Introduction to Genomic Prediction

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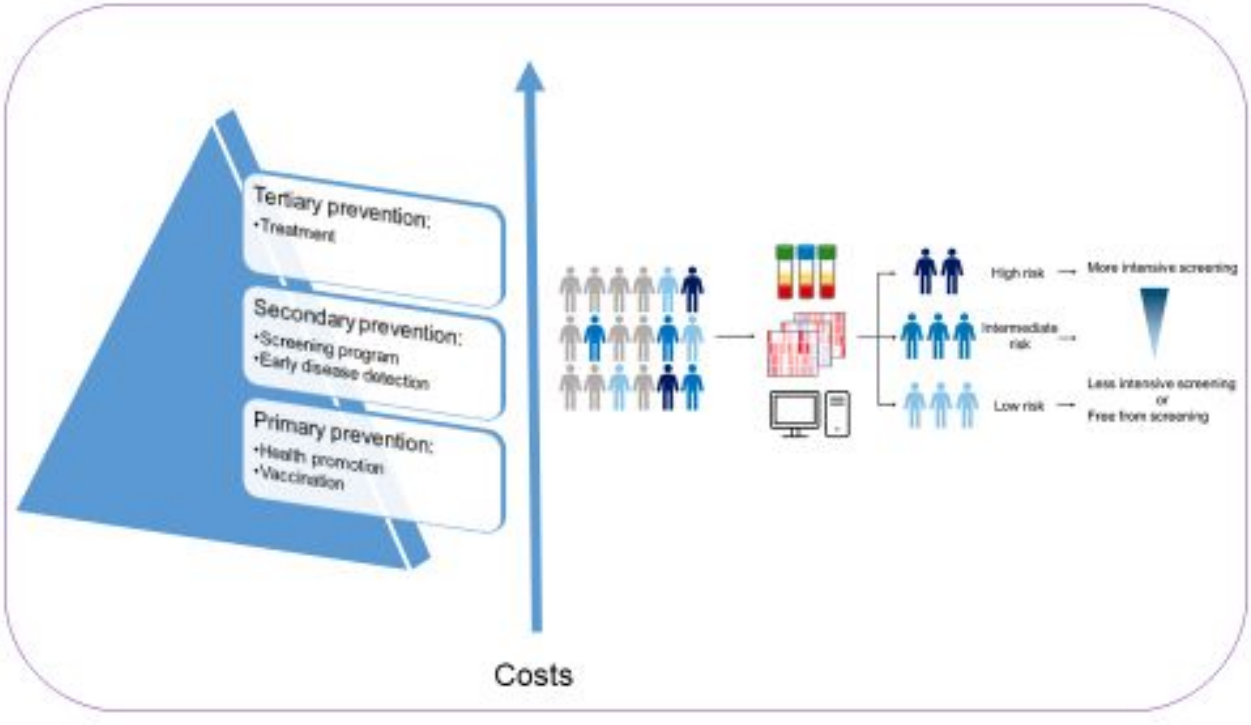
Topics

GP in human genetics	Polygenic risk scores	GP in animal and plant breeding	Comparison between PRS and GS
Background	Background	Overview	Overview
Particularities	PRS analysis process	Comparison of plant and animal breeding approaches	
GWAS in human genetics	Accuracy	Accuracy	
	Limitations		
	Other considerations		
	Examples		
	Resources		
	PRS applications		

Preventive strategies against disease

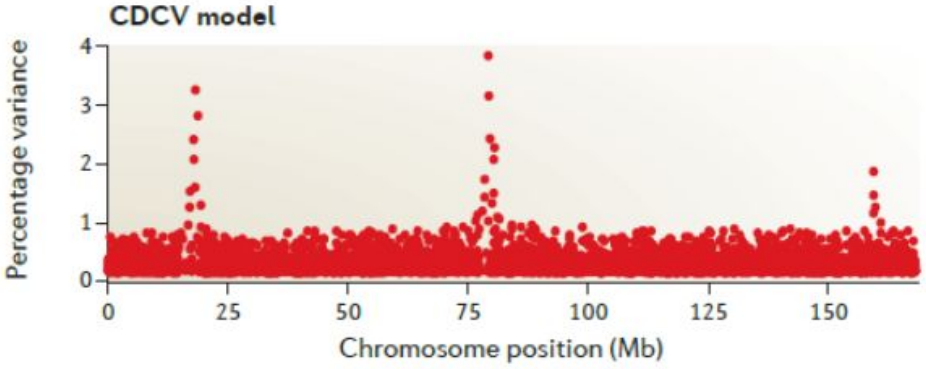


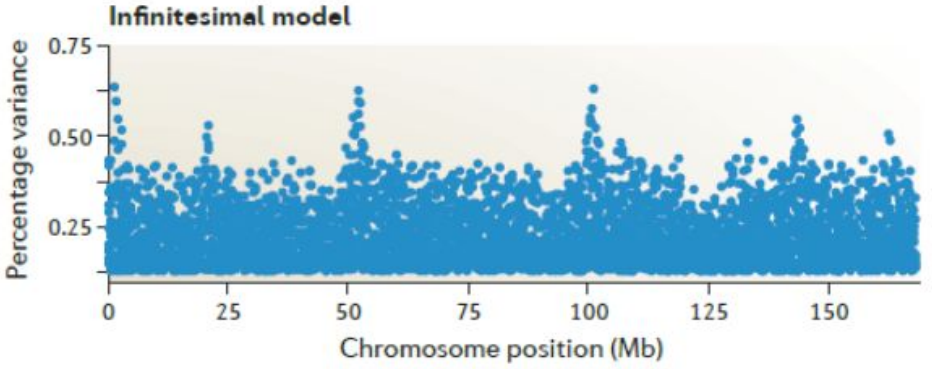
Genome-wide Prediction in Human Genetics

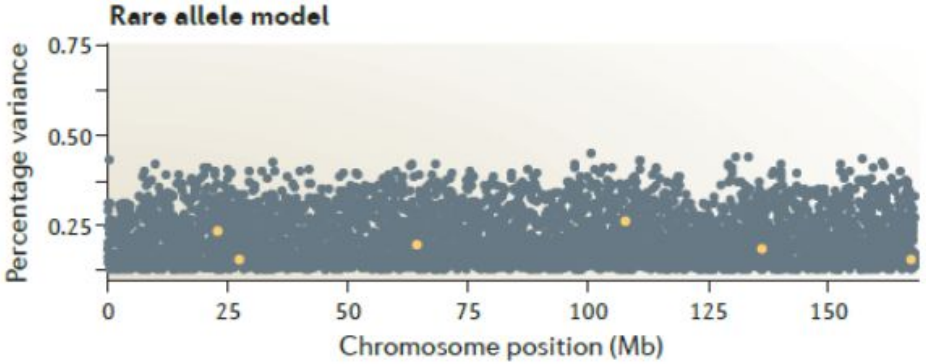
Prediction of disease risk is an essential part of preventative medicine, often guiding clinical management

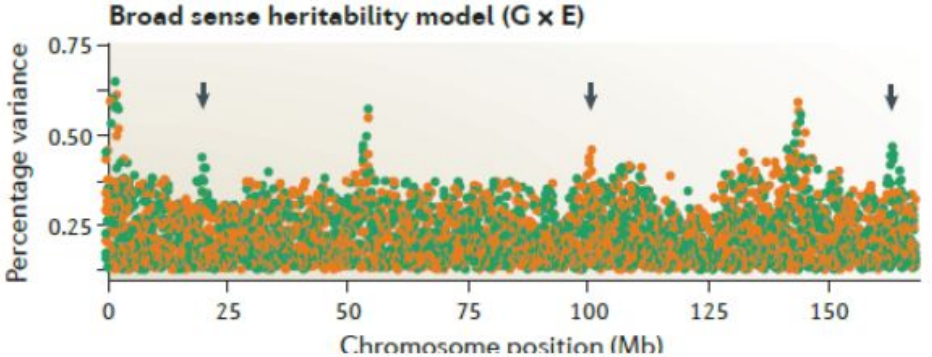
Improving effective medical treatment and preventative interventions needs to know how modifiable social, behavioural and physiological factors influence risk of disease (Abraham et al., 2016), as well as the non-modifiable factors:

- Non-genetic risk factors: age, sex, family history of disease, lifestyle factors (smoking status, alcohol consumption ...), comorbidities (e.g., diabetes)
- Genetic risk factors: the genetic basis for many human traits and diseases has been established as polygenic (contributions of many genes each of them contributing very little to the trait), in contrast to Mendelian diseases (caused by variation in one or few genes with large effect)









Gibson (2012). Nat Rev Genetics 13,135-145

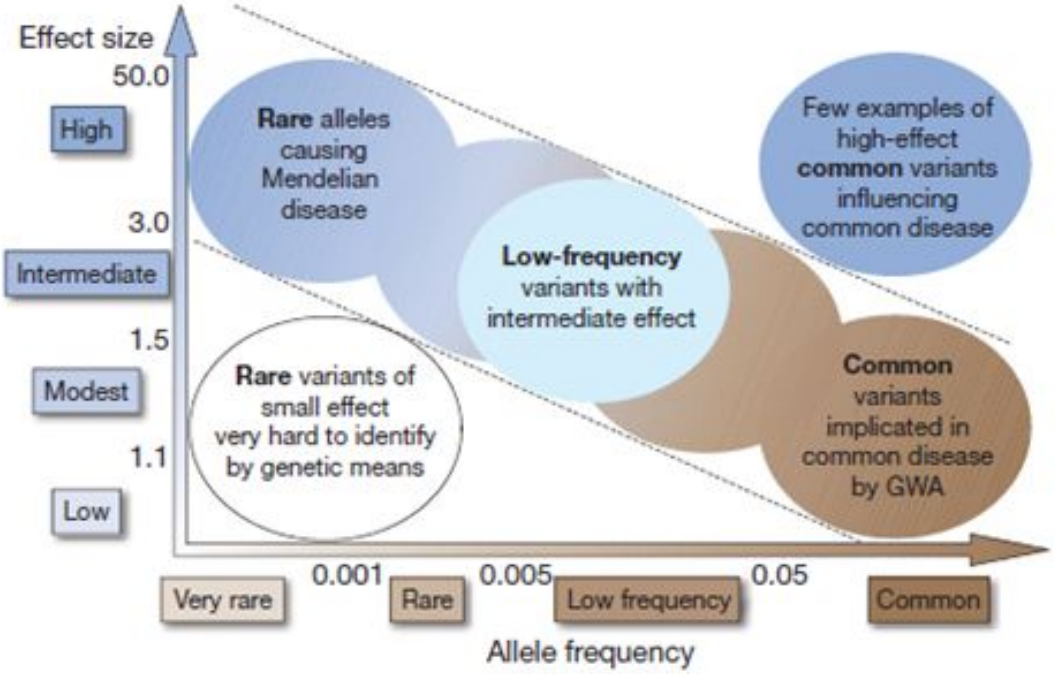
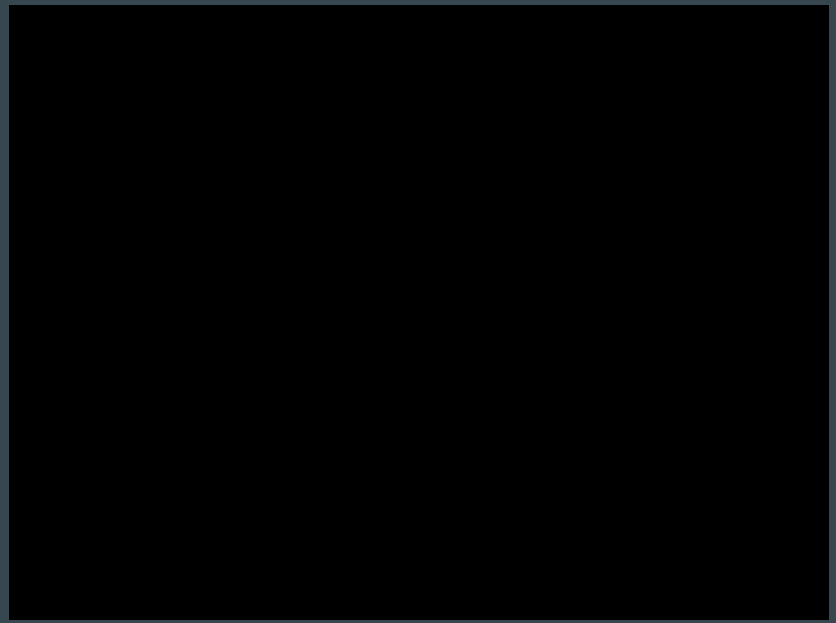


