PRS Research



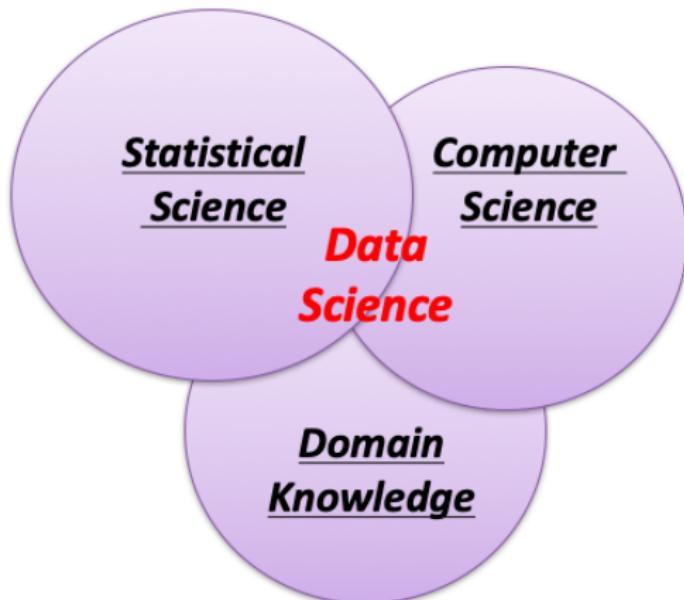
If interested: Not a Linear Growth!

```
# Search query: polygenic risk score;
# Search date: March 17, 2021
year=c(2007,2008,2009,2010,2011,2012,2013,2014,2015,2016,2017,2018,2019,2020)
count=c(35,38,43,60,57,75,108,139,186,206,270,399,474,679)
plot(year,count,col="red",pch=16)
lines(year,fitted(lm(count~year)),col='blue',lwd=3)
lines(year,fitted(lm(count~poly(year,2))),col='black',lwd=3)
lines(year,fitted(lm(count~poly(year,3))),col='red',lwd=3)
```



N.B. prediction \neq model fitting \neq 'best' fit

If interested: Discussion, PRS research is data science =
interdisciplinary/multidisciplinary research



If interested: Discussion cont'd

Harvard Data Science Review (HDSR)

Data Science Education

Reproducibility and Replicability

AI and Responsible Data Science

Genetic Diversity and Ancestry

Akinyemi Oni-Orisan, Yusuph Mavura, Yambazi Banda, Timothy A Thornton, Ronnie Sebro (2021). *New England Journal of Medicine*
Embracing Genetic Diversity to Improve Black Health

Topic-Stratified References

Not an Exhaustive List

Reference – PRS tutorial and ‘famous’ software

- ▶ Choi et al. (2019). *Nature Protocols*. Tutorial: a guide to performing polygenic risk score analyses.
- ▶ Purcell et al. (2007). *American Journal of Human Genetics*. PLINK: a toolset for whole-genome association and population-based linkage analysis. (PLINK)
- ▶ Vilhjalmsson et al.(2015). *American Journal of Human Genetics*. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. (LDpred)
- ▶ Euesden et al. (2015). *Bioinformatics*. PRSice: Polygenic Risk Score software. (PRSice)
- ▶ Mak et al. (2017). *Genetic Epidemiology*. Polygenic scores via penalized regression on summary statistics. (lassosum; R package).

Reference – PRS review and perspectives

- ▶ Dudbridge (2013). *PLOS Genetics*. Power and predictive accuracy of polygenic risk scores.
- ▶ Wray et al. (2014). *Journal of Child Psychology and Psychiatry*. Research review: Polygenic methods and their application to psychiatric traits.
- ▶ Chatterjee et al. (2016). *Nature Review Genetics*. Developing and evaluating polygenic risk prediction models for stratified disease prevention.
- ▶ Visscher et al. (2017). *American Journal of Human Genetics*. 10 Years of GWAS Discovery: Biology, Function, and Translation. (*The Utility of GWAS-Derived Genetic Predictors*)
- ▶ Dudbridge et al. (2018) *Genetic Epidemiology*. Predictive accuracy of combined genetic and environmental risk scores.
- ▶ See a full [video](#) of “Panel Discussion: The Personal and Clinical Utility of Genetic Risk Scores: Are they ready for PRIME TIME?” from the CANSSI-Ontario Research Day on March 5, 2020.

