

Supplementary Materials for “A penalized regression framework for building polygenic risk models based on summary statistics from genome-wide association studies and incorporating external information”

### S.1 Summary Lasso incorporating multiple traits

Consider  $Q$  quantitative traits, each of which has  $n_q$  subjects in GWAS. All studies are assumed to share the same set of  $M$  SNPs. For the  $q^{th}$  trait, let  $\mathbf{Y}_q = (y_{q1}, \dots, y_{qn_q})$  be the phenotypic values and  $\mathbf{X}_q = (x_{qij})$  for  $n_q$  subjects. Let  $\boldsymbol{\beta}_q = (\beta_{q1}, \dots, \beta_{qM})$  be the coefficients for  $M$  SNPs for trait  $q$ . Let  $\mathbf{B} = (\boldsymbol{\beta}_1, \dots, \boldsymbol{\beta}_Q)'$  be the coefficient matrix for all traits. We propose to obtain a sparse PRS by solving the following penalized least squares problem:

$$\sum_{q=1}^Q \frac{1}{2n_q} \|\mathbf{Y}_q - \mathbf{X}_q \boldsymbol{\beta}_q\|_2^2 + \sum_{q=1}^Q \sum_{j=1}^M \lambda_1 |\beta_{qj}| + \sum_{j=1}^M \lambda_2 \log \left( \sum_{q=1}^Q |\beta_{qj}| + \tau \right), \quad (1)$$

where  $\lambda_1 (> 0)$ ,  $\lambda_2 (> 0)$  and  $\tau (> 0)$  are tuning parameters.

The solution to (1) can be obtained by applying a local linear approximation (LLA) and the coordinate descent algorithm. Let  $\mathbf{B}^{(t)} = (\hat{\beta}_{qj}^{(t)})$  denote the estimate at the  $t^{th}$  iteration and

$P_{(\theta=(\lambda_2, \tau))}(\sum_{q=1}^Q |\beta_{qj}|) = \lambda_2 \log(\sum_{q=1}^Q |\beta_{qj}| + \tau)$ . We apply LLA to the log penalty function:

$$P_{(\lambda_2, \tau)}(\sum_{q=1}^Q |\beta_{qj}|) \approx P_{(\lambda_2, \tau)}(\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}|) + \sum_{q=1}^Q \frac{\partial P_{(\lambda_2, \tau)}(\sum_{q=1}^Q |\beta_{qj}|)}{\partial |\beta_{qj}|} \Big|_{|\beta_{qj}|=|\hat{\beta}_{qj}^{(t)}|} (|\beta_{qj}| - |\hat{\beta}_{qj}^{(t)}|) = \sum_{q=1}^Q \frac{\lambda_2 |\beta_{qj}|}{\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}| + \tau} + \text{Constant}.$$

The objective function (1) becomes

$$U_1(\mathbf{B}|\mathbf{B}^{(t)}) = \sum_{q=1}^Q \frac{1}{2n_q} \|\mathbf{Y}_q - \mathbf{X}_q \boldsymbol{\beta}_q\|_2^2 + \sum_{q=1}^Q \sum_{j=1}^M \left( \lambda_1 + \frac{\lambda_2}{\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}| + \tau} \right) |\beta_{qj}|.$$

We update the estimate at the  $(t + 1)^{th}$  iteration by letting  $\frac{\partial}{\partial \beta_{qj}} U_1(\mathbf{B}|\mathbf{B}^{(t)}) = 0$ . Since the penalty is in linear form for  $\beta_{qj}$ , it can be solved by the same coordinate descent algorithm designed for the standard Lasso problem, where the standard Lasso tuning parameter  $\lambda$  is replaced by  $(\lambda_1 + \frac{\lambda_2}{\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}| + \tau})$ .