Figure 1 | Feasibility of identifying genetic variants by risk allele frequency and strength of genetic effect (odds ratio). Most emphasis and interest lies in identifying associations with characteristics shown within diagonal dotted lines. Adapted from ref. 42.

GWAS in Human Genetics

- Genome-wide association studies (GWAS) have identified many SNPs-trait associations
- GWAS catalog (https://www.ebi.ac.uk/gwas/home) contains a high-quality collection of all published (and since 2020 also unpublished) GWAS studies
- As of 2023-01-30, the GWAS Catalog contains 6245 publications, 471482 top associations and 55228 full summary statistics
- GWAS data are often made available only as summary statistics (Estimated Beta, *p*-value).

GWAS in Human Genetics



GWAS in Human Genetics

These GWAS SNP-trait associations have provided:

- insights into the genes and pathways that cause disease
- more recently the use of these data for disease risk prediction

Polygenic risk scores

Polygenic risk scores (PRS) (also referred as genomic risk scores) is a method to predict an individual's genetic predisposition for a given disease

It is a single value estimate of an individual's genetic liability to a phenotype

Simplest form:

$$PRS_i = \sum_{j=1}^{m} x_{ij}\hat{\beta}_j$$

Genotype for the *i* individual for the *j* SNP (allelic dosage of the minor or effect allele)

Estimated SNP effect (obtained from GWAS summary statistics)

The genotypes are typically those of common (minor allele frequency > 0.01) biallelic SNPs

Polygenic risk scores

PRS can be constructed from genome-wide significant SNPs ($p < 5x10^{-8}$):

Weakly predictive PRS when the set of GWAS hits is small

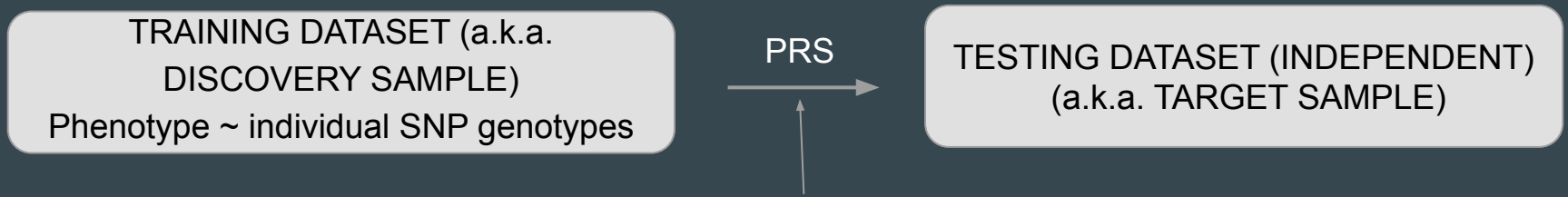
PRS with larger number of SNPs (e.g., ($p < 5x10^{-5}$)):

Large # of SNPs with increasingly less precise effect estimates

Small # of SNPs with a more precise effect estimates

Polygenic risk scores

Optimization of PRS:



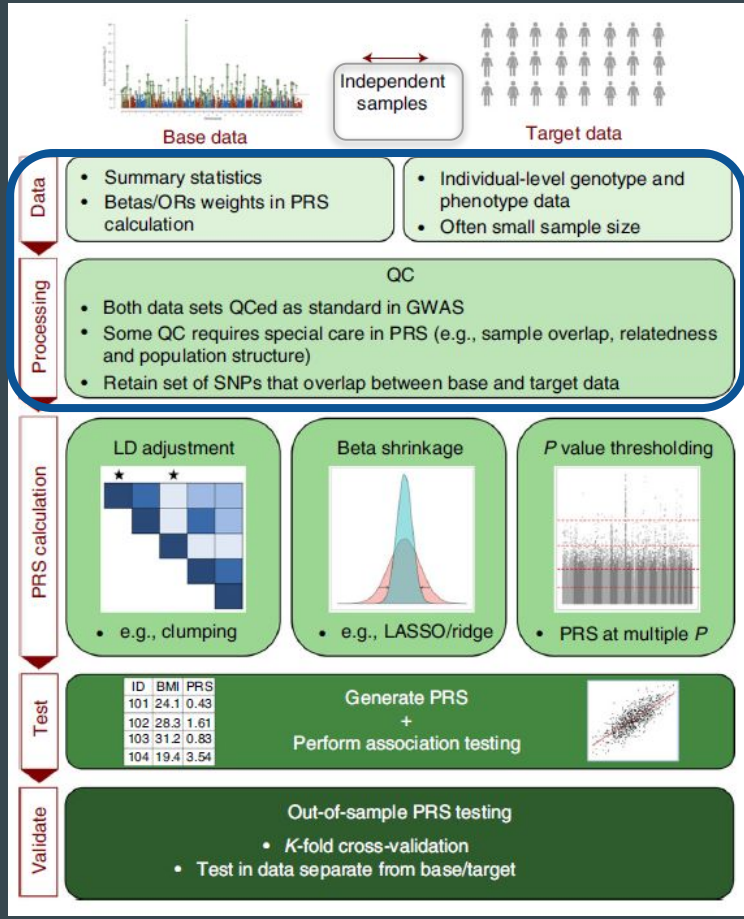
Accounting for LD:
LD pruning (remove one SNP from a pair in high LD)
LD cumpling (LD pruning + most significant SNPs)

Important: No overlap between training and testing datasets

PRS analysis process (https://choishingwan.github.io/PRS-Tutorial/base/)

Most powerful GWAS results available on the phenotype

- Important to check the effect allele:
  - Contact authors if not clear from the summary data
  - Ambiguous alleles (A/T, C/G): check MAF or discard them
  - Mismatching alleles: remove non-resolvable matching SNPs
- Target data with effective samples with >100 indiv
- Check if corrupted files
- Base and target data SNPs assigned to the same genome build
- Base and target data SNPs with good quality:
  - MAF, genotyping rate, HWE, heterozygosity, info



