**File S1. Calibration Approach to Ensemble Learning**

In addition to the stacked ensemble approach that is presented in the manuscript, we employed a calibration-set approach to ensemble learning using random forest and generalized linear regression models.

**Methods**

For random forest, the ‘ranger’ package [1] was used to implement the ensemble function. We implemented the model using classification forest, which is suitable for binary and categorical response variables. In each fold of the 10-fold cross validation procedure, the training set was partitioned into 60% and 40% randomly. The random forest model was fitted to the 60%, and predicted values were obtained using the 40% partition. This procedure was repeated 20 times, then the average of all iterations was used to estimate probabilities in the testing set.

For the generalized linear predictor, the ensemble predictor function from the ‘randomGLM’ package [2] was used to implement the approach. In this approach, 20 bootstrapped data sets (bags) were generated based on random sampling from the original training set. For each bag, features were randomly selected without replacement and ranked according to their correlation with the outcome measure. Forward variable selection was employed to define a generalized linear model for the outcome of each bag. Finally, the predictions of each forward selected multivariate model (one per bag) were aggregated across bags to arrive at a final ensemble prediction on the training set, then the output estimates used for prediction on the testing set. For more information please see the illustrative Figure 1 in Song et al. (2013).

**Results**

Results from the above procedures are presented in the following table. This method did not lead to appreciable gains in prediction performance compared to base-level models.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Mean and standard deviation (in parenthesis) ofHighest performing of ensemble machine learning (ENS) models in 10-fold cross validation for prediction of ACL rupture in Labrador Retriever dogs. | | | | |
| **Model** | **Feature Selection** | **No. SNPs** | | **AUC** |
| *No SNPs removed for LD; Covariates not considered* | | | | |
| Ens-RF | GWAS | 15000 | | 0.586 (0.053) |
| meanDiff | 7500 | | 0.591 (0.055) |
| Ens-GLM | GWAS | 12500 | | 0.593 (0.047) |
| meanDiff | 10000 | | 0.597 (0.057) |
| *Highly correlated SNPs removed; Covariates not considered* | | | | |
| Ens-RF | GWAS | 12500 | | 0.598 (0.058) |
| meanDiff | 12500 | | 0.589 (0.056) |
| Ens-GLM | GWAS | 250 | | 0.590 (0.060) |
| meanDiff | 12500 | | 0.595 (0.056) |
| *No SNPs removed for LD; Covariates added to model* | | | | |
| Ens-RF | GWAS | 10 | 0.713 (0.031) | |
| meanDiff | 5 | 0.718 (0.029) | |
| Ens-GLM | GWAS | 5 | 0.726 (0.026) | |
| meanDiff | 5 | 0.729 (0.028) | |
| *Highly correlated SNPs removed; Covariates added to model*  **Feature Selection**  **No. SNPs**  **AUC**  **rs** | | | | |
| Ens-RF | GWAS | 5 | 0.719 (0.036) | |
| meanDiff | 5 | 0.731 (0.032) | |
| Ens-GLM | GWAS | 5 | 0.729 (0.038) | |
| meanDiff | 5 | 0.733 (0.032) | |

**References**

1. Wright MN, Ziegler A. ranger: A fast implementation of random forests for high dimensional data in C++ and R. arXiv preprint arXiv:1508.04409. 2015 Aug 18.

2. Song L, Langfelder P, Horvath S. Random generalized linear model: a highly accurate and interpretable ensemble predictor. BMC bioinformatics. 2013 Dec 1;14(1):5.