Benchmark Details

Differences between PGSFusion and existing platforms

While we have implemented in the updated PGSFusion the user-friendly interface for the PGS construction methods and the detailed epidemiological analyses for 201 complex traits and, we note that the main purpose of our PGSFusion platform is not only to provide “expert bioinformatician” easy to use different tools for evaluating the prediction performance but also to allow “non-expert” to easily constructing PGS, along with epidemiological analysis, so that we can democratize and power the use and analysis of PGS across biological research areas. From this aspect, the implementation of PGSFusion is different from existing platforms, such as PGS Catalog, PGS-Depot, PGS-Server, and GenoPred, in four important aspects.

Firstly, PGSFusion distinguishes itself by providing a user-friendly interface that allows users to easily input GWAS summary statistics in various formats and download SNP effect sizes with detailed information. This makes it possible for users with no prior coding experience to construct Polygenic Scores (PGS), broadening the accessibility of PGS construction across different research areas. In comparison, existing platforms have more restrictions. For example, PGS-Server, Imputation Server PGS, and GenoPred require users to conform to a fixed format for GWAS summary statistics, while PGS-Depot and pgs_calc in PGS Catalog necessitate manual processing of summary statistics. To illustrate, the 2024 updated version of PGS Catalog includes pgs_calc [1], a software that calculates PGS using SNP effect sizes from the PGS Catalog, which is similar to the method used by Imputation Server PGS [2]. PGS-Depot allows users to upload summary statistics, but they must manually provide additional details like trait, sample size, SNP names, alleles, beta values, and P-values. Similarly, PGS-Server requires that summary statistics be uploaded in the GEMMA format, which limits flexibility.

Secondly, PGSFusion offers a broader selection of widely used PGS methods across four categories—single-trait, multiple-trait, annotation-based, and cross-ancestry methods. Users can choose the most appropriate method based on available computational resources (e.g., memory and CPU), with a built-in benchmark to help select between multiple methods. In contrast, existing platforms typically provide more limited options. For example, pgs_calc in PGS Catalog focuses on multiplying genotype data by SNP effect sizes to calculate PGS. PGS-Depot supports only 11 single-trait PGS methods and requires manual calculations. PGS-Server allows users to upload summary statistics, choose from 12 single-trait PGS methods, and outputs inferred SNP weights for PGS construction. GenoPred offers only 6 single-trait methods and provides SNP weights.

Finally, PGSFusion offers a comprehensive set of traits for validation and covariates for conducting epidemiological analyses of PGS, such as evaluating prediction performance and joint effects. In contrast, existing platforms either focus mainly on compiling PGS for different traits (e.g., PGS-Depot and PGS Catalog) or do not provide support for downstream analyses. For instance, PGS Catalog, which indexes 656 complex traits, is a valuable resource that compiles published PGS along with metadata describing how the scores were developed and evaluated, based on data from curation or author submissions [3, 4]. PGS-Depot houses 5,585 high-quality summary statistics from 1,564 traits across European and East Asian populations [5]. On the other hand, PGS-Server and GenoPred only output the SNP weights from the selected methods.

Difference between PGSFusion and GenoPred

GenoPred is a comprehensive PGS construction tool. It performs direct PGS calculation considering ancestry inference and estimates the effect size of SNP with seven PGS construction methods [6]. The PGS construction

pipeline in GenoPred contains only single-trait methods and needs the users to build the reference panel themselves.

Compared to GenoPred, PGSFusion is primarily focused on different scenarios and epidemiological application for PGS while GenoPred is primarily focused on upstream analysis. As a result, PGSFusion provides a much more comprehensive set of PGS construction methods that can be widely applied for various scenarios. The unique analytic tasks that can be carried out by PGSFusion but not GenoPred include multiple-trait (e.g. mtPGS), annotation-based (e.g. SbayesRC and AnnoPred) and cross-ancestry (e.g. PRS-CSx, SDPRX, and XPASS) methods. Even for the single-trait method that can be carried out by both PGSFusion and GenoPred, PGSFusion provides a much more comprehensive selection of methods and more setting for the common method. For example, for CT, PGSFusion provides three tuning parameters, including window size, correlation among SNPs, and number of P value thresholding. In contrast, GenoPred only provides P value thresholding. As another example, for DBSLMM, PGSFusion provides three models, including DBSLMM, DBSLMM-auto, and DBSLMM-lmm. In contrast, GenoPred only provides one model. As the third example, for lassosum, PGSFusion provides a more efficient version, lassosum2 in *bigsnpr* R package, and automatically tunes 120 parameter combinations [7]. In contrast, GenoPred only used 80 parameter combinations.

In addition, PGSFusion provides flexible GWAS summary statistics format and various downstream epidemiological analysis and contains the comprehensive reference panel for different methods that GenoPred is not well equipped to handle. For example, PGSFusion supports automatically recognition of the variables of GWAS summary statistics. In contrast, GenoPred needs the fixed data format. For the second example, when the GWAS summary statistics excluded UKBB individuals, PGSFusion provides downstream analysis with 15 covariates, including joint analysis (e.g. interaction analysis and subgroup analysis). In contrast, GenoPred only

outputs the effect size file which is also provided by PGSFusion. For the third example, in default, PGSFusion provides pre-processed EUR reference panels with 2,000 UKBB individuals for each method, enabling more accurate PGS construction.

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