## S.2 SummaryLasso incorporating functional annotations and pleiotropic information

Assume that the GWAS of the  $q^{th}$  trait has  $n_q$  subjects and there exists  $r$  functional annotation categories, we now derive regularized estimates of effect sizes of SNPs for SummaryLasso incorporating functional annotations and pleiotropic information by minimizing the following cost function using a similar coordinate descent algorithm:

$$\sum_{q=1}^Q \frac{1}{2n_q} \|\mathbf{Y}_q - \mathbf{X}_q \boldsymbol{\beta}_q\|_2^2 + \sum_{q=1}^Q \sum_{j=1}^M \left( \lambda_0 + \sum_{s=1}^r \lambda_s R_{js} \right) |\beta_{qj}| + \sum_{j=1}^M \lambda \log \left( \sum_{q=1}^Q |\beta_{qj}| + \tau \right).$$

Similarly, based on the same local linear approximation applied to  $\lambda \log(\sum_{q=1}^Q |\beta_{qj}| + \tau)$  presented in the previous section, the above objective function becomes

$$U_2(\mathbf{B}|\mathbf{B}^{(t)}) = \sum_{q=1}^Q \frac{1}{2n_q} \|\mathbf{Y}_q - \mathbf{X}_q \boldsymbol{\beta}_q\|_2^2 + \sum_{q=1}^Q \sum_{j=1}^M \left( \lambda_0 + \sum_{s=1}^r \lambda_s R_{js} + \frac{\lambda}{\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}| + \tau} \right) |\beta_{qj}|.$$

Since the penalty is in linear form for  $\beta_{qj}$ , it can be solved by the same coordinate descent algorithm for the standard Lasso problem, where the standard Lasso tuning parameter  $\lambda$  is replaced by  $(\lambda_0 + \sum_{s=1}^r \lambda_s R_{js} + \frac{\lambda}{\sum_{q=1}^Q |\hat{\beta}_{qj}^{(t)}| + \tau})$ . Therefore, the procedure for SummaryLasso follows.

