Cohort analysis: Hypertension in children with T1D

In this report, we analyzed the Hypertension in children with T1D cohort to understand the elevated BP subjects. Specifically, we focused on :

- undercoving the determing factors, among potential clinical/demographic/family/immune/genetic variables, for elevated BP in children with T1D.
- developing a machine learning model to predict elevated BP in children with T1D.

In conclusion, we found that:

- With univariate association analysis (i.e. testing the direct association of each feature with the elevated BP group):
    - the age at BP measurement, age at antibody measurement, and IA2 are the three most significant features associated with the elevated BP group ($p<0.05$). All three features effects are also significant after multiple testing correction (i.e. Bonferroni correction).
    - all other features are not significantly associated with the elevated BP group.
- With machine learning models to capture complext interactions among features:
    - **Random Forest** achieved the highest discrimination (ROC AUC = 0.78) (Figure 1), markedly outperforming all other models.
    - the Top 5 dominate features in the random forest model are: IA2, x96GAD, ZnT8, AIC, autoimmune disease.
    - The prediction performance for identifying elevated BP subjects is impressive, neverthless further efforts should be made to uncover genetic signals in the BP group.

Variables of interest

Response Variable

elevated_BP:

- Case group (Y=1): if the subject has elevated BP, i.e. pediatric patients who have any BP >90th % at both dates that BP was measured.
- Control group (Y=0): otherwise.

- We corrected the "elevated BP" calculation according to the updated script from Ayo.

- We remove a single subject 01-309-04. He is an outlier in the age group: he is born on 1999-08-01, and at least 5 years older than any other participants in the final cohort. We remove him to avoid outlier bias effect on the model.

Predictors: Genetic Risk Score (GRS)

T1D genetic risk score 2 (GRS2) was calculated using the SNPs from GRS2 paper (Sharp et al. 2019).

- **Features generated:**
  - `IID`, `GRS` (standardized score)

Predictors: Ancestry & Family History

- Ethnicity (self-reported ethnic origin of 4 grandparents)
- Family history of T1D (yes/no)
- Family history of T1D, T2D or other forms of diabetes in 1st or 2nd degree relatives (yes/no)

- **Features generated:**
  - `cluster_pred_ancestry` (predominant continent where grandparents were born)
  - `cluster_shannon` (ancestry diversity): high value reflect higher diversity.
  - `Cluster_family_diabetes` ((yes/no))
  - `cluster_family_12_degree_bin` (Yes/No for 1st/2nd degree relatives)

Predictors: Clinical Features

- Age at antibody test (days)
- age at BP measurement (days)
- Age at analysis (days)
- BMI (SDS)
- Total daily insulin dose (units/kilogram/day)
- Personal history of other autoimmune disease (yes/no, type of autoimmune disease)
- Markers of diabetes control over the last 3 months: Hemoglobin A1C (%)

- **Features generated:**
  - `cluster_BMI`
  - `cluster_autoimmune_disease`
  - `Cluster_age`
  - `Cluster_insulin`
  - `Cluster_A1c`
  - `age_at_antibody_test` (days)
  - `age_at_BP_measurement` (days)

Predictors: Antibody Data

- Glutamic acid decarboxylase 65 (GAD65) autoantibody titers (nmol/L)
- Insulinoma-associated antigen 2 (IA-2) autoantibody titers (nmol/L)
- Zinc transporter 8 (ZnT8) autoantibody titers (nmol/L)