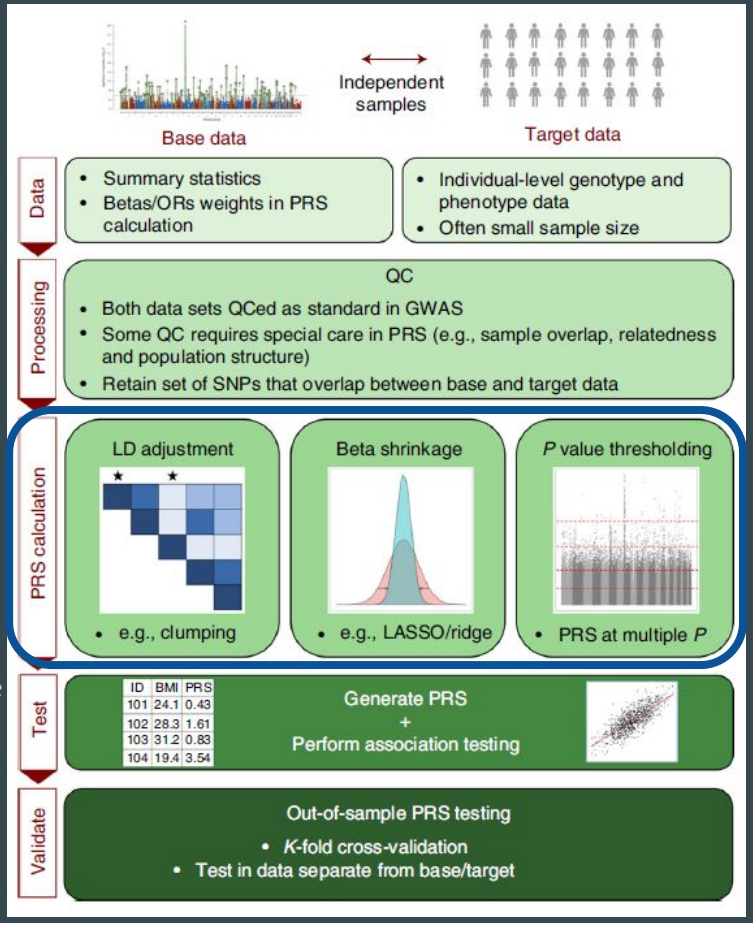
Choi et al, 2020

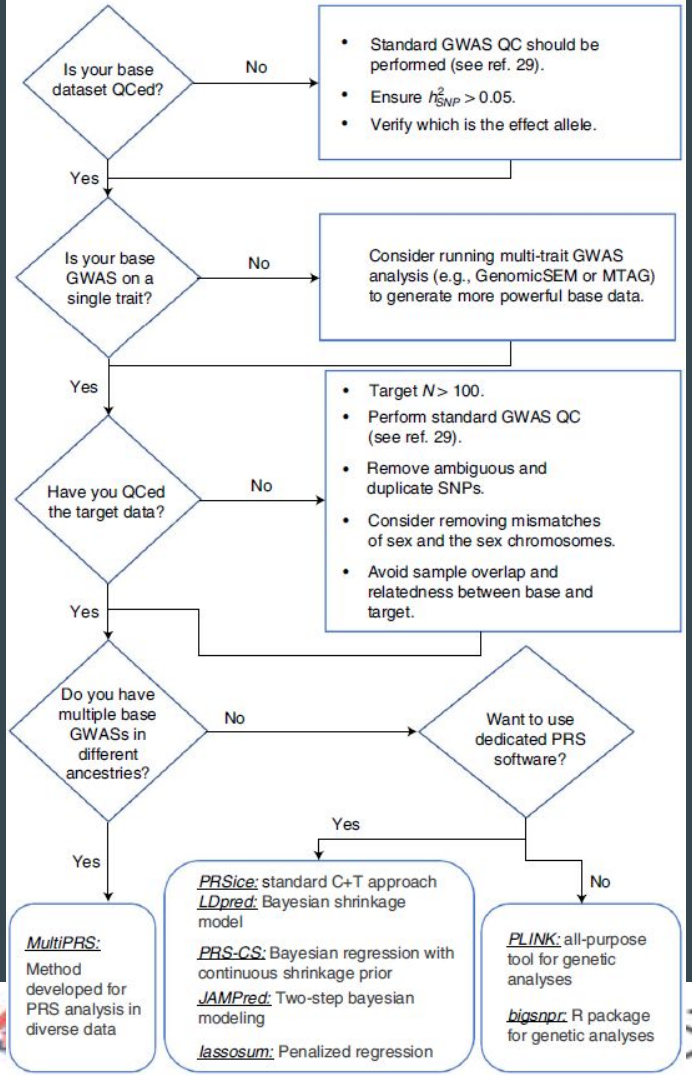
PRS analysis process (https://choishingwan.github.io/PRS-Tutorial/base/)

To calculate PRSs for all individuals in the base sample

Key factors in the development of methods for calculating PRSs:

1. Accounting for LD (if single SNP analysis was used):
   a. clumping (prioritization of SNPs in the locus based on their *p*-value)
   b. Inclusion of all SNPs accounting for LD among them
2. Potential adjustment of GWAS estimated effect sizes:
   a. shrinkage of the effect estimates of all SNPs via standard or tailored statistical techniques
   b. use of P value selection thresholds as inclusion criteria for SNPs into the score (Variable selection)
3. Tailoring of PRSs to target populations:
   a. standardization of the units
   b. Standardization (same scale)
   c. Transformation of the phenotype should be taken into account

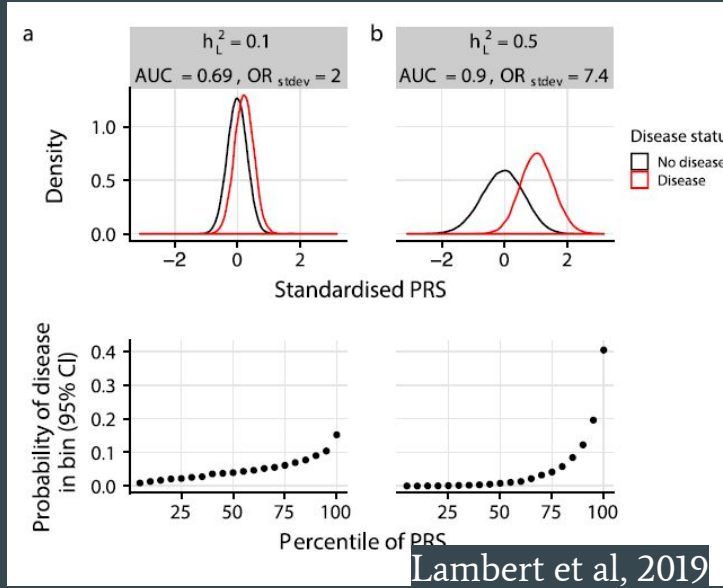




https://doi.org/10.1038/s41596-020-0353-1

Accuracy of PRS

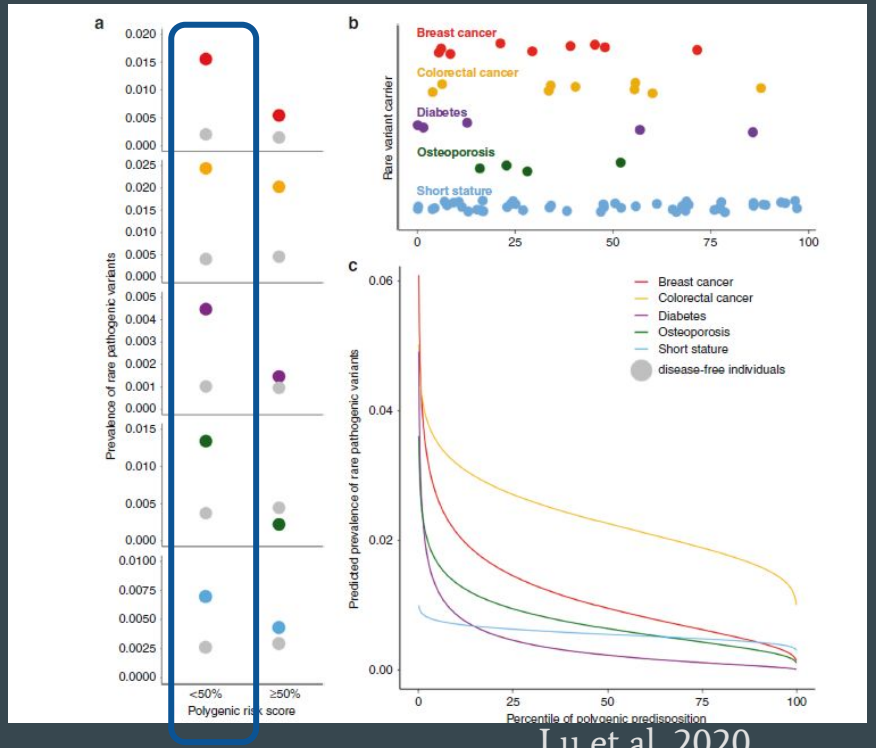
- Disease heritability ($h^2_{SNP} > 0.05$) :
  - Software to estimate h^2_{SNP} from GWAS sum stat:
    - LD score regression (Bullik-Sullivan, 2015)
    - SumHer (Speed and Balding, 2019)



Lambert et al, 2019

Accuracy of PRS

- Disease heritability
- Genetic architecture:
  - Rare genetic causes are more prevalent among patients with a low PRS
  - These patients may be prioritized for deep-depth sequencing of relevant genes



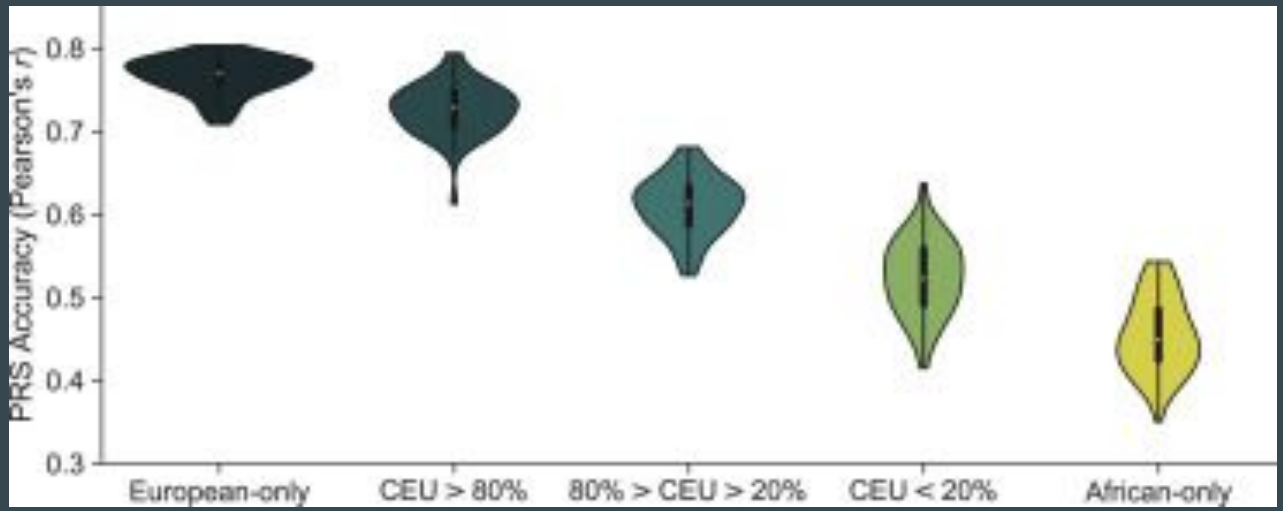
Lu et al, 2020

Accuracy of PRS

- Disease heritability and genetic architecture
- cor(PRS,PRS_estimated). It depends on:
  - Method used to construct the PRS
  - Sample size
- Update of PRSs:
  - GWASs expand in size
  - additional risk loci are identified
  - Alternative methods for score calculation
- Imputation variability in underrepresented populations → health disparities
- Different genetic background (one-third as informative for African ancestry individuals (Duncan et al, 2020)

Accuracy of PRS

Accuracy of PRSs, with variants and weights from a European GWAS, decreases linearly with increasing proportion of African ancestry



Cavazos and Witte, 2021

Polygenic Risk Scores - Limitations

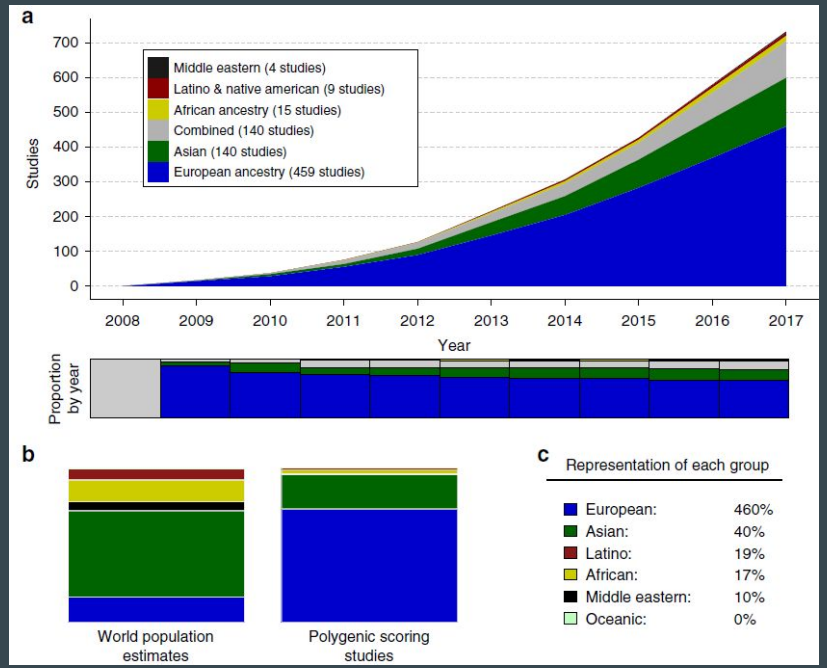
- Individualized PRS should be updated over time → Fluctuations in individual-level scores → may affect the application of PRSs in practice which relates to prioritization of preventative behaviors
- Sparse genotyping approaches (SNP arrays or low-pass WGS) → Need of imputing → Variability introduction at the individual level