### S.3 Enrichment analysis of the 16 secondary traits for type 2 diabetes

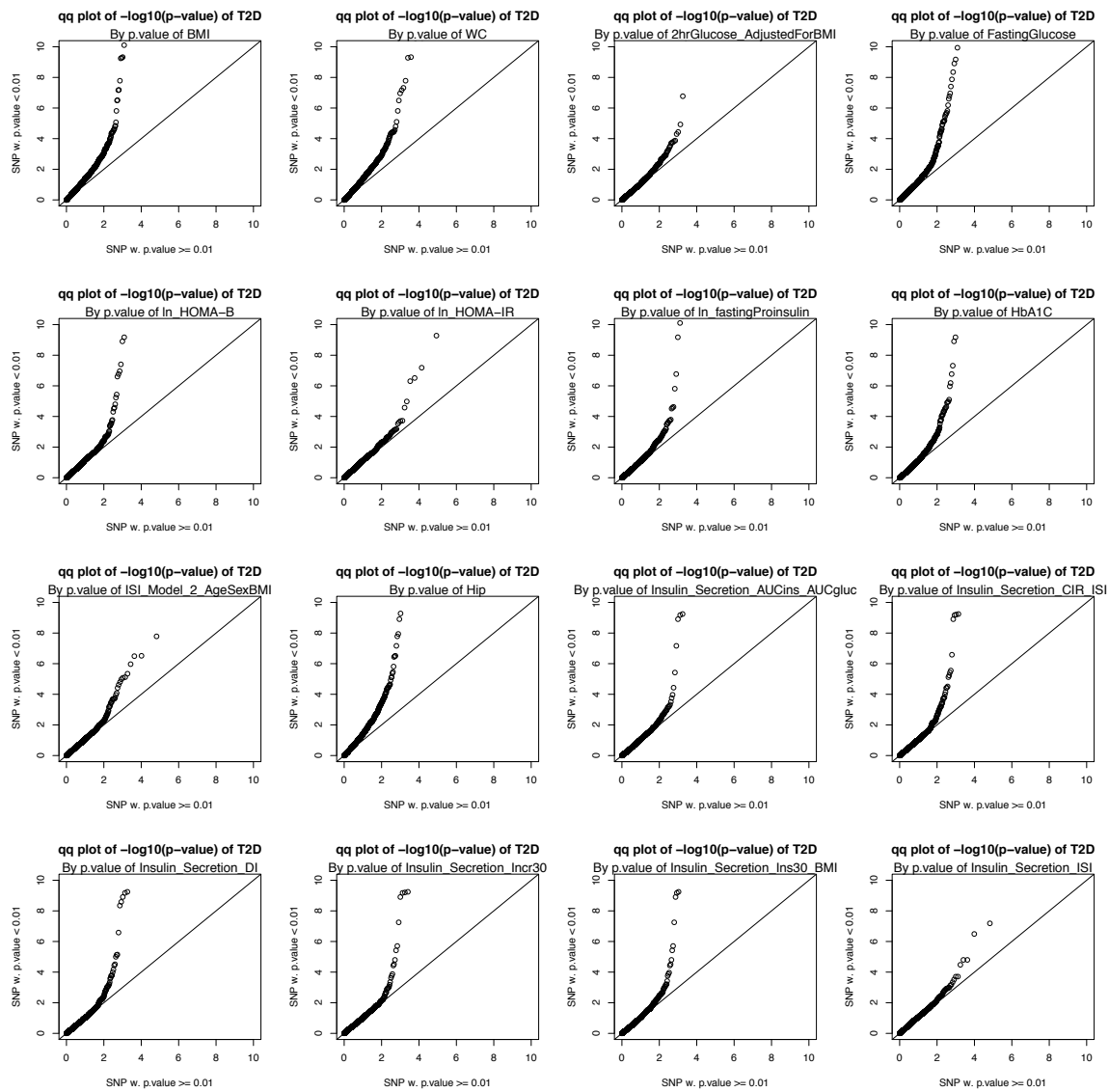


Figure S.1. Enrichment analysis of the sixteen secondary traits for type 2 diabetes. For a given secondary trait, SNPs can be classified into two groups: one group has p-value less than 0.01 (denoted as  $S_1$ ) and the other group has p-value  $> 0.01$ . Here,  $S_1$  represents SNPs that are more likely to be associated with the trait and  $S_2$  represents SNPs that are less likely to be associated with the trait. We then made a quantile-quantile plot, comparing T2D association p-values for SNPs in  $S_1$  and in  $S_2$ . If the secondary trait shares genetic basis with T2D, the QQ plot would deviate from the expected 45-degree line. To minimize the artifact of linkage disequilibrium (LD), we performed LD-pruning using PLINK with  $r^2 = 0.1$ . The sixteen traits include the three traits from the GIANT consortium website: BMI, WC = waist circumference, Hip = hip measurement and the remaining traits from MAGIC (the Meta-Analyses of Glucose and Insulin-related traits Consortium) website, where the names described in the Figures can be matched to the information of traits on the MAGIC website.

Supplementary Table 1. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 1250$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PTWC	LD-Pred	PANPRS	PANPRS-Func
PT	1.83% (1.7%, 1.9%) < 2.2e-16	1.67% (1.5%, 1.8%) < 2.2e-16	1.63% (1.4%, 1.8%) < 2.2e-16	3.16% (2.9%, 3.4%) < 2.2e-16
PTWC		-0.16% (-0.28%, -0.036%) 0.0057	-0.202% (-0.4%, -0.00074%) 0.025	1.33% (1.1%, 1.5%) < 2.2e-16
LD-Pred			-0.0422% (-0.28%, 0.20%) 0.37	1.49% (1.3%, 1.7%) < 2.2e-16
PANPRS				1.53% (1.5%, 1.6%) < 2.2e-16

PANPRS: Single trait analysis, without functional annotation data.

PANPRS-Func: PANPRS incorporating functional annotation data.

