In addition, transfer learning and meta-GWAS approaches are widely used. Heterogeneity-aware meta-analysis and random-effects models can reduce estimation bias across studies, while stacking or reweighting methods can be applied when target population data are limited, enabling recalibration and adaptation of multiple ancestry-specific scores (Cai et al., 2021; Gunn et al., 2024).

Within a unified statistical framework, multi-ancestry approaches can be viewed as mechanisms for integrating and reconstructing the underlying estimands across populations. Rather than simply pooling data from multiple sources, these methods recharacterize the target estimand by balancing shared genetic effects against population-specific heterogeneity, typically through weighting schemes or hierarchical modeling. This allows the resulting predictive function to better accommodate cross-population variation.

The core challenge lies in accommodating differences in LD structure, allele frequency spectra, and effect heterogeneity across populations. In practice, this requires ancestry inference, local LD similarity assessment, and frequency-aware weighting of training data. Evaluation should include relative R^2/AUC, calibration metrics, and decision-curve net benefit in the target population to comprehensively assess portability (Jung et al., 2025).

1.5 Relationship between PRS and SNP heritability: a unified view of variance explanation and individual prediction

Within the statistical genetics framework, PRS and SNP heritability are not independent quantities but rather complementary representations of the same underlying genetic information at different levels. SNP heritability is typically defined as the proportion of phenotypic variance explained by additive genetic effects captured by a given set of markers under specific model assumptions, representing a population-level variance decomposition. In contrast, PRS aggregates these effects into an individual-level predictive function that quantifies relative genetic risk.

Theoretically, the predictive performance of PRS is bounded by SNP heritability. Under ideal conditions-unbiased effect estimation, perfectly matched LD structure, and infinite sample size-PRS can approach the maximum variance explained by SNP heritability. In practice, however, PRS performance is typically lower due to estimation error, LD mismatch, and shrinkage-induced bias. Therefore, PRS performance should not be interpreted as a direct measure of trait heritability, but rather as an indicator of how effectively genetic signals can be identified and utilized under given data and model constraints.

This relationship can be formalized as a variance-prediction duality in statistical genetics (Fang, 2026): SNP heritability quantifies variance explained at the population level, whereas PRS reflects predictive ability at the individual level. The former corresponds to variance component estimation in random-effects models, while the latter corresponds to predictive functions constructed under shrinkage and regularization. Although both are theoretically linked through effect size distributions and LD structure, they often correspond to different estimands in practice due to differences in model assumptions and data structures.

This perspective is particularly important for understanding cross-population prediction. When allele frequency spectra, LD structure, or effect distributions differ across populations, both SNP heritability and PRS estimands may change, with PRS being more sensitive due to its dependence on specific effect estimates and LD modeling. Thus, the decline in cross-population predictive performance can be viewed as a manifestation of estimand mismatch at the level of individual prediction.

Based on this understanding, both PRS construction and evaluation should explicitly consider its relationship with SNP heritability. On the one hand, heritability estimates provide a theoretical upper bound and reference for PRS performance; on the other hand, improvements in effect estimation, ancestry-aware LD modeling, and target-specific recalibration are essential to narrow the gap between PRS performance and its theoretical limit, thereby enhancing predictive accuracy and cross-population portability.