Polygenic Risk Scores - Limitations

- Findings regarding genetic liability from resources such as UKBiobank or GWAS results may not be generalizable to individuals who are not of European descent:
  - Differences in variant frequencies
  - LD patterns artifactual differences due to uncorrected population stratification (Berg et al, 2019)

Polygenic Risk Scores - Limitations

Ancestry representation in the first decade of polygenic scoring studies (2008–2017; N = 733 studies)



Duncan et al, 2020

Polygenic Risk Scores - Limitations

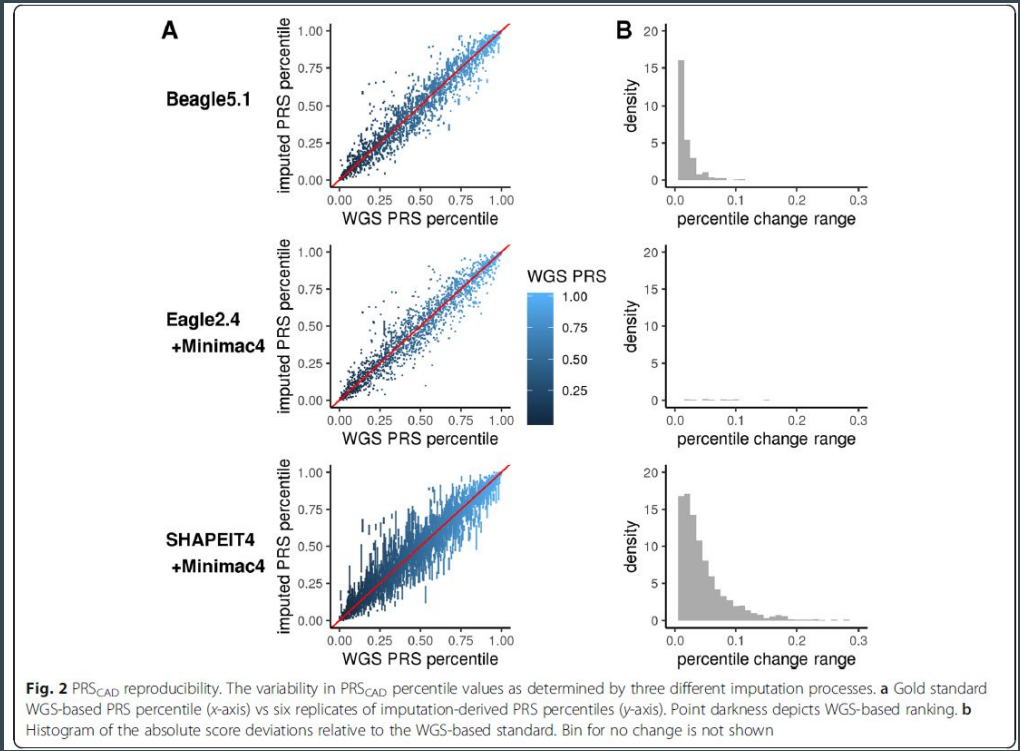


Fig. 2 PRS_{CAD} reproducibility. The variability in PRS_{CAD} percentile values as determined by three different imputation processes. **a** Gold standard WGS-based PRS percentile (*x*-axis) vs six replicates of imputation-derived PRS percentiles (*y*-axis). Point darkness depicts WGS-based ranking. **b** Histogram of the absolute score deviations relative to the WGS-based standard. Bin for no change is not shown

IMPUTATION:

- Pre-phasing step introduces the bulk of the stochasticity in imputation and PRS results
- SHAPEIT+Minimac leads to the most intra-individual variability, followed by Beagle and Eagle+Minimac
- This algorithm-level variability is observed regardless of the original approach used to derive the PRS and the number of SNPs included in the score

Chen et al, 2020

Polygenic Risk Scores - Limitations

- Variability of the PRS percentile is greatest in the middle of the distribution and lowest at the tails (Chen et al, 2020)
  Solution: deterministic imputation processes should be favored or stochastic imputation processes could be run multiple times in order to select the most common result

- Both the clumping and thresholding steps are arbitrary, and reporting the results from the P-value threshold that maximizes out-of-sample prediction in a single cohort is a form of Winner's curse (Wray et al, 2019)

- GWAS one-SNP-at-a-time regression may not the optimal way to estimate SNP effects for use in prediction (Wray et al, 2007):
  - Methods that fit all SNPs simultaneously usually generate more accurate out-of sample prediction than those fitting one SNP at a time

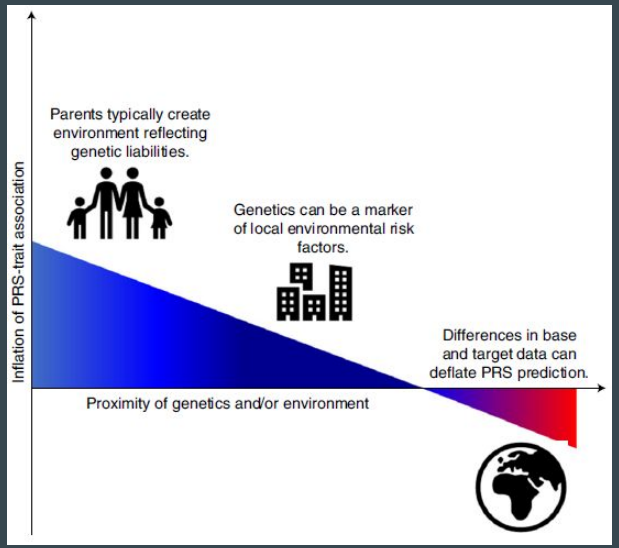
Chen et al, 2020

Polygenic Risk Scores - Other considerations

- Having relatives in the discovery sample will improve the prediction for an individual (Lee et al, 2017):
  - However, having first/second degree relatives may inflate the association between PRS and phenotype (target sample) → removal of those ind (Choi et al., 2020)
- Include Family History as predictor, because it captures genetic and not genetic factors not captured by PRS (Inouye et al, 2018)
  - PRS is an estimate of the aggregate genetic value of an individual, tracking only the genetic contribution to the trait tagged by common DNA polymorphisms.
  - Family history reflects the phenotypes of relatives of the individual.

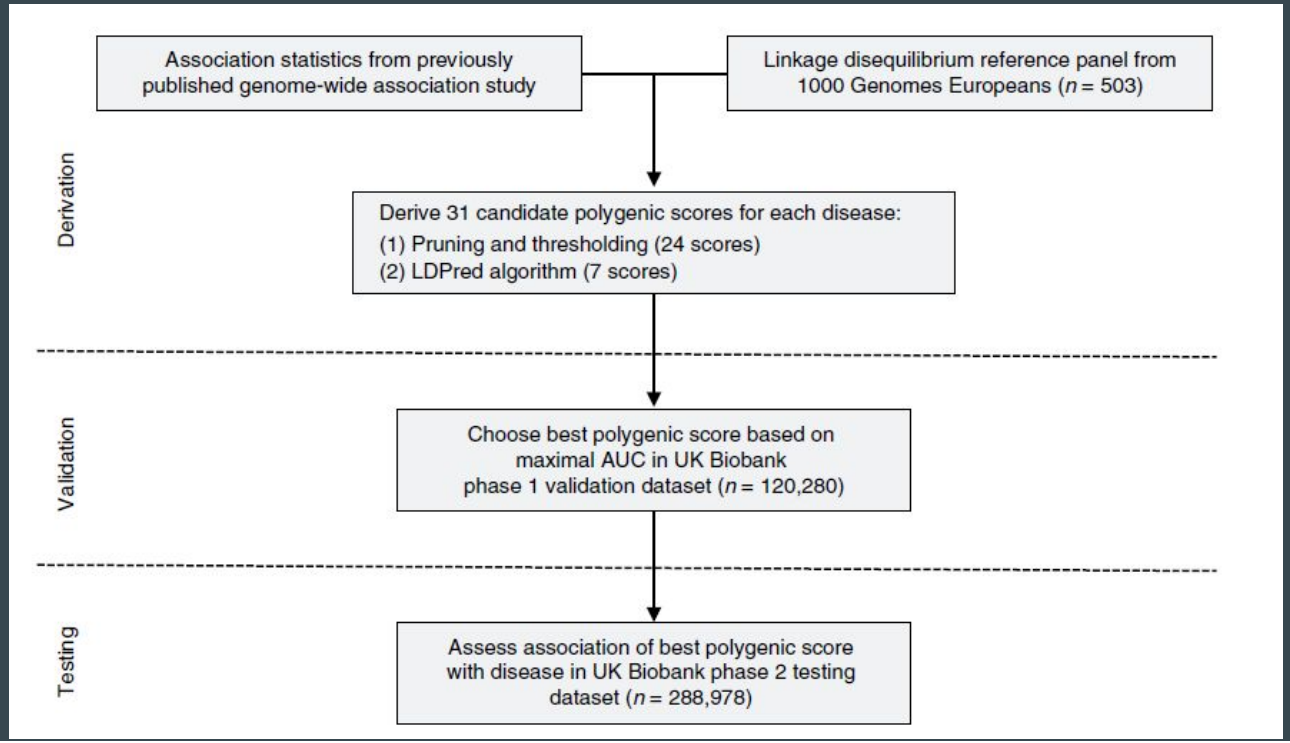
Polygenic Risk Scores - Other considerations