Supplementary Table 2. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 2500$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PTWC	LD-Pred	PANPRS	PANPRS-Func
PT	0.932% (0.88%, 0.98%) < 2.2e-16	0.829% (0.76%, 0.9%) < 2.2e-16	1.32% (1.2%, 1.5%) < 2.2e-16	2.58% (2.4%, 2.7%) < 2.2e-16
PTWC		-0.104% (-0.15%, -0.058%) 4.04e-06	0.39% (0.25%, 0.53%) 2.7e-08	1.65% (1.5%, 1.8%) < 2.2e-16
LD-Pred			0.493% (0.35%, 0.63%) 4.16e-12	1.75% (1.6%, 1.9%) < 2.2e-16
PANPRS				1.26% (1.2%, 1.3%) < 2.2e-16

PANPRS: Single trait analysis, without functional annotation data.

PANPRS-Func: PANPRS incorporating functional annotation data.

Supplementary Table 3. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 1250, \gamma = 0.3, \rho = 0.5$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	2.85% (2.7%, 3.0%) < 2.2e-16	4.18% (4.0%, 4.3%) < 2.2e-16	3.79% (3.6%, 3.9%) < 2.2e-16	5.02% (4.9%, 5.2%) < 2.2e-16
PTWC	1.02% (0.94%, 1.1%) < 2.2e-16	2.35% (2.3%, 2.4%) < 2.2e-16	1.96% (1.9%, 2%) < 2.2e-16	3.19% (3.1%, 3.3%) < 2.2e-16
LD-Pred	1.18% (1.0%, 1.3%) < 2.2e-16	2.51% (2.4%, 2.7%) < 2.2e-16	2.12% (2%, 2.3%) < 2.2e-16	3.35% (3.2%, 3.5%) < 2.2e-16
PANPRS	1.22% (1.0%, 1.4%) < 2.2e-16	2.55% (2.3%, 2.8%) < 2.2e-16	2.16% (1.9%, 2.4%) < 2.2e-16	3.39% (3.2%, 3.6%) < 2.2e-16
PANPRS-Func	-0.305% (-0.51%, -0.1%) 0.0016	1.02% (0.82%, 1.2%) < 2.2e-16	0.631% (0.41%, 0.85%) 1.1e-08	1.86% (1.7%, 2.1%) < 2.2e-16
PANPRS- 2traits		1.33% (1.2%, 1.4%) < 2.2e-16	0.936% (0.86%, 1%) < 2.2e-16	2.17% (2.1%, 2.3%) < 2.2e-16
PANPRS-Func 2traits			-0.391% (-0.49%, -0.29%) 6.4e-15	0.84% (0.76%, 0.92%) < 2.2e-16
PANPRS- 4traits				1.23% (1.1%, 1.3%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation data

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation data and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation data and 4 secondary traits