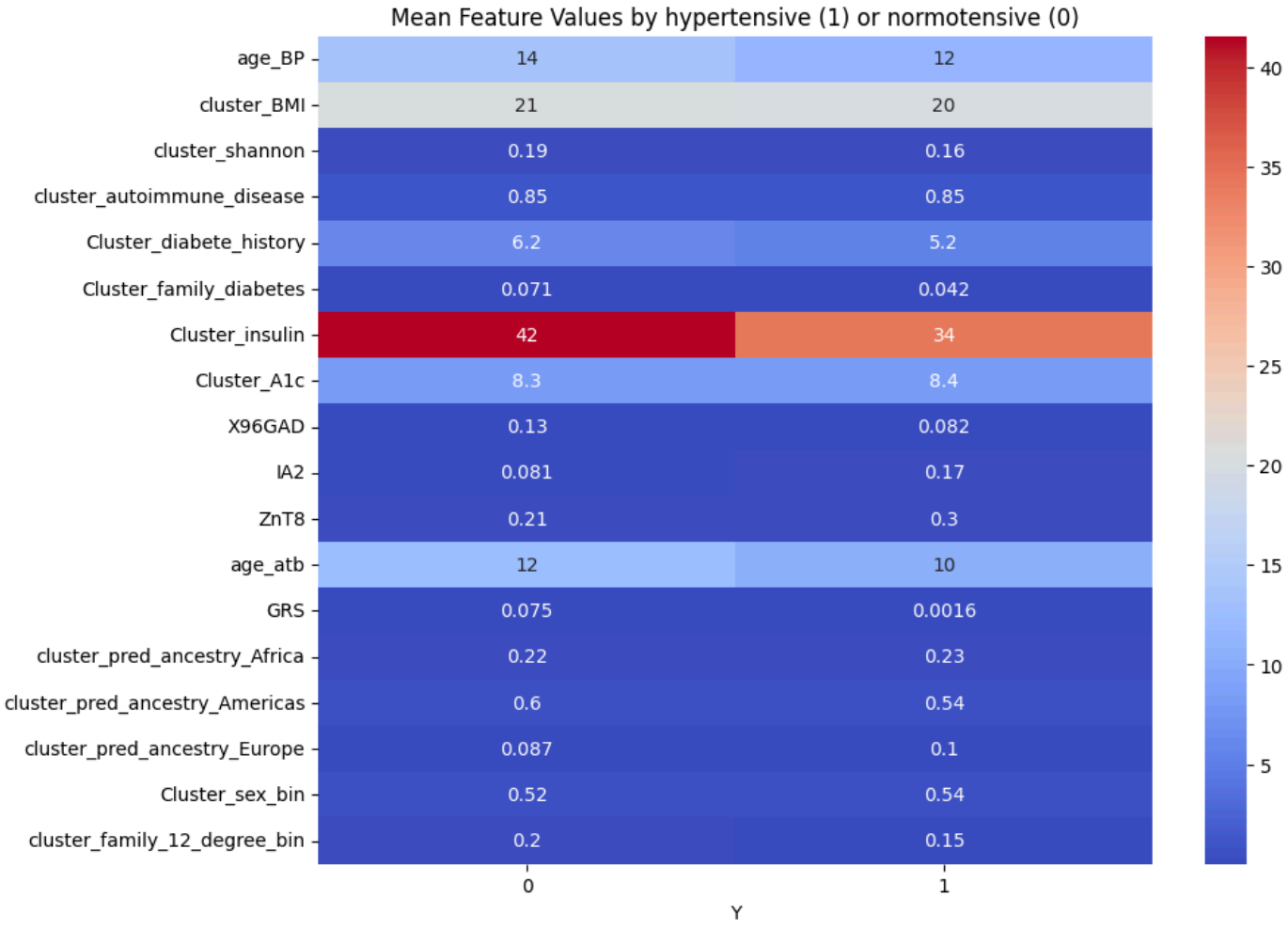
- **Features generated:**
  - `96GAD`
  - `IA2`
  - `ZnT8`

Data Processing

- In total, we obtained 289 subjects, and 20 features of interest.
- Sample size: 48 Hypertensive vs 241 normotensive subjects.
- note that the reduced number of samples (from 350 subjects) is due to the removal of subjects that have missing values in response or any features of interest.
- We processed the highly correlated features (rho>0.95) and normalized the predictors.
- We split the data into training and testing sets (75/25), i.e. we randomly selected 75% of the data for training and 25% for testing.
- We used the training set to train the model and the testing set to evaluate the model performance.

Summary Statistics

We first conducted summary statistics of the cohort. The summary statistics include the mean, standard deviation, median, minimum, maximum, and interquartile range (IQR) of the features of interest. We also conducted a t-test to compare the means of the features between the elevated BP group and the control group. The results are shown in the table below.