Reference – PRS utility and clinical implication

- ▶ Lewis and Vassos (2017). *Genome Medicine*. Prospects for using risk scores in polygenic medicine.
- ▶ Hasin et al. (2017). *Genome Biology*. Multi-omics approaches to disease.
- ▶ Torkamani et al. (2018). *Nature Reviews Genetics*. The personal and clinical utility of polygenic risk scores.
- ▶ Lambert et al. (2019). *Human Molecular Genetics*. Towards clinical utility of polygenic risk scores.
- ▶ Janssens (2019). *Human Molecular Genetics*. Validity of polygenic risk scores: are we measuring what we think we are?.
- ▶ Lewis and Vassos (2020). *Genome Medicine*. Polygenic risk scores: from research tools to clinical instruments.
- ▶ Li et al. (2020). *Nature Review Genetics*. Electronic health records and polygenic risk scores for predicting disease risk.

References - PRS in action

- ▶ Khera et al. (2018). *Nature Genetics*. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations.
- ▶ Mavaddat et al. (2019). *American Journal of Human Genetics*. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes.
- ▶ Lee et al. (2019). *Genetics in Medicine* BOADICEA: A comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors.
- ▶ Fritsche et al. (2020). *The American Journal of Human Genetics*. Cancer PRSweb: An Online Repository with Polygenic Risk Scores for Major Cancer Traits and Their Evaluation in Two Independent Biobanks.
- ▶ Mars et al. (2020). *Nature Medicine*. Polygenic and clinical risk scores and their impact on age at onset and prediction of cardiometabolic diseases and common cancers.
- ▶ Richardson et al. (2020). *Elife*. An atlas of polygenic risk score associations to highlight putative causal relationships across the human genome.
- ▶ Yanes et al. (2020). *Clinical Genetics*. Uptake of polygenic risk information among women at increased risk of breast cancer.
- ▶ Meyers et al. (2021). *Translational Psychiatry*. The association of polygenic risk for schizophrenia, bipolar disorder, and depression with neural connectivity in adolescents and young adults: examining developmental and sex differences.

Reference – PRS methods with ‘famous’ acronyms

- ▶ Vilhjalmsson et al.(2015). *American Journal of Human Genetics* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. (LDpred)
- ▶ Prive et al.(2020). *Bioinformatics*. LDpred2: better, faster, stronger. (LDpred2)
- ▶ Euesden et al. (2015). *Bioinformatics* PRSice: Polygenic Risk Score software. (PRSice)
- ▶ Choi and O'Reilly (2019). *Giga Science*. PRSice-2: Polygenic Risk Score software for biobank-scale data. (PRSice-2)
- ▶ Mak et al. (2017). *Genetic Epidemiology*. Polygenic scores via penalized regression on summary statistics. (lassosum).
- ▶ Turley et al. (2018). *Nature Genetics*. Multi-trait analysis of genome-wide association summary statistics using MTAG. (MTAG)

Reference – PRS methods on J and Σ (LD)

- ▶ International Schizophrenia Consortium; Purcell et al. (2009). *Nature*. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. (Pruning and Thresholding; P+T)
- ▶ Goldstein et al. (2015). *Genetic Epidemiology*. Contemporary Considerations for Constructing a Genetic Risk Score: An Empirical Approach.
- ▶ Prive (2019). *American Journal of Human Genetics*. Making the Most of Clumping and Thresholding for Polygenic Scores. (Stacked Clumping + Thresholding)

Reference – PRS methods on J and Σ (LD) and $\hat{\beta}_j$

- ▶ de Vlaming and Groenen (2015). *BioMed Research International*. The Current and Future Use of Ridge Regression for Prediction in Quantitative Genetics.
- ▶ Shi et al. (2016). *PLoS Genetics*. Winner's Curse Correction and Variable Thresholding Improve Performance of Polygenic Risk Modeling Based on Genome-Wide Association Study Summary-Level Data.
- ▶ Mak et al. (2016). *Behavior Genetics*. Local True Discovery Rate Weighted Polygenic Scores Using GWAS Summary Data.
- ▶ Mak et al. (2017). *Genetic Epidemiology*. Polygenic scores via penalized regression on summary statistics. (lassosum).
- ▶ Zhang et al. (2018). *Nature Genetics*. Estimation of complex effect-size distributions using summary-level statistics from genome-wide association studies across 32 complex traits.

