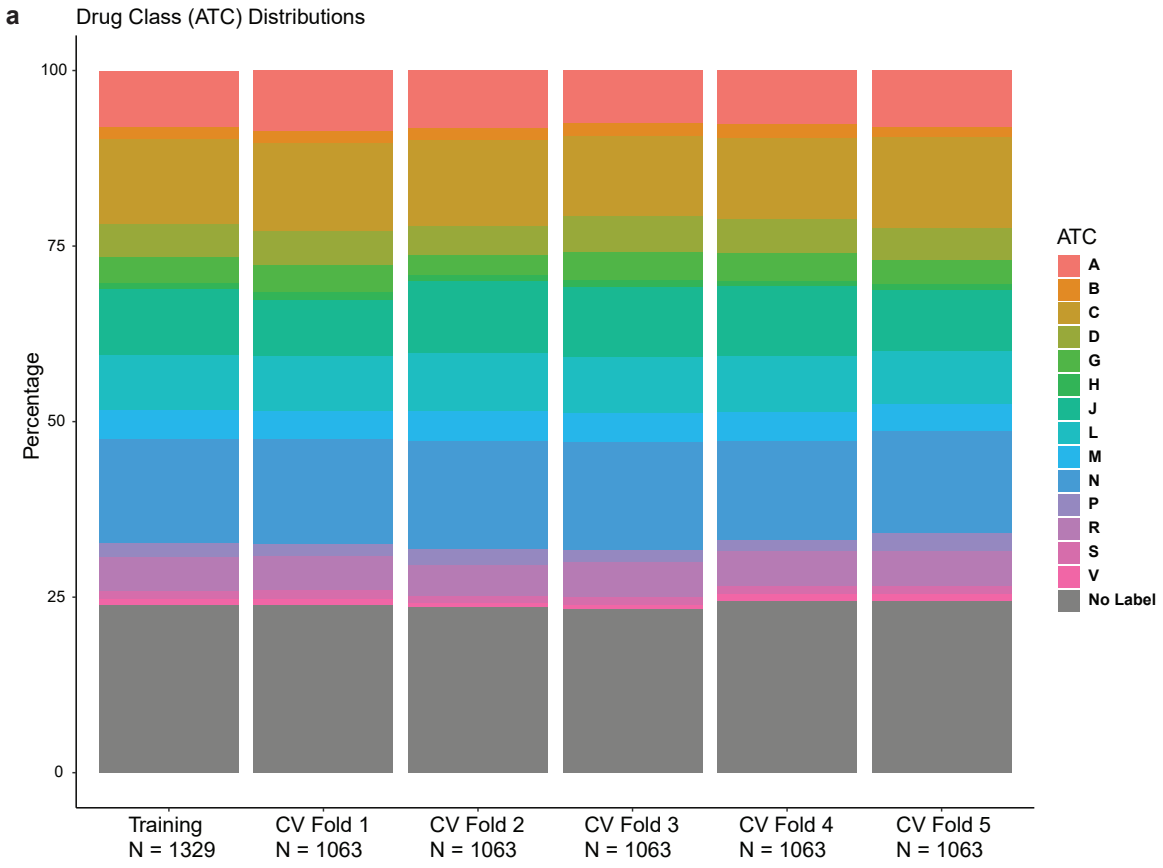
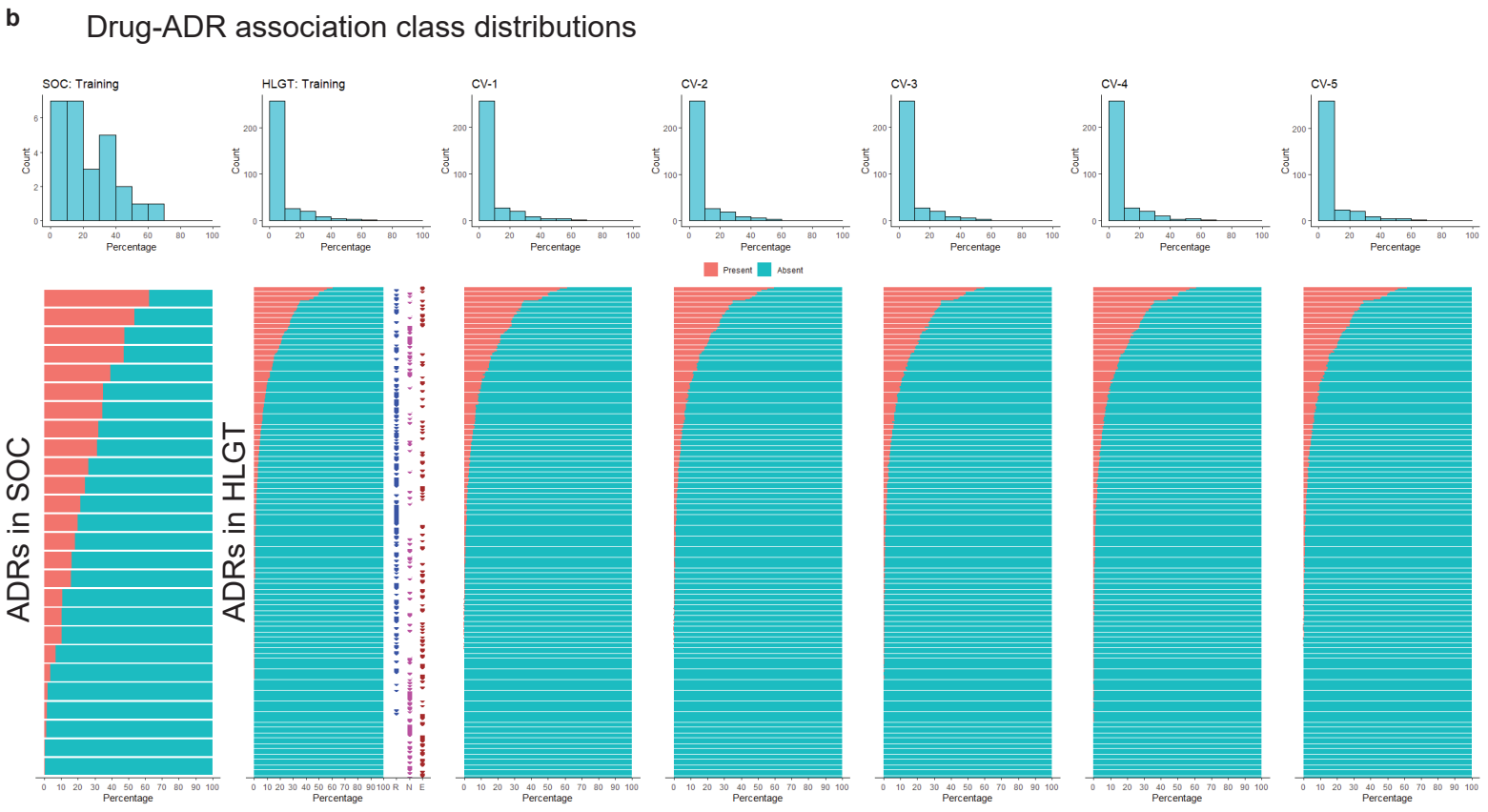
SUPPLEMENTARY FIGURE 1