Supplementary Table 4. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 1250, \gamma = 0.3, \rho = 0.8$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	3.71% (3.6%, 3.8%) < 2.2e-16	4.98% (4.8%, 5.1%) < 2.2e-16	4.58% (4.4%, 4.7%) < 2.2e-16	5.86% (5.7%, 6%) < 2.2e-16
PTWC	1.88% (1.8%, 2.0%) < 2.2e-16	3.14% (3.1%, 3.2%) < 2.2e-16	2.75% (2.7%, 2.8%) < 2.2e-16	4.03% (3.9%, 4.2%) < 2.2e-16
LD-Pred	2.04% (1.9%, 2.2%) < 2.2e-16	3.31% (3.2%, 3.5%) < 2.2e-16	2.91% (2.8%, 3.1%) < 2.2e-16	4.19% (4%, 4.4%) < 2.2e-16
PANPRS	2.08% (1.9%, 2.3%) < 2.2e-16	3.35% (3.1%, 3.6%) < 2.2e-16	2.95% (2.7%, 3.2%) < 2.2e-16	4.23% (4%, 4.5%) < 2.2e-16
PANPRS- Func	0.551% (0.34%, 0.76%) 8.6e-08	1.82% (1.6%, 2%) < 2.2e-16	1.42% (1.2%, 1.6%) < 2.2e-16	2.7% (2.5%, 2.9%) < 2.2e-16
PANPRS- 2traits		1.27% (1.2%, 1.3%) < 2.2e-16	0.869% (0.78%, 0.95%) < 2.2e-16	2.15% (2%, 2.3%) < 2.2e-16
PANPRS- Func 2traits			-0.397% (-0.5%, -0.3%) 7.8e-16	0.886% (0.78%, 0.99%) < 2.2e-16
PANPRS- 4traits				1.28% (1.2%, 1.4%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 5. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 1250, \gamma = 0.7, \rho = 0.5$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	2.54% (2.4%, 2.7%) < 2.2e-16	3.67% (3.5%, 3.8%) < 2.2e-16	4.19% (4.1%, 4.3%) < 2.2e-16	5.67% (5.5%, 5.8%) < 2.2e-16
PTWC	0.708% (0.63%, 0.79%) < 2.2e-16	1.84% (1.7%, 2%) < 2.2e-16	2.36% (2.3%, 2.5%) < 2.2e-16	3.84% (3.7%, 3.9%) < 2.2e-16
LD-Pred	0.869% (0.71%, 1%) < 2.2e-16	2% (1.8%, 2.2%) < 2.2e-16	2.52% (2.4%, 2.7%) < 2.2e-16	4% (3.8%, 4.2%) < 2.2e-16
PANPRS	0.911% (0.69%, 1.1%) 1.1e-15	2.04% (1.8%, 2.3%) < 2.2e-16	2.56% (2.4%, 2.8%) < 2.2e-16	4.04% (3.8%, 4.3%) < 2.2e-16
PANPRS-Func	-0.619% (-0.84%, -0.4%) 1.4e-08	0.508% (0.27%, 0.75%) 1.7e-05	1.03% (0.83%, 1.2%) < 2.2e-16	2.51% (2.3%, 2.7%) < 2.2e-16
PANPRS-2traits		1.13% (1%, 1.2%) < 2.2e-16	1.65% (1.6%, 1.7%) < 2.2e-16	3.13% (3%, 3.2%) < 2.2e-16
PANPRS-Func 2traits			0.524% (0.4%, 0.65%) < 2.2e-16	2% (1.9%, 2.1%) < 2.2e-16
PANPRS-4traits				1.48% (1.4%, 1.6%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits