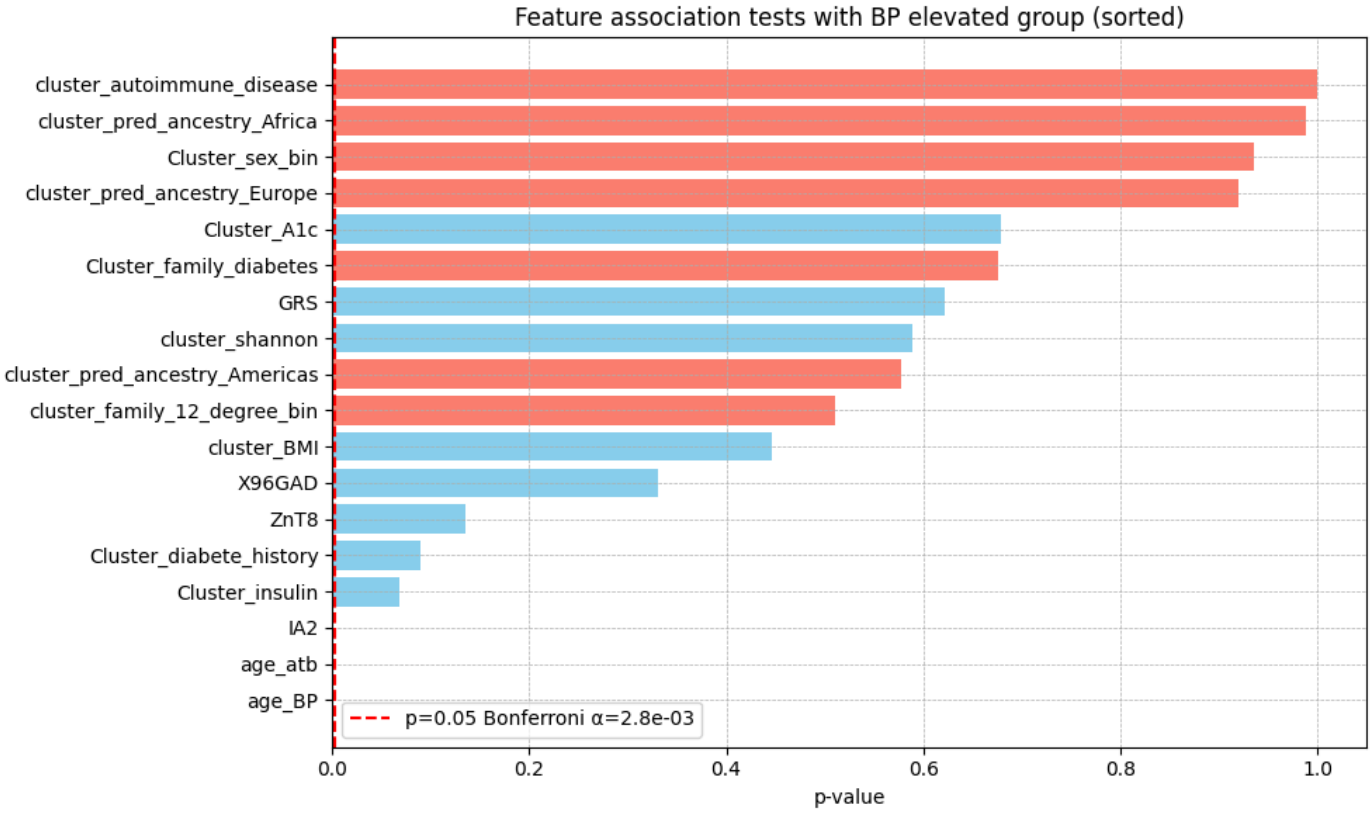
We then examine the statistical significance of each feature in the clinical data between clusters. We use ANOVA tests to test the association between the features and the elevated BP group. The results are shown in

the table below.

In conclusion, we found that for univariate association analysis (i.e. testing the direct association of each feature with the elevated BP group):

- the age at BP measurement, age at antibody measurement, and IA2 are the three most significant features associated with the elevated BP group ($p<0.05$).
- All three features effects are also significant after multiple testing correction (i.e. Bonferroni correction).
- all other features are not significantly associated with the elevated BP group.