Reference – PRS Bayesian methods

- ▶ Vilhjalmsson et al.(2015). *American Journal of Human Genetics*. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. (LDpred)
- ▶ So and Sham (2017). *Scientific Reports*. Improving polygenic risk prediction from summary statistics by an empirical Bayes approach.
- ▶ Zeng and Zhou (2017). *Nature Communications*. Non-parametric genetic prediction of complex traits with latent Dirichlet process regression models.
- ▶ Zhu and Stephens (2017). *Annals of Applied Statistics*. Bayesian large-scale multiple regression with summary statistics from genome-wide association studies. (RSS)
- ▶ Ge et al. (2019). *Nature Communications*. Polygenic prediction via Bayesian regression and continuous shrinkage priors. (PRS-CS)

Reference – PRS Bayesian methods, cont'd

- ▶ Lloyd-Jones et al. (2019). *Nature Communications*. Improved polygenic prediction by Bayesian multiple regression on summary statistics. (SBayesR)
- ▶ Newcombe (2019). *Genetic Epidemiology*. A flexible and parallelizable approach to genome-wide polygenic risk scores. (JAMPred).
- ▶ Song et al. (2020). *PLoS Computational Biology*. Leveraging effect size distributions to improve polygenic risk scores derived from summary statistics of genome-wide association studies. (EB-PRS;Empirical Bayes)
- ▶ Yang et al. (2020). *The American Journal of Human Genetics*. Accurate and Scalable Construction of Polygenic Scores in Large Biobank Data Sets. (DBSLMM)

Reference – PRS methods on data integration – diverse populations

- ▶ Marquez-Luna et al. (2017). *Genetic Epidemiology*. Multiethnic polygenic risk scores improve risk prediction in diverse populations.
- ▶ Duncan et al. (2019). *Nature Communications*. Analysis of polygenic risk score usage and performance in diverse human populations.
- ▶ Grinde et al. (2019). *Genetic Epidemiology*. Generalizing polygenic risk scores from Europeans to Hispanics/Latinos.
- ▶ Gola et al. (2020). *Circulation: Genomic and Precision Medicine*. Population Bias in Polygenic Risk Prediction Models for Coronary Artery Disease.
- ▶ Cavazos and Witte (2021). *Human Genetics and Genomics Advances*. Inclusion of variants discovered from diverse populations improves polygenic risk score transferability.
- ▶ Atkinson et al. (2021). *Nature Genetics*. Tractor uses local ancestry to enable the inclusion of admixed individuals in GWAS and to boost power (from global to local ancestry and admixture.)

Reference – PRS methods on data integration – pleiotropy

- ▶ Hu et al. (2017). *PLoS Genetics*. Joint modeling of genetically correlated diseases and functional annotations increases accuracy of polygenic risk prediction. (PleioPred)
- ▶ Fritzsche et al. (2018). *The American Journal of Human Genetics*. Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-wide Study: Results from The Michigan Genomics Initiative.
- ▶ Krapohl (2018). *Molecular Psychiatry*. Multi-polygenic score approach to trait prediction. (MPS)
- ▶ Maier (2018). *Nature Communications*. Improving genetic prediction by leveraging genetic correlations among human diseases and traits. (SMTpred)
- ▶ Turley et al. (2018). *Nature Genetics*. Multi-trait analysis of genome-wide association summary statistics using MTAG. (MTAG)
- ▶ Chung et al. (2019). *Nature Communications*. Efficient cross-trait penalized regression increases prediction accuracy in large cohorts using secondary phenotypes. (CTPR)
- ▶ Chen et al. (2021). *Journal of the American Statistical Association*. A Penalized Regression Framework for Building Polygenic Risk Models Based on Summary Statistics From Genome-Wide Association Studies and Incorporating External Information. (PANPRS; also annotation)

Reference – PRS methods on data integration – others (e.g. gene-expression, functional annotation)

- ▶ Hasin et al. (2017). *Genome Biology*. Multi-omics approaches to disease.
- ▶ Hu et al. (2017). *PLoS Computational Biology*. Leveraging functional annotations in genetic risk prediction for human complex diseases. (AnnoPred)
- ▶ Marigorta et al. (2017). *Nature Genetics*. Transcriptional risk scores link GWAS to eQTLs and predict complications in Crohn's disease.
- ▶ Pare et al. (2017) *Scientific Reports*. A machine-learning heuristic to improve gene score prediction of polygenic traits. (GraBLD)
- ▶ Wu and Pan. (2018). *Genetic Epidemiology*. Integrating eQTL data with GWAS summary statistics in pathway-based analysis with application to schizophrenia.
- ▶ Gusev et al. (2019). *Nature Genetics*. Transcriptome-wide association study of schizophrenia and chromatin activity yields mechanistic disease insights.