Major sources of inflation/deflation of PRS-trait associations



Choi et al, 2020

Polygenic Risk Scores - Examples



Khera et al, 2018

Polygenic Risk Scores - Examples

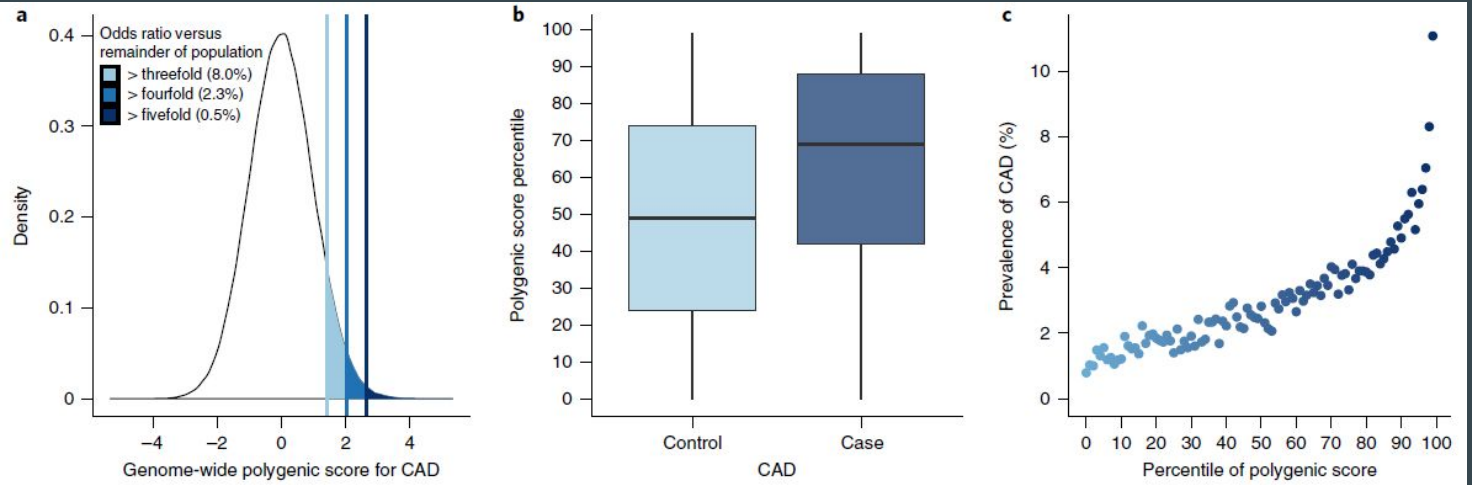


Fig. 2 | Risk for CAD according to GPS. a, Distribution of GPS_{CAD} in the UK Biobank testing dataset ($n = 288{,}978$). The *x* axis represents GPS_{CAD}, with values scaled to a mean of 0 and a standard deviation of 1 to facilitate interpretation. Shading reflects the proportion of the population with three-, four-, and fivefold increased risk versus the remainder of the population. The odds ratio was assessed in a logistic regression model adjusted for age, sex, genotyping array, and the first four principal components of ancestry. **b**, GPS_{CAD} percentile among CAD cases versus controls in the UK Biobank testing dataset. Within each boxplot, the horizontal lines reflect the median, the top and bottom of each box reflect the interquartile range, and the whiskers reflect the maximum and minimum values within each grouping. **c**, Prevalence of CAD according to 100 groups of the testing dataset binned according to the percentile of the GPS_{CAD}.

Khera et al, 2018

A

White non-Hispanic males

Absolute risk, %

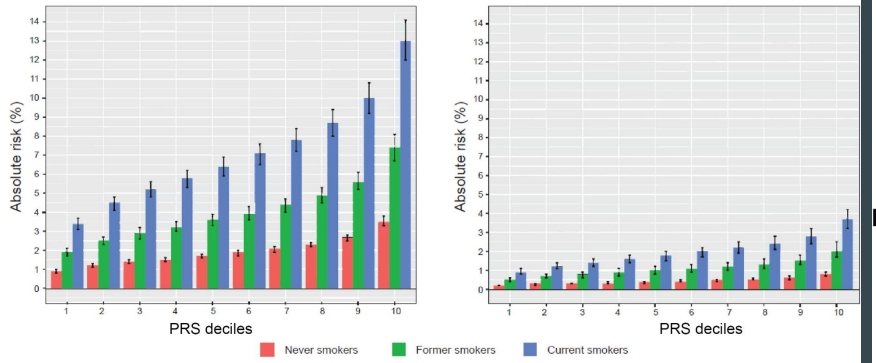
	Never smoker	Former smoker	Current smoker
	Average risk, 95% CI	Average risk, 95% CI	Average risk, 95% CI
Overall	1.9 (1.8, 2.0)	4.0 (3.7, 4.4)	7.1 (6.6, 7.7)
PRS, decile 1	0.9 (0.8, 1.0)	1.9 (1.7, 2.1)	3.4 (3.1, 3.7)
PRS, decile 2	1.2 (1.1, 1.3)	2.5 (2.3, 2.7)	4.5 (4.1, 4.8)
PRS, decile 3	1.4 (1.3, 1.5)	2.9 (2.6, 3.2)	5.2 (4.8, 5.6)
PRS, decile 4	1.5 (1.4, 1.6)	3.2 (3.0, 3.5)	5.8 (5.3, 6.2)
PRS, decile 5	1.7 (1.6, 1.8)	3.6 (3.3, 3.9)	6.4 (5.9, 6.9)
PRS, decile 6	1.9 (1.7, 2.0)	3.9 (3.6, 4.3)	7.1 (6.5, 7.6)
PRS, decile 7	2.1 (1.9, 2.2)	4.4 (4.0, 4.7)	7.8 (7.2, 8.4)
PRS, decile 8	2.3 (2.2, 2.4)	4.9 (4.5, 5.3)	8.7 (8.0, 9.4)
PRS, decile 9	2.7 (2.5, 2.8)	5.6 (5.2, 6.1)	10 (9.2, 10.8)
PRS, decile 10	3.5 (3.3, 3.8)	7.4 (6.7, 8.1)	13 (12.0, 14.1)
Top 5%	4.0 (3.7, 4.2)	8.3 (7.5, 9.1)	14.6 (13.4, 15.8)
Top 1%	5.0 (4.6, 5.4)	10.3 (9.4, 11.4)	18.0 (16.4, 19.8)

White non-Hispanic females

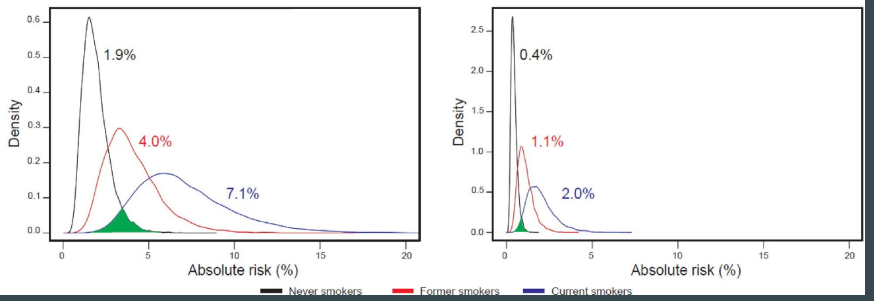
Absolute risk, %

	Never smoker	Former smoker	Current smoker
	Average risk, 95% CI	Average risk, 95% CI	Average risk, 95% CI
Overall	0.4 (0.4, 0.5)	1.1 (0.9, 1.3)	2.0 (1.7, 2.3)
PRS, decile 1	0.2 (0.2, 0.2)	0.5 (0.4, 0.6)	0.9 (0.8, 1.1)
PRS, decile 2	0.3 (0.2, 0.3)	0.7 (0.6, 0.8)	1.2 (1.1, 1.4)
PRS, decile 3	0.3 (0.3, 0.3)	0.8 (0.6, 0.9)	1.4 (1.2, 1.6)
PRS, decile 4	0.3 (0.3, 0.4)	0.9 (0.7, 1.1)	1.6 (1.4, 1.8)
PRS, decile 5	0.4 (0.3, 0.4)	1.0 (0.8, 1.2)	1.8 (1.5, 2.0)
PRS, decile 6	0.4 (0.4, 0.5)	1.1 (0.9, 1.3)	2.0 (1.7, 2.2)
PRS, decile 7	0.5 (0.4, 0.5)	1.2 (1.0, 1.4)	2.2 (1.9, 2.5)
PRS, decile 8	0.5 (0.5, 0.6)	1.3 (1.1, 1.6)	2.4 (2.1, 2.8)
PRS, decile 9	0.6 (0.5, 0.7)	1.5 (1.3, 1.8)	2.8 (2.4, 3.2)
PRS, decile 10	0.8 (0.7, 0.9)	2.0 (1.7, 2.5)	3.7 (3.2, 4.2)
Top 5%	0.9 (0.8, 1.0)	2.3 (1.9, 2.8)	4.2 (3.6, 4.8)
Top 1%	1.2 (1.0, 1.3)	2.9 (4.5, 6.0)	5.3 (4.5, 6.0)

B



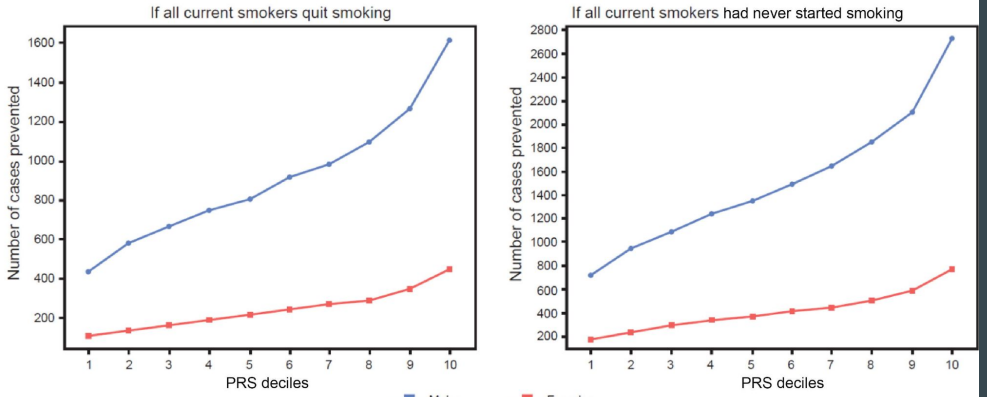
C



A

Population of 50-yr-old individuals	Males	Females
Resident population (census estimate, July 1, 2017), *n*	1 990 382	2 045 713
Non-Hispanic Whites (National Health Interview Survey 2015-2017), %	65.7	62.4
Resident population: non-Hispanic Whites, *n*	1 307 681	1 276 525
Never smokers, *n* (%) Average risk, % Number of cases	623 764 (47.7) 1.9 11 852	741 661 (58.3) 0.4 2,967
Former smokers, *n* (%) Average risk, % Number of cases	396 227 (30.3) 4.0 15 849	270 623 (21.2) 1.1 2,977
Current smokers, *n* (%) Average risk, % Number of cases	287 690 (22.0) 7.1 20 426	264 241 (20.7) 2.0 5,285

B



C

Decile	1	2	3	4	5	6	7	8	9	10
Males	431	576	662	748	805	921	978	1093	1266	1611
Females	106	132	159	185	212	237	264	290	344	450

Decile	1	2	3	4	5	6	7	8	9	10
Males	719	950	1093	1237	1352	1496	1640	1841	2100	2733
Females	185	238	291	344	370	422	449	502	581	767