	Feature	p-value	Test
0	age_BP	0.000201	anova
11	age_atb	0.000566	anova
9	IA2	0.001651	anova
6	Cluster_insulin	0.068364	anova
4	Cluster_diabete_history	0.089864	anova
10	ZnT8	0.134754	anova
8	X96GAD	0.330373	anova
1	cluster_BMI	0.446587	anova
17	cluster_family_12_degree_bin	0.510337	chi2
14	cluster_pred_ancestry_Americas	0.577319	chi2
2	cluster_shannon	0.589111	anova
12	GRS	0.622534	anova
5	Cluster_family_diabetes	0.675811	chi2
7	Cluster_A1c	0.678683	anova
15	cluster_pred_ancestry_Europe	0.920067	chi2
16	Cluster_sex_bin	0.935835	chi2
13	cluster_pred_ancestry_Africa	0.988903	chi2
3	cluster_autoimmune_disease	1.000000	chi2



Modeling Srategy

We applied and evaluated the following classifiers on a held-out test set using two evaluataion metrics: **ROC** curve and **Precision-Recall** curve.. The ROC AUC measures the model's ability to distinguish between the two classes, while the PR AUC focuses on the model's performance on the positive class (elevated BP).

We considered the follwing models:

1. Logistic Regression (standardized)

Standardized logistic regression fits a linear model linking predictor variables to the log-odds of the binary outcome. This model serves as our baseline: it’s fast to train, yields easily interpretable odds-ratios, and sets a performance floor against which more complex learners can be judged.

1. LASSO Logistic (`glmnet`)

LASSO logistic regression introduces an L_1 penalty on the magnitude of coefficients, shrinking many to exactly zero. This regularization both guards against over-fitting (especially when the number of predictors is large relative to sample size) and performs automatic feature selection by excluding weakly predictive variables. We fit via glmnet::cv.glmnet() using AUC-optimized cross-validation to select the penalty strength (λ). The resulting sparse model highlights only the strongest predictors, simplifying interpretation and often improving generalization.

1. Random Forest (caret)

Random forests build an ensemble of decision trees, each grown on a bootstrap-sample of the training set and considering a random subset of predictors at each split. By averaging across many decorrelated trees, the model captures non-linear relationships and high-order interactions while reducing variance. We used caret::train(method = "rf") with repeated cross-validation to tune the number of variables tried at each split (mtry). Random forests are robust to outliers, handle mixed-type features, and provide built-in measures of variable importance.

1. XGBoost (mlr)

XGBoost implements gradient boosting of decision trees, sequentially fitting each new tree to the residual errors of its predecessors. This method excels at capturing complex interactions and skewed distributions by optimizing a regularized objective (including L_1/L_2 penalties) under a fast, distributed framework. We wrapped it in mlr, tuning tree depth, learning rate, and sampling parameters via randomized search on PR-AUC. XGBoost often outperforms other algorithms when appropriately tuned, at the cost of more hyperparameter complexity. However, it turns out our data is not large enough to benefit from the XGBoost algorithm and the perofmance is dominated by the age factor. Therefore, we do not recommend using XGBoost for this dataset.