Supplementary Table 6. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 1250, \gamma = 0.7, \rho = 0.8$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	3.35% (3.2%, 3.5%) < 2.2e-16	4.19% (4%, 4.4%) < 2.2e-16	5.15% (5%, 5.3%) < 2.2e-16	6.38% (6.2%, 6.6%) < 2.2e-16
PTWC	1.52% (1.4%, 1.6%) < 2.2e-16	2.36% (2.2%, 2.5%) < 2.2e-16	3.32% (3.2%, 3.4%) < 2.2e-16	4.55% (4.4%, 4.7%) < 2.2e-16
LD-Pred	1.68% (1.5%, 1.8%) < 2.2e-16	2.52% (2.3%, 2.7%) < 2.2e-16	3.48% (3.3%, 3.7%) < 2.2e-16	4.71% (4.5%, 4.9%) < 2.2e-16
PANPRS	1.72% (1.5%, 1.9%) < 2.2e-16	2.56% (2.3%, 2.8%) < 2.2e-16	3.53% (3.3%, 3.8%) < 2.2e-16	4.76% (4.5%, 5%) < 2.2e-16
PANPRS-Func	0.188% (-0.035%, 0.41%) 0.049	1.03% (0.79%, 1.3%) < 2.2e-16	2% (1.8%, 2.2%) < 2.2e-16	3.23% (3%, 3.5%) < 2.2e-16
PANPRS- 2traits		0.845% (0.74%, 0.95%) < 2.2e-16	1.81% (1.7%, 1.9%) < 2.2e-16	3.04% (2.9%, 3.1%) < 2.2e-16
PANPRS-Func 2traits			0.962% (0.85%, 1.1%) < 2.2e-16	2.19% (2.1%, 2.3%) < 2.2e-16
PANPRS- 4traits				1.23% (1.1%, 1.3%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 7. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 2500, \gamma = 0.3, \rho = 0.5$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	1.72% (1.7%, 1.8%) < 2.2e-16	2.89% (2.8%, 3%) < 2.2e-16	1.88% (1.8%, 2%) < 2.2e-16	3.08% (3%, 3.2%) < 2.2e-16
PTWC	0.789% (0.73%, 0.84%) < 2.2e-16	1.96% (1.9%, 2%) < 2.2e-16	0.949% (0.89%, 1%) < 2.2e-16	2.15% (2.1%, 2.2%) < 2.2e-16
LD-Pred	0.892% (0.82%, 0.97%) < 2.2e-16	2.07% (2%, 2.2%) < 2.2e-16	1.05% (0.98%, 1.1%) < 2.2e-16	2.25% (2.2%, 2.3%) < 2.2e-16
PANPRS	0.399% (0.25%, 0.54%) 4.18e-08	1.57% (1.4%, 1.7%) < 2.2e-16	0.559% (0.41%, 0.71%) 2.03e-13	1.76% (1.6%, 1.9%) < 2.2e-16
PANPRS-Func	-0.859% (-1%, -0.71%) < 2.2e-16	0.314% (0.16%, 0.46%) 2.05e-05	-0.699% (-0.85%, -0.54%) < 2.2e-16	0.501% (0.34%, 0.66%) 7.57e-10
PANPRS- 2traits		1.17% (1.1%, 1.3%) < 2.2e-16	0.16% (0.12%, 0.2%) 1.63e-14	1.36% (1.3%, 1.4%) < 2.2e-16
PANPRS-Func 2traits			-1.01% (-1.1%, -0.93%) < 2.2e-16	0.187% (0.12%, 0.25%) 2.51e-08
PANPRS- 4traits				1.2% (1.1%, 1.3%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 8. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 2500, \gamma = 0.3, \rho = 0.8$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	1.75% (1.7%, 1.8%) < 2.2e-16	2.97% (2.9%, 3.1%) < 2.2e-16	2.17% (2.1%, 2.2%) < 2.2e-16	3.51% (3.4%, 3.6%) < 2.2e-16
PTWC	0.819% (0.77%, 0.87%) < 2.2e-16	2.03% (1.9%, 2.1%) < 2.2e-16	1.24% (1.2%, 1.3%) < 2.2e-16	2.58% (2.5%, 2.7%) < 2.2e-16
LD-Pred	0.922% (0.86%, 0.99%) < 2.2e-16	2.14% (2%, 2.2%) < 2.2e-16	1.35% (1.3%, 1.4%) < 2.2e-16	2.68% (2.6%, 2.8%) < 2.2e-16
PANPRS	0.429% (0.28%, 0.57%) 3.45e-09	1.64% (1.5%, 1.8%) < 2.2e-16	0.852% (0.71%, 1%) < 2.2e-16	2.19% (2%, 2.3%) < 2.2e-16
PANPRS-Func	-0.829% (-0.98%, -0.68%) < 2.2e-16	0.386% (0.24%, 0.53%) 1.74e-07	-0.406% (-0.56%, -0.25%) 6.92e-08	0.932% (0.77%, 1.1%) < 2.2e-16
PANPRS-2traits		1.21% (1.1%, 1.3%) < 2.2e-16	0.423% (0.37%, 0.48%) < 2.2e-16	1.76% (1.7%, 1.8%) < 2.2e-16
PANPRS-Func 2traits			-0.792% (-0.89%, -0.7%) < 2.2e-16	0.546% (0.48%, 0.62%) < 2.2e-16
PANPRS-4traits				1.34% (1.3%, 1.4%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 9. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 2500, \gamma = 0.7, \rho = 0.5$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	2.08% (2%, 2.2%) < 2.2e-16	3.37% (3.3%, 3.5%) < 2.2e-16	2.55% (2.5%, 2.6%) < 2.2e-16	3.69% (3.6%, 3.8%) < 2.2e-16
PTWC	1.14% (1.1%, 1.2%) < 2.2e-16	2.43% (2.3%, 2.5%) < 2.2e-16	1.62% (1.5%, 1.7%) < 2.2e-16	2.76% (2.7%, 2.8%) < 2.2e-16
LD-Pred	1.25% (1.2%, 1.3%) < 2.2e-16	2.54% (2.4%, 2.7%) < 2.2e-16	1.72% (1.6%, 1.8%) < 2.2e-16	2.86% (2.8%, 3%) < 2.2e-16
PANPRS	0.755% (0.61%, 0.9%) < 2.2e-16	2.04% (1.9%, 2.2%) < 2.2e-16	1.23% (1.1%, 1.4%) < 2.2e-16	2.37% (2.2%, 2.5%) < 2.2e-16
PANPRS- Func	-0.503% (-0.66%, -0.35%) 5.16e-11	0.787% (0.63%, 0.94%) < 2.2e-16	-0.0273% (-0.18%, 0.13%) 0.366	1.11% (0.95%, 1.3%) < 2.2e-16
PANPRS- 2traits		1.29% (1.2%, 1.4%) < 2.2e-16	0.476% (0.42%, 0.53%) < 2.2e-16	1.61% (1.5%, 1.7%) < 2.2e-16
PANPRS- Func 2traits			-0.814% (-0.9%, -0.73%) < 2.2e-16	0.325% (0.25%, 0.4%) < 2.2e-16
PANPRS- 4traits				1.14% (1.1%, 1.2%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 10. The difference  $\Delta$  of  $R^2$  and its 95% confidence interval for each pair of methods, estimated based on 200 simulations ( $M_1 = 2500, \gamma = 0.7, \rho = 0.8$ ). Significance for testing if  $\Delta = 0$  is also reported.