Reference – PRS Other Topics

- ▶ Weiner et al. (2017). *Nature Genetics*. Polygenic transmission disequilibrium confirms that common and rare variation act additively to create risk for autism spectrum disorders. (pTDT)
- ▶ Meisner et al. (2019) *American Journal of Epidemiology*. Case-Only Analysis of Gene-Environment Interactions Using Polygenic Risk Scores. (Interaction)
- ▶ Deng et al. (2019). *Genetic Epidemiology*. Analytical strategies to include the X-chromosome in variance heterogeneity analyses: Evidence for trait-specific polygenic variance structure. (Xchr & Interaction)
- ▶ Yonova-Doing et al. (2021). *Nature Genetics*. An atlas of mitochondrial DNA genotype– phenotype associations in the UK Biobank (mitochondrial DNA)
- ▶ Andrews et al. (2020). *Neurobiology Aging*. Mitonuclear interactions influence Alzheimer's disease risk (mito-nuclear Interaction)

A recent method comparison study **in the context of psychiatric disorders**

Ni et al. (2021). *Biological Psychiatry. A Comparison of Ten Polygenic Score Methods for Psychiatric Disorders Applied Across Multiple Cohorts.*

Methods: The Psychiatric Genomics Consortium Working Groups for schizophrenia and major depressive disorder bring together many independently collected case-control cohorts. We used these resources (31,328 schizophrenia cases, 41,191 controls; 248,750 major depressive disorder cases, 563,184 controls) in repeated application of leave-one-cohort-out meta-analyses, each used to calculate and evaluate PGS in the left-out (target) cohort.

Ten PGS methods (the baseline PC+T method and 9 methods that model genetic architecture more formally: SBLUP, LDpred2-Inf, LDpred-funct, LDpred2, Lassosum, PRS-CS, PRS-CS-auto, SBayesR, MegaPRS) were compared.

Conclusions: Although the methods that more formally model genetic architecture have similar performance, . . .

Personal opinion: no UMP tests/methods for complex problems.

Reference – PRS ‘bad news’ (= more opportunities)

- ▶ Martin et al. (2019). *Nature Genetics*. Clinical use of current polygenic risk scores may exacerbate health disparities
- ▶ Mostafavi (2020). *eLIFE*. Variable prediction accuracy of polygenic scores within an ancestry group
- ▶ Gola et al. (2020). *Circulation: Genomic and Precision Medicine*. Population Bias in Polygenic Risk Prediction Models for Coronary Artery Disease.
- ▶ Wang et al. (2020). *Nature Communication*. Theoretical and empirical quantification of the accuracy of polygenic scores in ancestry divergent populations.
- ▶ Wand et al. (2021). *Nature*. Improving reporting standards for polygenic scores in risk prediction studies

Recap the goal of this lecture

- ▶ PRS is intuitive with a simple expression:

$$PRS_i = \sum_{j=1}^J \hat{\beta}_j G_{ij}$$

- ▶ But, there are many (answered or open) complex (methodological and practical) questions.
- ▶ Provide a topic-stratified reference list for self-study.

What's next?

Overview of the topics to be covered and learning goal: a deeper understanding of

1. PRS foundation: GWAS, h² and prediction

- ▶ the multiple hypothesis testing issue inherent in GWAS
- ▶ the (high) variability inherent in the h² estimates
- ▶ h² as a function of both genetic effect beta and MAF
- ▶ the 'genetic effect size' of a SNP as a function of beta and MAF
- ▶ a conceptual PRS construction based on the ground truth, PRS.oracle
- ▶ DIY ROC plotting and AUC calculation for a PRS-based prediction

2. PRS basic: PRS calculation and performance evaluation

- ▶ the complexity of constructing a good PRS even under the simplest setting without LD or any heterogeneities; 10 out 5000 independent SNPs are truly associated with the same effect size of 0.3 but varying MAFs.
- ▶ the trouble introduced by false positives, due to multiple hypothesis testing and low power.
- ▶ 'the more is not always better' statement: PRS based on 6 'genome-wide' significant SNPs vs. 66 SNPs significant at 0.01.
- ▶ the various over-fitting or selection biases, and winner's curse in beta estimates for both false positives and true positives.

Learning goal cont'd, a **deeper** understanding of

3. PRS basic-plus: some obvious or not so obvious follow-up Qs

- ▶ effects of sample size n and genetic effect beta on AUC: easy to answer.
- ▶ answers to these Qs are less obvious. If we decrease beta from 0.3 to 0.1 but increase the number of truly associated SNPs from 10 to 90:
h² and SNP h²? AUC in general? AUC between PRS.gw and PRS.01?

4. PRS heterogeneity and transportability

- ▶ first, why reference allele (genome build) matching is so consequential
- ▶ population heterogeneity
- ▶ locus heterogeneity

5. PRS LD consideration (TBA)

Ready for the ride? (Hopefully a fun one!)