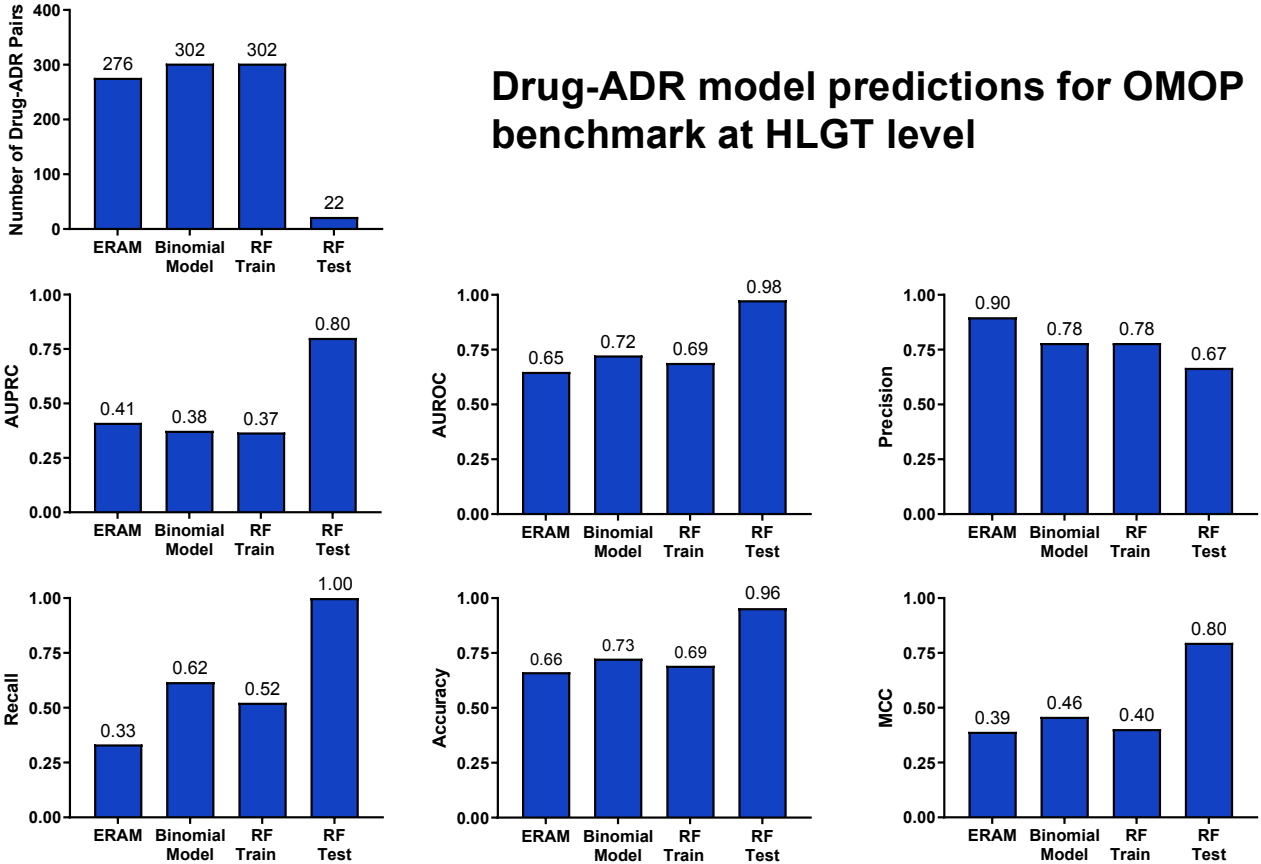
Percentage association present and absent across drugs