Koutros*, ..., López de Maturana* et al, 2023

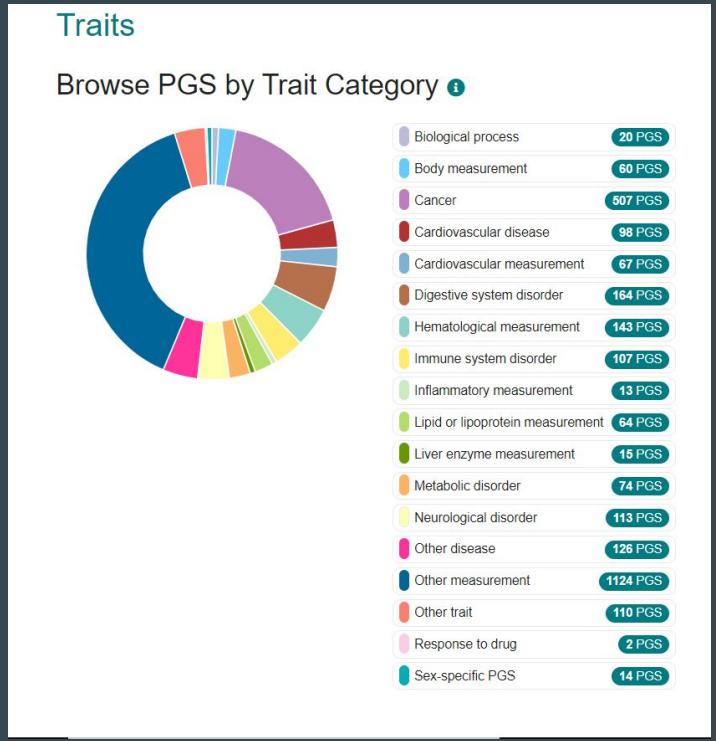
Genome-wide prediction

Polygenic Risk Scores - Resources

An open database of polygenic scores and the relevant metadata

- PGS Catalog - The Polygenic Score Catalog

- https://pgsc-calc.readthedocs.io/en/latest/



Polygenic Risk Scores - Resources

- An atlas of polygenic burden associations across the human phenome
  - A resource to unravel the causal determinants of complex disease from an analysis of 162 PRS and 551 complex traits (Richardson et al, 2020)
  - PRS constructed with GWAS hits considering a more lenient threshold ($p<10^{-5}$) may improve detection rates for causal relationships (phenome wide association studies)

Polygenic Risk Scores - Resources

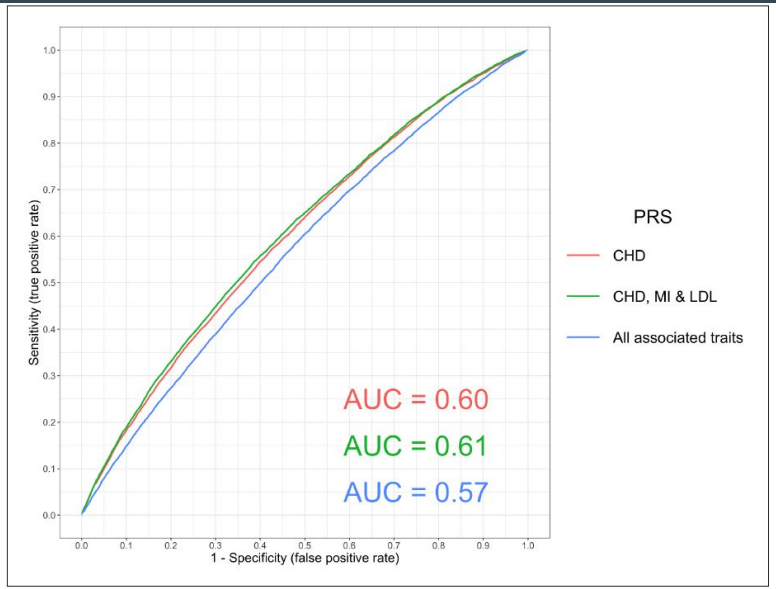


Figure 2. A receiver operator curve for ischaemic heart disease polygenic prediction. A receiver operating characteristic (ROC) curve to compare the sensitivity and specificity of polygenic risk scores (PRS) and individuals with ischaemic heart disease (defined using ICD 10 codes 'I25') in the UK Biobank study. The scores evaluated were 1. Coronary Heart Disease (CHD), 2. A combined scored of CHD, Myocardial Infarction (MI) and Low Density Lipoprotein cholesterol (LDL), 3. All traits with a p-value<1×10^{-06} in our PRS analysis (excluding scores from GWAS overlapping with the UK Biobank sample). These were CHD, MI, LDL, Total cholesterol, Triglycerides, High Density Lipoprotein cholesterol, Years of schooling, Height and Waist Circumference. All PRS were constructed from GWAS using independent SNPs with p<5×10^{-05}.

DOI: https://doi.org/10.7554/eLife.43657.004

(Richardson et al, 2020)

Polygenic Risk Scores - Resources

Polygenic Risk Score software for calculating, applying, evaluating and plotting the results of polygenic risk scores (PRS) analyses (https://choishingwan.github.io/PRS-Tutorial/cal_prs/)

- Different methods (PLINK, PRSice-2, LDPred-2 and lassosum) with tutorials
- It handles both genotyped and imputed data
- it provides empirical association P-values free from inflation due to overfitting
- It supports different inheritance models
- it can evaluate multiple continuous and binary target traits simultaneously

PRS applications

PRS likely to be used in the near future due to:

- data sharing restrictions to individual-level data;
- heterogeneity across cohorts
- the largest sources of individual-level data—population cohorts, such as the UK Biobank—generally have relatively few individuals with specific diseases compared to dedicated case/control studies, for which there is typically only summary statistic data

Genome-wide Prediction in Animal and Plant breeding

Quantitative genetics is a cornerstone of both plant and animal breeding for the last century

Genomic selection has led to the re-emergence of quantitative genetics as a framework for incorporating marker and sequence information to supplement and complement standard phenotypic descriptors and pedigree information (Hickey et al 2017)

Access to large-scale sequence and phenotypic information would provide opportunities to unify breeding methods and tools across several plant and animal species → Modernization of breeding programs (Hickey et al 2017)

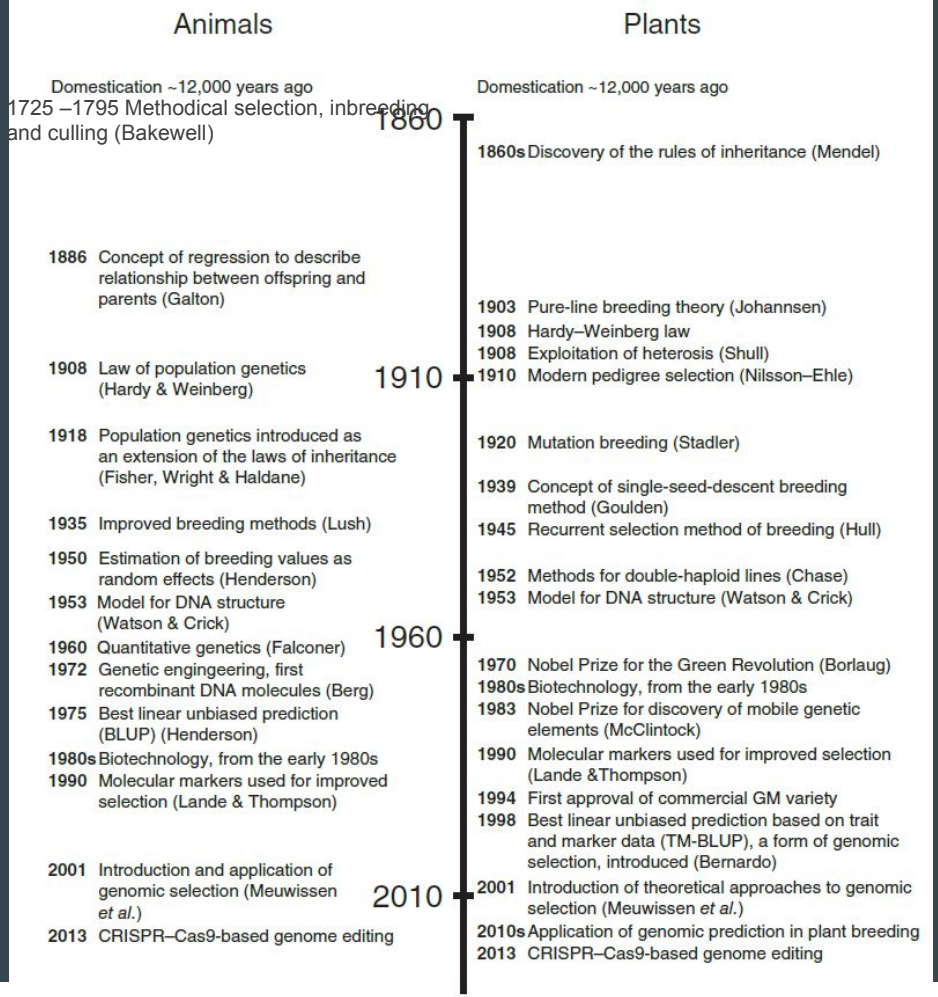


Figure 1 Some key milestones of selective animal and plant breeding.

(Hickey et al 2017)

Differences in plant and animal breeding

Although there are conceptual similarities between animal and plant breeding, breeding methods have diverged:

- Species specific characteristics: reproduction mode, # of progeny per cycle ...
- Plants: breeding since domestication; consisted mainly in selection (need for hybridization recognized in the last 250 years (Kingsbury, 2009))
- Animals: a more structured approach adopted earlier than in plants (Bakewell, 18 century → herdbooks)

Although both plant and animal breeders deal with complex traits, individual mutations with moderate to large effects have been exploited more importantly in plant breeding than in animal breeding (Hickey et al, 2017)

Differences in plant and animal breeding

Other differences:

- Plant breeders used well-designed trials to measure phenotype to inform their selection, and animal breeders use complex statistical methods to estimate breeding value
- Animal breeders use information from the relatives of selection candidates (milk yield in bulls), with low heritability or measured late in the breeding process (longevity); Plant breeders don't have the problem of 'sex-limited' traits and could increase the accuracy growing more plants from the same cultivar

Genomic selection in plant and animal species

GS was adopted rapidly in the more technologically developed livestock sectors (dairy cattle)