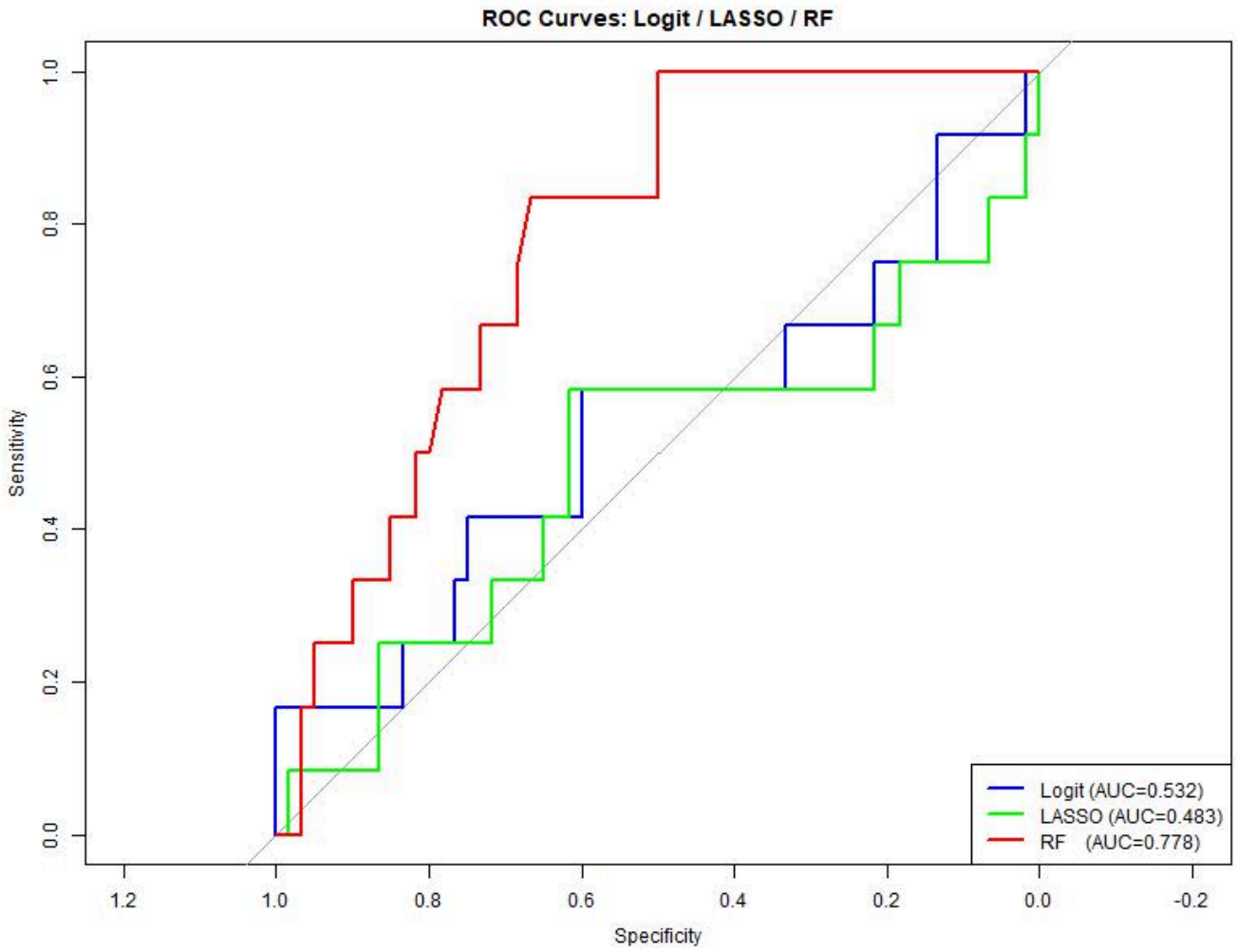
1. Linear SVM (caret)

A linear Support Vector Machine seeks the hyperplane that maximizes the margin between classes in feature space. It’s effectively a large-margin classifier that’s robust to high-dimensional data and can be less sensitive to outliers than logistic regression. We trained with caret::train(method = "svmLinear"), tuning the cost