Supplementary Figure 1. Drug and ADR class distributions of random forest model

a. **Stacked bar charts comparing drug class distributions of the complete training set (1329 drugs) and each 5-fold cross validation (CV) fold (1063 drugs).** No significant differences were observed: (χ^2-test: p-value > 0.99). Drug class labels (ATC) are as described in Figure 1d.

b. **Horizontal bar charts of ADR class balances across training and 5x CV folds for all ADRs at System Organ Class (SOC, n=26) and High Level Group Term (HLGT, n=321) level.** Percentage present in red (absent in blue) indicates the percentage of drugs that have an (no) association with the particular ADR. Histograms in the top panel indicate the count of ADRs with a percentage as indicated on the X axis. Also indicated for all HLGT ADRs is whether it is represented (R, blue triangle) among the 221 target-ADR associations, excluded for analysis (E, brown triangle) because they are part of 6 excluded SOC classes that do not involve human physiology (see Methods), or whether they were not represented otherwise (N, magenta triangle). Represented ADRs tend to have a more balanced class distribution due to the presence of more positive training data as compared to not represented ADRs, which enables robust and reproducible target-ADR association identification through our statistical methodology (see Methods).

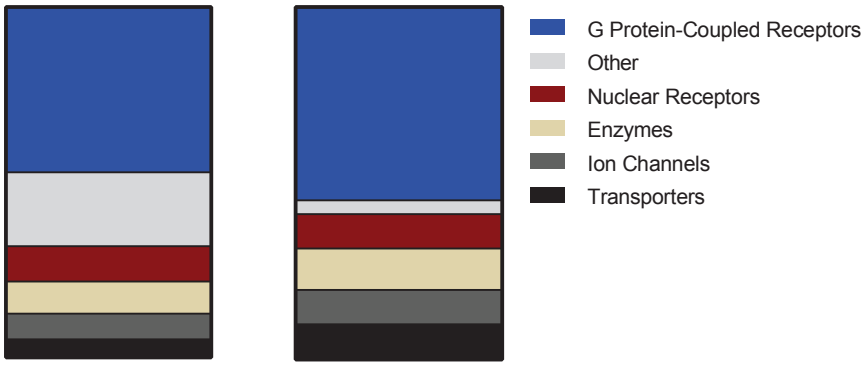
SUPPLEMENTARY FIGURE 2



Supplementary Figure 2. Drug-ADR model predictions on OMOP benchmark at high level group term (HLGT) ADR level

Bar charts with summary statistics of overall model performances on the OMOP benchmark for ERAM, our binomial model based on FAERS ADR occurrences, and our random forest (RF) ADR models. The number of drug-ADR pairs in OMOP with available model predictions is also shown. RF Train and RF Test indicate the performance of the trained RF ADR models using the *in vitro* profiles of drugs from the overlap of drugs in OMOP with those drugs that were also present in RF training and test sets, respectively. AUPRC: area under precision recall curve, AUROC: area under receiver operating characteristic, MCC: Matthew's correlation coefficient. For more details, see Supplementary Table 9.

SUPPLEMENTARY FIGURE 3



All Target Assays
N = 218

Targets Represented
in Associations
N = 51

Supplementary Figure 3. Target class distributions of target-ADR associations

Stacked bar charts comparing target assay class distributions of all target assays (N=218) to the targets represented in the target-ADR associations (N=51, see also Figure 4b). No significant differences were observed (χ^2-test: p-value = 0.09), although the "other" class (grey) had slightly lower representation among the associations. This is expected, since very few drugs were tested on these "other" class assays (Figure 1d), and data availability itself affects the representation in the associations (Figure 4c). Indeed, without considering this "other" class, the distributions were very similar (χ^2-test: p-value = 0.90), further validating that our algorithm does not bias towards any particular target class.