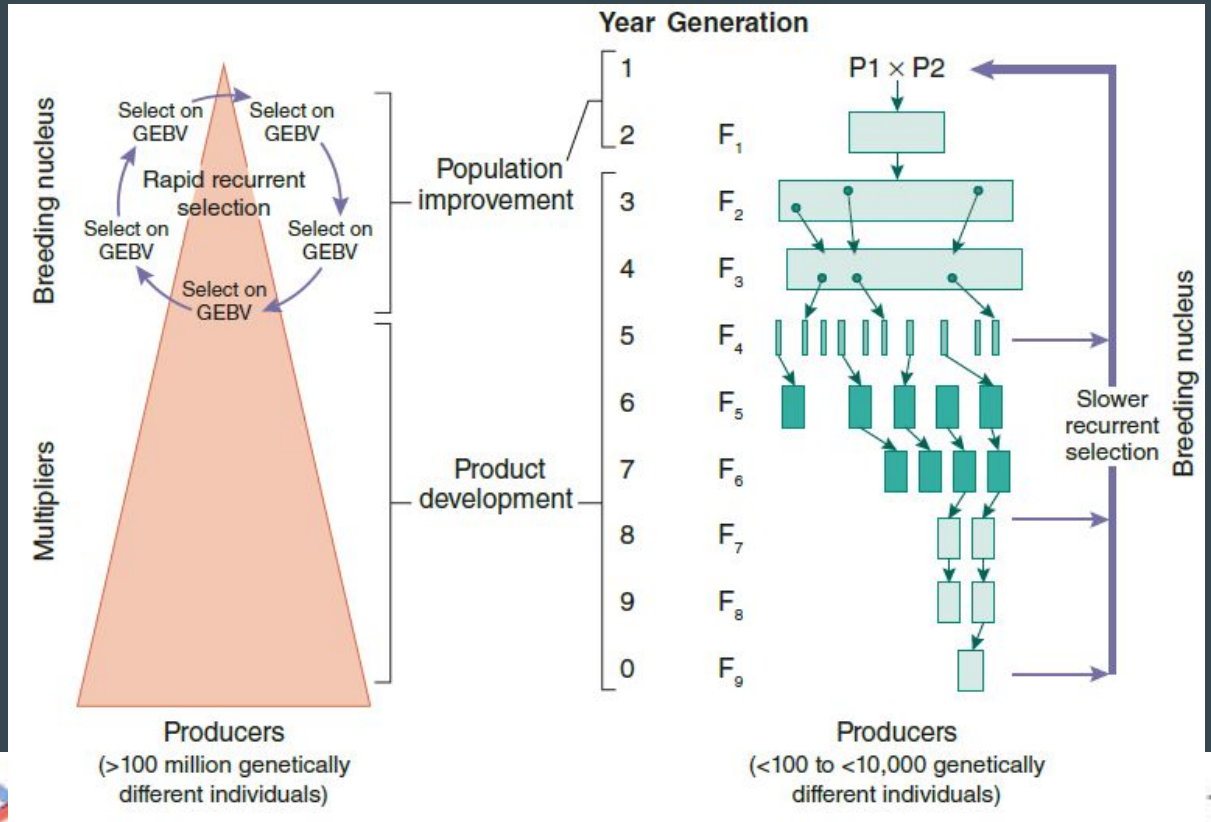
Major international seed companies are routinely using genomic selection

Many public-sector breeding programs are exploring this technology

Bottleneck:

- Computational and recording infrastructure
- Genotypic and phenotypic data to implement GS
- Complexity of genomes of many plant species

Comparison of plant (inbreeding cereal) and animal breeding approaches

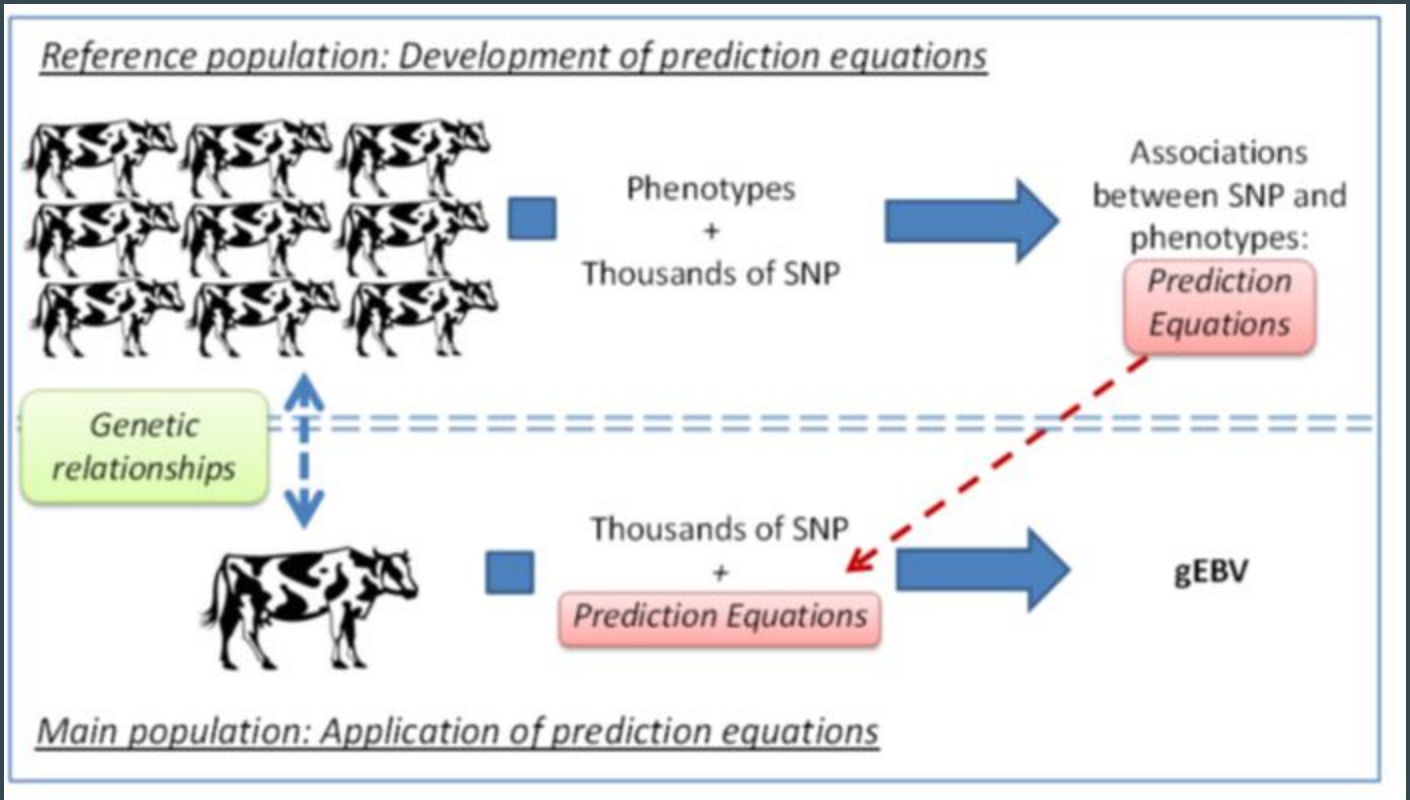


Hickey et al, 2017

Joining efforts between animal and plant breeders

Plant and animal breeders will benefit from working together to address problems that are common to the two disciplines, such as prediction of traits in structured populations (Schön and Simianer, 2015)

Examples of GS in animal and plant breeding



Groen Kennisnet (2017), Textbook animal breeding and genetics

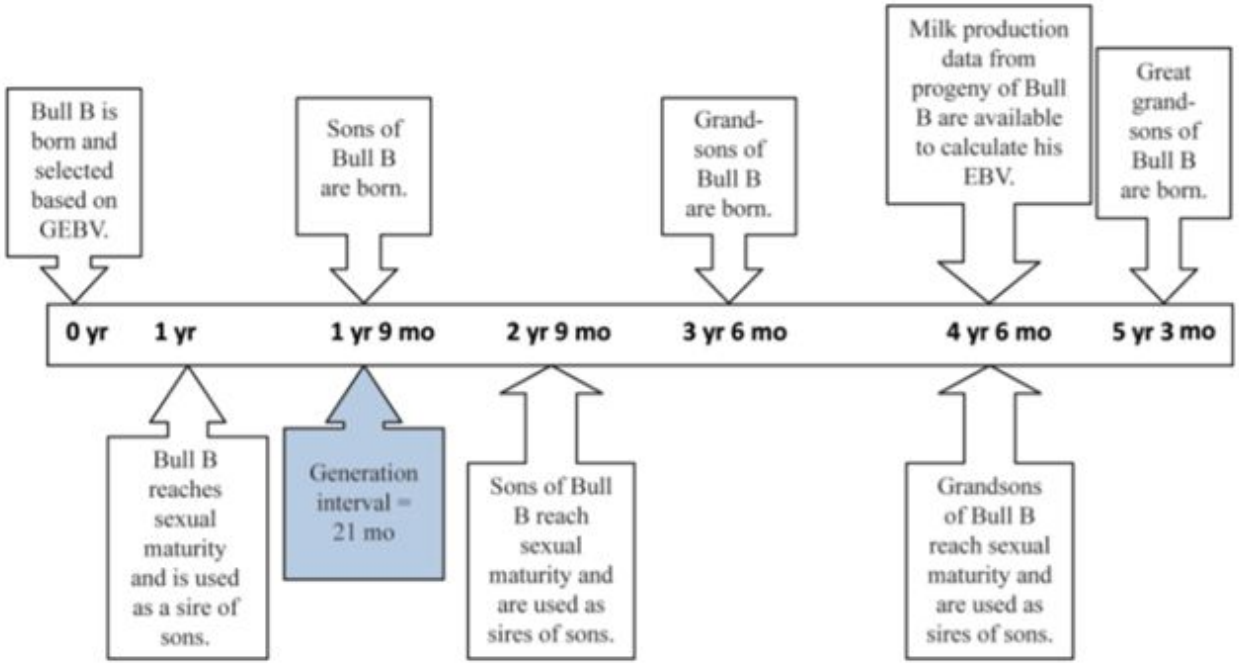
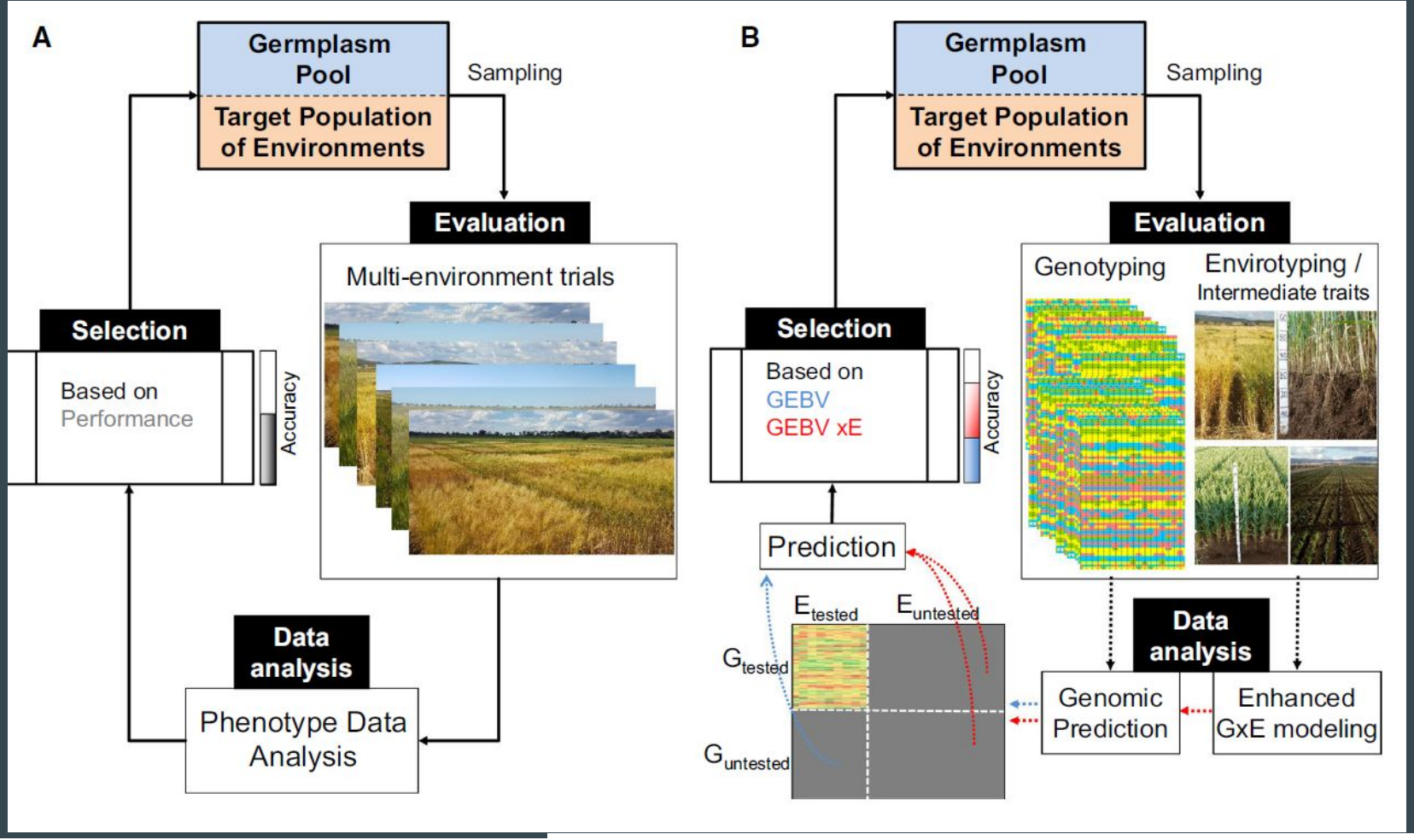


