

**A**

$Y$	$X_1$	...	$X_p$
-1	0	...	1
-2	2	...	1
.			
.			
.			
.			
3	1	...	2

Full Individual-level Dataset ( $N$ )

$$(\mathbf{X}^{(tr)}, \mathbf{Y}^{(tr)})$$

Training Dataset (60%)

$$(\mathbf{X}^{(tn)}, \mathbf{Y}^{(tn)})$$

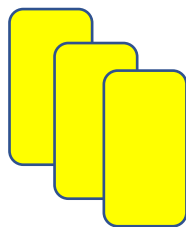
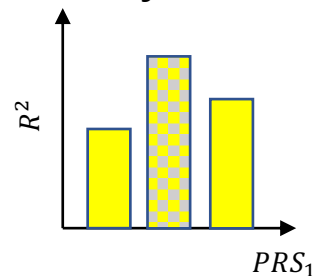
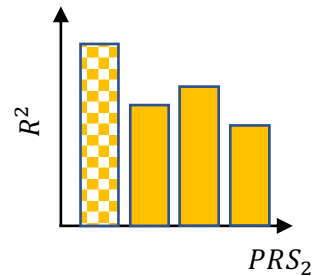
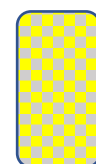
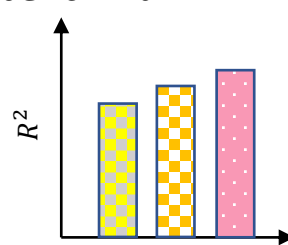
Tuning Dataset (20%)

$$(\mathbf{X}^{(etr)}, \mathbf{Y}^{(etr)})$$

Ensemble Training Dataset (10%)

$$(\mathbf{X}^{(t)}, \mathbf{Y}^{(t)})$$

Testing Dataset (10%)

Conduct GWAS  
and train PRS  
modelsCalculate PRS  
and  $R^2$  and pick  
the best modelsLearn  $\alpha$  via  
multiple linear  
regressionCompute and  
benchmark all  
PRS models**1. PRS training**3 models in  
PRS method 14 models in  
PRS method 2**2. PRS fine-tuning** $PRS_1$  $PRS_2$ **3. Ensemble PRS training**Ensemble  
PRS $= \hat{\alpha}_1$ Fine-tuned  
 $PRS_1$  $+ \hat{\alpha}_2$ Fine-tuned  
 $PRS_2$ **4. PRS benchmark**

Optimized PRSs

**B**Train PRS  
modelsUse SS-based  
 $R^2$  to pick the  
best modelsUse SS-based  
regression to  
learn  $\alpha$ Use SS-based  $R^2$   
to benchmark  
PRS models

$$\mathbf{X}^{(tr)T} \mathbf{Y}^{(tr)}$$

Training SS (60%)

$$\mathbf{X}^{(tn)T} \mathbf{Y}^{(tn)}$$

Tuning SS (20%)

$$\mathbf{X}^{(etr)T} \mathbf{Y}^{(etr)}$$

Ensemble Training SS (10%)

$$\mathbf{X}^{(t)T} \mathbf{Y}^{(t)}$$

Testing SS (10%)

*PUMAS*

SNP	A1	A2	$\hat{\beta}$	P
rsxxx	A	C	0.005	0.1
.				
.				
.				
rsxxx	G	T	-0.01	0.002

Full GWAS Summary  
Statistics ( $N$ )