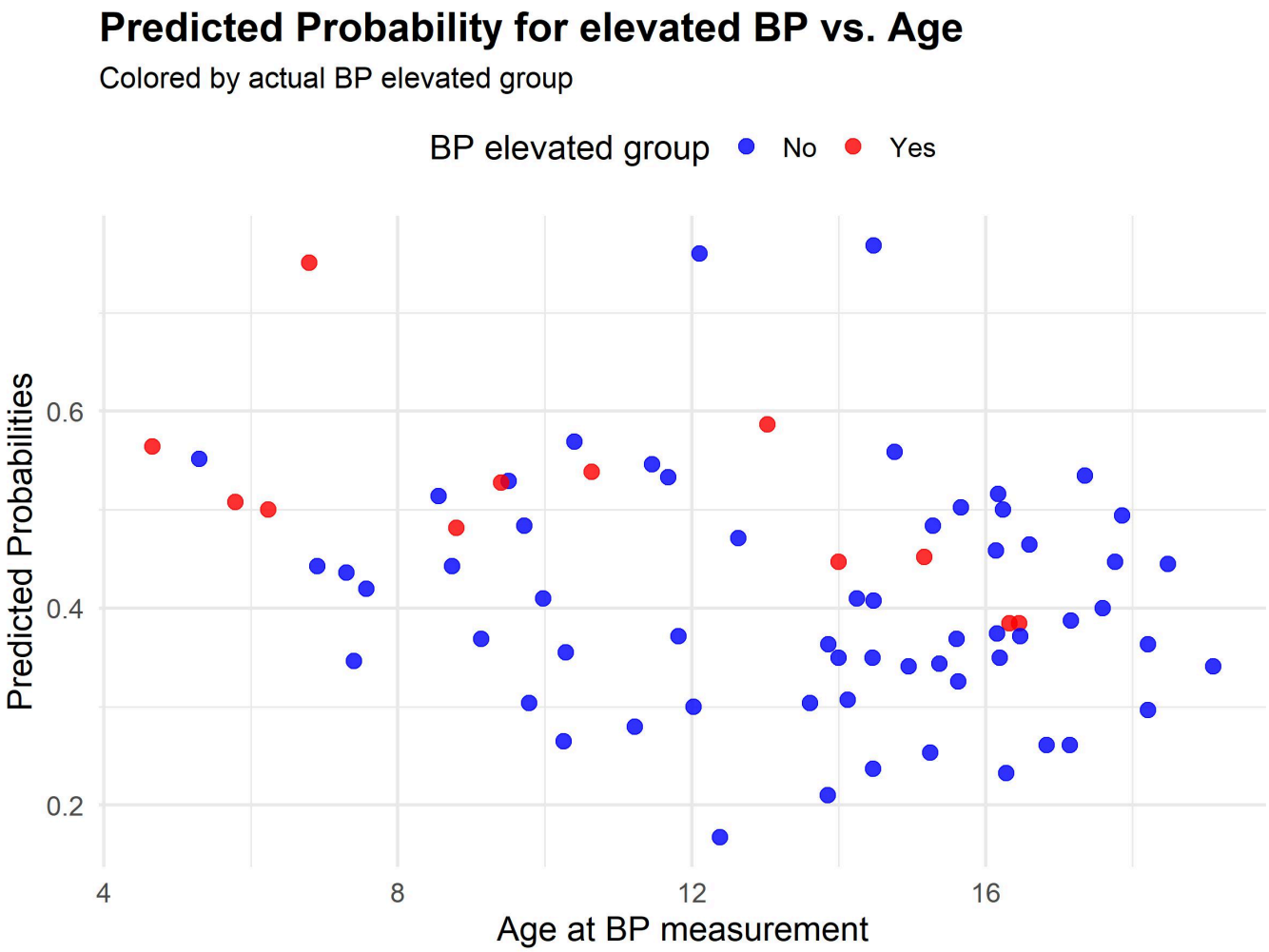
parameter (C) via cross-validation to balance margin width against misclassification error. Although its decision boundary is linear, SVMs can yield strong performance in cases where classes are well-separated in a high-dimensional feature representation. However, due to limited samle size of this project, the performance of SVM is not as good as the Random Forest model on our dataset.