Figure 2. Timeline of an aggressive artificial insemination breeding program based on the use of genomic bulls as sires of sons. GEBV = genomic estimated breeding value; EBV = estimated breeding value.

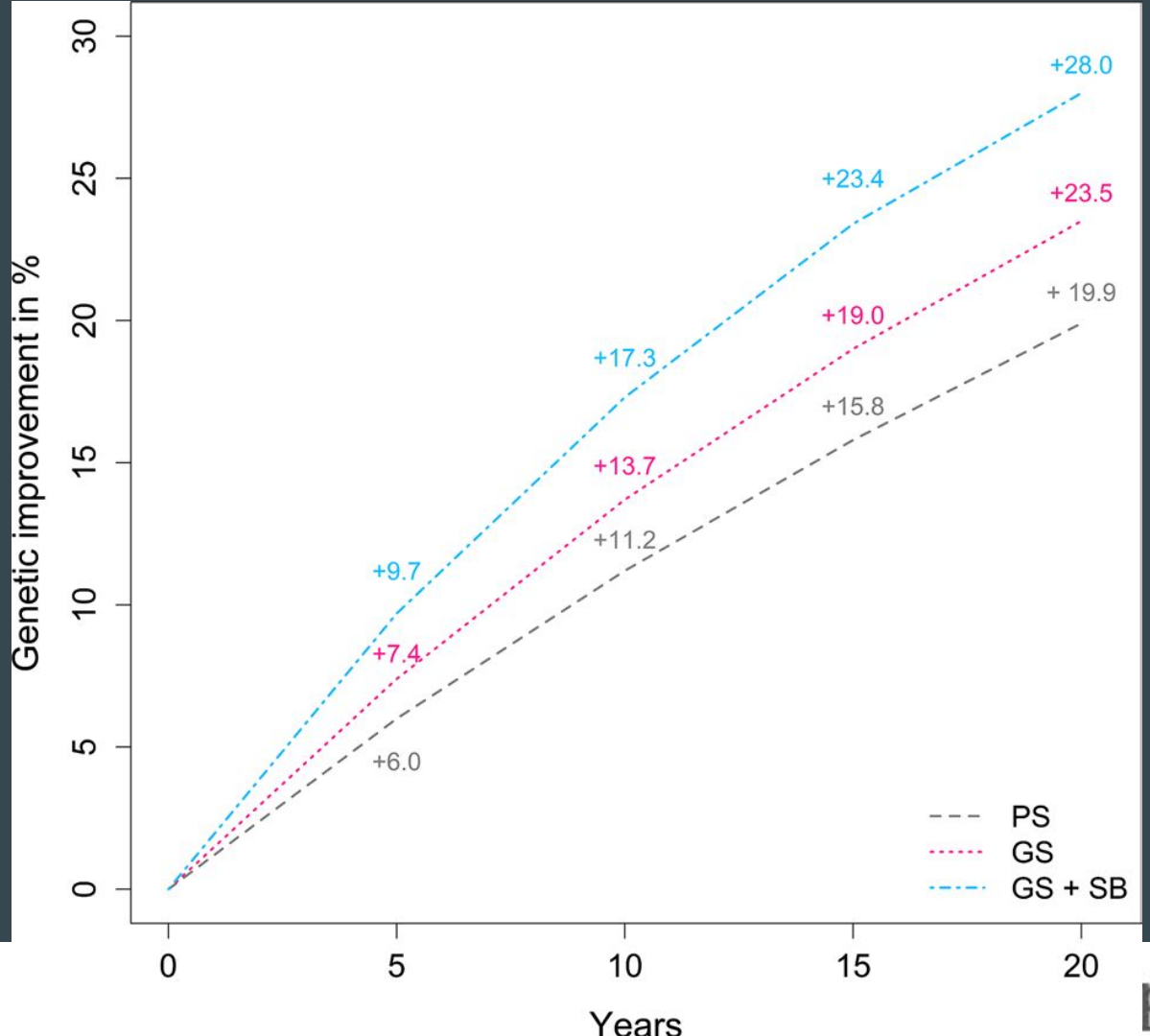
Animal **Frontiers**

Schefers and Weigel 2012, Vol. 2, No. 1

Genome-wide prediction



Voss-Fels et al, 2019 (https://doi.org/10.1007/s00122-018-3270-8)



PS: phenotypic selection

GS: genomic selection

SB: Speed breeding

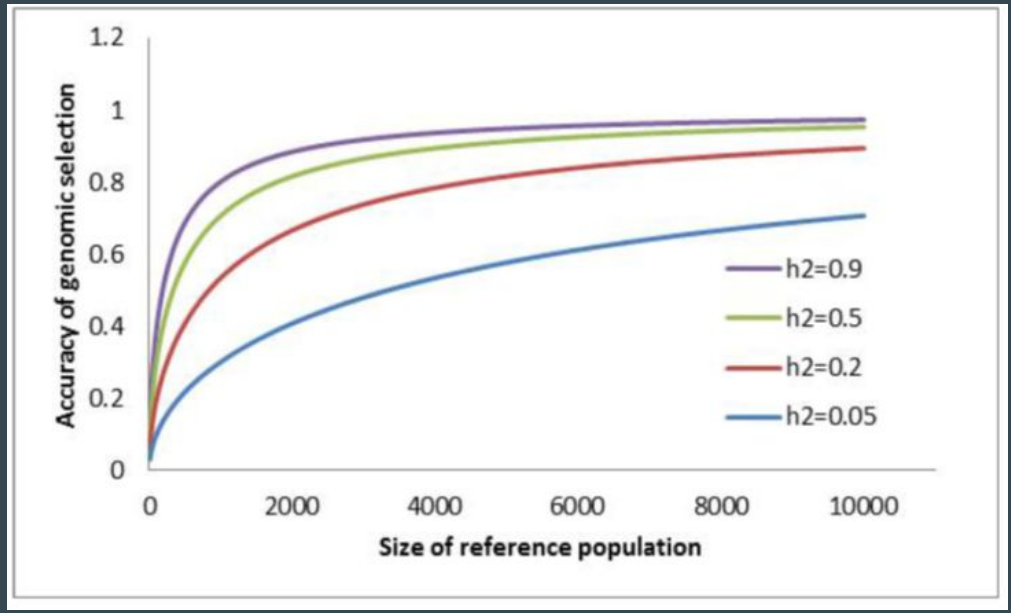
Voss-Fels et al, 2019

Accuracy of Genomic predictions

- Quality of phenotypes in the training population
- Size of reference population
- Reference population must be updated (Poldich et al, 2004)
- Training and testing should be closely related

$$\sqrt{Nh^2/(Nh^2+M_e)}$$ Daetwyler et al, 2008

$$M_e = 2N_eL$$ Hayes et al, 2009b



Groen Kennisnet (2017), Textbook animal breeding and genetics

Similarities and differences in performance of PRS and GS

Both PRS and GEBV are estimates of the additive genetic value of a trait of an individual (Wray et al, 2019)

Higher proportion of genetic variance explained by SNPs in livestock than in humans is due to the greater LD in livestock

SNP-based heritability estimates in humans are lower than those in animal, due to differences in recent effective sample size:

- In animals, common SNPs tag causal variants at much greater physical distance, compared to in humans, and including across chromosomes

Similarities and differences in performance of PRS and GS

* Different in purpose:

- PRS: predict the future phenotype of an individual (efficacy depends on the SNP h2)
- GEBV: predict the average value of an animal's genetic material to its offspring

The use of summary statistic data for the genotype effect size estimates distinguishes PRS from phenotypic prediction approaches that exploit individual-level data only

In the latter, genotype effect sizes are usually estimated in joint models of multiple variants and prediction performed simultaneously, using approaches such as best linear unbiased prediction or (LASSO)

Similarities and differences in performance of PRS and GS

* Effect sizes estimation:

- PRS: usually, one SNPs at a time
- GEBV: all SNPS jointly fitted

Topics

GP in human genetics	Polygenic risk scores	GP in animal and plant breeding	Comparison between PRS and GS
Background	Background	Overview	Overview
Particularities	PRS analysis process	Comparison of plant and animal breeding approaches	
GWAS in human genetics	Accuracy	Accuracy	
	Limitations		
	Other considerations		
	Examples		
	Resources		
	PRS applications		