	PANPRS-2traits	PANPRS-Func 2traits	PANPRS-4traits	PANPRS-Func 4traits
PT	2.77% (2.7%, 2.8%) < 2.2e-16	3.82% (3.7%, 3.9%) < 2.2e-16	3.75% (3.6%, 3.9%) < 2.2e-16	4.73% (4.6%, 4.8%) < 2.2e-16
PTWC	1.83% (1.8%, 1.9%) < 2.2e-16	2.89% (2.8%, 3%) < 2.2e-16	2.82% (2.7%, 2.9%) < 2.2e-16	3.79% (3.7%, 3.9%) < 2.2e-16
LD-Pred	1.94% (1.8%, 2%) < 2.2e-16	3.0% (2.9%, 3.1%) < 2.2e-16	2.92% (2.8%, 3.1%) < 2.2e-16	3.9% (3.8%, 4%) < 2.2e-16
PANPRS	1.44% (1.3%, 1.6%) < 2.2e-16	2.5% (2.4%, 2.6%) < 2.2e-16	2.43% (2.3%, 2.6%) < 2.2e-16	3.4% (3.2%, 3.6%) < 2.2e-16
PANPRS-Func	0.187% (0.033%, 0.34%) 0.00851	1.24% (1.1%, 1.4%) < 2.2e-16	1.17% (1.0%, 1.3%) < 2.2e-16	2.15% (2%, 2.3%) < 2.2e-16
PANPRS- 2traits		1.06% (0.97%, 1.1%) < 2.2e-16	0.982% (0.91%, 1.1%) < 2.2e-16	1.96% (1.9%, 2%) < 2.2e-16
PANPRS-Func 2traits			-0.0757% (-0.19%, 0.036%) 0.091	0.901% (0.81%, 0.99%) < 2.2e-16
PANPRS- 4traits				0.977% (0.89%, 1.1%) < 2.2e-16

PANPRS-Func: PANPRS with functional annotation

PANPRS- 2 traits: PANPRS with 2 secondary traits

PANPRS- 4 traits: PANPRS with 4 secondary traits

PANPRS-Func-2 traits: PANPRS with functional annotation and 2 secondary traits

PANPRS-Func-4 traits: PANPRS with functional annotation and 4 secondary traits

Supplementary Table 11: The difference  $\Delta$  of  $R^2$  for each pair of methods and its 95% confidence interval based on bootstrap for analyzing the type 2 diabetes data. P-values for testing  $\Delta = 0$  is also reported based on bootstrap.