Conclusion

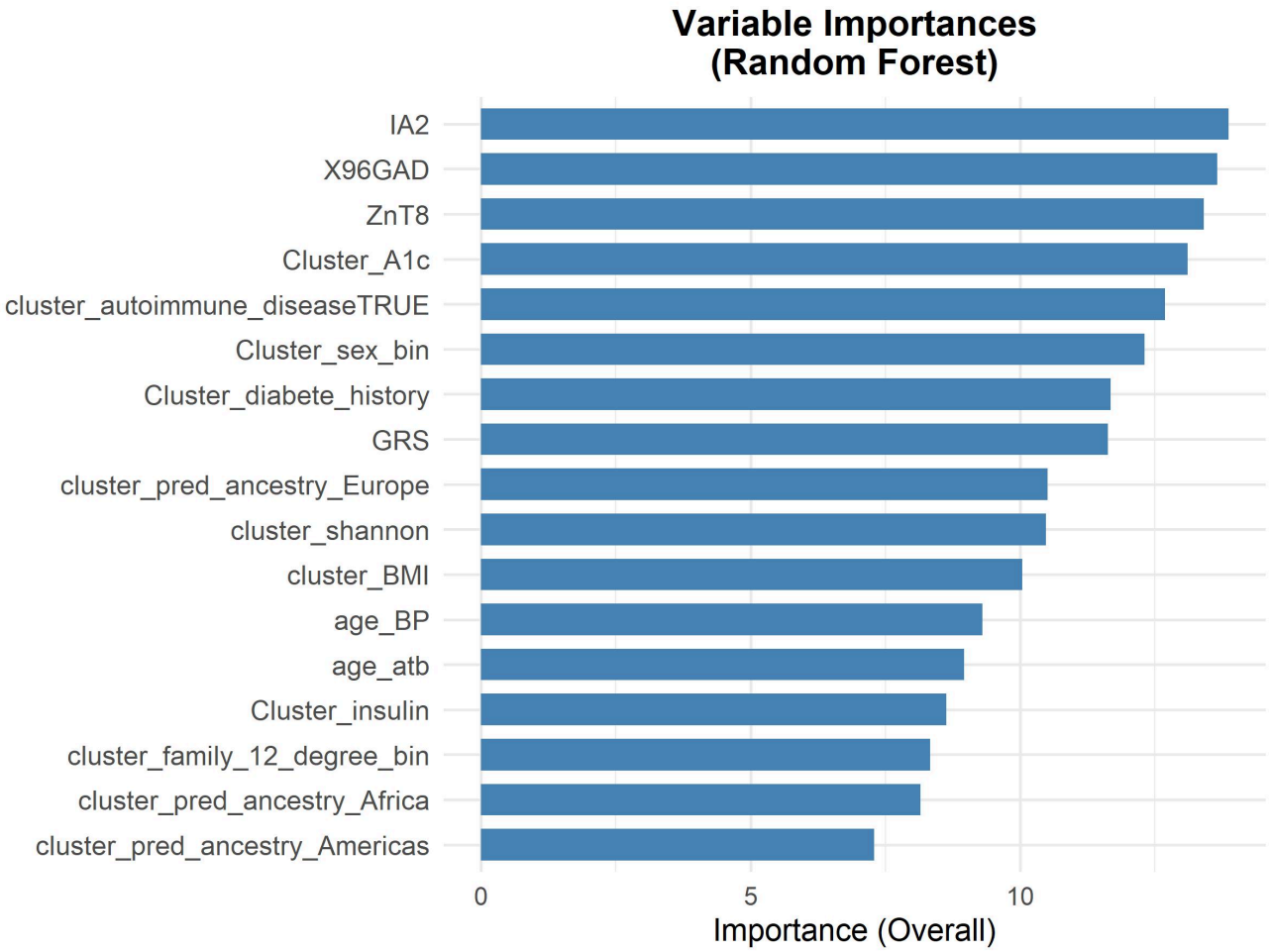
1. **Model Performance:**
   - **Random Forest** achieved the highest discrimination (ROC AUC ≈ 0.78) among all methods (Figure 1), markedly outperforming all other models. The SVM and xgboost models performed similarly to the LASSO model and therefore not included in the figure below.
   - Note that the curve is not smooth due to the small sample size. We used 25% data as test-set.



- The model performance is generally good with respect to identifying elevated BP subjects, even though the type 1 error (ie. false psoitive) is high.



- **Feature Importance:** the Top 5 dominate features in the random forest model are: IA2, x96GAD, ZnT8, AIC, autoimmune disease (Figure 3), though many features have significant contribution to the model.



1. **Key Take-away:**
   - This demonstrate that the machine learning model is able to capture complex interactions between features to predict the elevated BP group, regarless of the fact that univariate analysis identified age at BP and antibody measurement as deceisively the most significant features.
   - However, the prediction performance is limited by the small sample size, and lack of genetic signals in the dataset.

1. **Next Steps:**

   - **Genetic Features:** The GRS score is not performing as it is expected. We need to investigate the orignal genotypes (e.g. SNP dosage data) to see is any SNPs can be added as predictors.
   - **Other Features:** The model need to be updated with new data Imputed basal C-peptide (nmol/l), -Insulin pump therapy (yes/no) and duration (months),...etc, which have not been incorporated yet.
   - **Validation:** The current model performance is evaluated only on one randomly selected training/test split. We need to investigate if this is a robust model by using cross-validation and/or bootstrapping.