	PTWC	LD-Pred	PANPRS	PANPRS-Pleiotropy	PANPRS-Func	PANPRS-Func-P
PT	1.24% (1.2%, 1.3%) < 1e-5	1.2% (1.2%, 1.2%) < 1e-5	1.27% (1.2%, 1.3%) < 1e-5	1.5% (1.5%, 1.5%) < 1e-5	1.95% (1.9%, 2.0%) < 1e-5	2.24% (2.2%, 2.3%) < 1e-5
PTWC		-0.0402% (-0.068%, -0.013%) 0.0018	0.0297% (0.014%, 0.045%) 1e-05	0.26% (0.23%, 0.29%) < 1e-5	0.705% (0.68%, 0.73%) < 1e-5	0.995% (0.96%, 1.0%) < 1e-5
LD-Pred			0.0699% (0.042%, 0.098%) < 1e-5	0.3% (0.26%, 0.34%) < 1e-5	0.745% (0.71%, 0.78%) < 1e-5	1.04% (1.0%, 1.1%) < 1e-5
PANPRS				0.23% (0.2%, 0.26%) < 1e-5	0.675% (0.65%, 0.7%) < 1e-5	0.965% (0.94%, 1%) < 1e-5
PANPRS-Pleiotropy					0.445% (0.42%, 0.47%) < 1e-5	0.735% (0.70%, 0.77%) < 1e-5
PANPRS-Func						0.29% (0.27%, 0.32%) < 1e-5

PANPRS: Single trait analysis without functional annotation or pleiotropy

PANPRS-Func: PANPRS with functional annotation

PANPRS-Pleiotropy: PANPRS with 16 secondary traits

PANPRS-Func-P: PANPRS with functional annotation and 16 secondary traits

Supplementary Table 12: The difference  $\Delta$  of  $R^2$  for each pair of methods and its 95% confidence interval based on bootstrap for analyzing the melanoma data. P-values for testing  $\Delta = 0$  is also reported based on bootstrap.

	PTWC	LD-Pred	PANPRS	PANPRS-Pleiotropy	PANPRS-Func	PANPRS-Func-P
PT	0.0585% (0.031%, 0.086%) 2e-05	0.986% (0.95%, 1%) < 1e-5	0.999% (0.97%, 1%) < 1e-5	1.35% (1.3%, 1.4%) < 1e-5	1.16% (1.1%, 1.2%) < 1e-5	1.59% (1.5%, 1.6%) < 1e-5
PTWC		0.928% (0.89%, 0.96%) < 1e-5	0.94% (0.91%, 0.97%) < 1e-5	1.29% (1.3%, 1.3%) < 1e-5	1.1% (1.1%, 1.1%) < 1e-5	1.53% (1.5%, 1.6%) < 1e-5
LD-Pred			0.0127% (-0.019%, 0.045%) 0.21641	0.364% (0.32%, 0.4%) < 1e-5	0.176% (0.14%, 0.21%) < 1e-5	0.606% (0.55%, 0.66%) < 1e-5
PANPRS				0.351% (0.32%, 0.39%) < 1e-5	0.163% (0.14%, 0.19%) < 1e-5	0.593% (0.54%, 0.64%) < 1e-5
PANPRS-Pleiotropy					-0.188% (-0.22%, -0.15%) < 1e-5	0.242% (0.19%, 0.29%) < 1e-5
PANPRS-Func						0.43% (0.38%, 0.48%) < 1e-5

PANPRS: Single trait analysis without functional annotation or pleiotropy

PANPRS-Func: PANPRS with functional annotation

PANPRS-Pleiotropy: PANPRS with 7 secondary traits

PANPRS-Func-P: PANPRS with functional annotation and 7 secondary traits