A Machine Learning Approach for Predicting Hemophilia A Severity

U.S. FOOD & DRUG ADMINISTRATION

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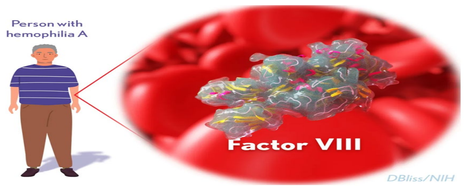
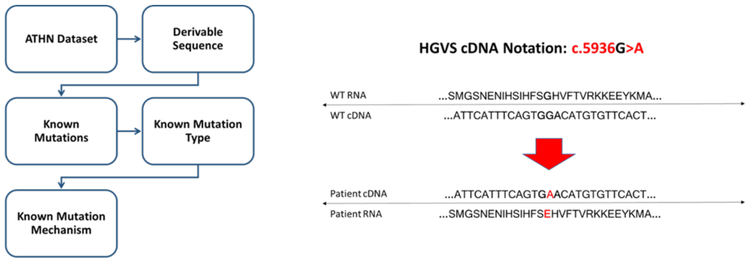
Hemophilia A

- Hemophilia A (HA) is a genetic deficiency in clotting Factor VIII, which mostly affects males as it is an X-linked recessive trait.
- This study aimed at predicting disease severity via patient characteristics using a machine learning approach.



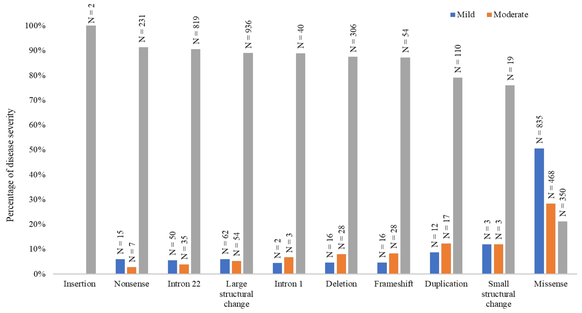
DATA

- Hemophilia treatment centers (HTCs) and the American Thrombosis and Hemostasis Network (ATHN) have created the MLOF dataset to support hemophilia research. The dataset includes biologically relevant variables such as the age, race, sex, ethnicity and the mutations involved in HA.
- The CHAMP F8 dataset created by the Centers for Disease Control and Prevention (CDC) includes information for mutations that have been reported worldwide, compiled from mutations listed in the Haemophilia A Mutation, Structure, Test and Resource Site (HAMSTeRS), in addition to numerous publications.
- We trained our model using the MLOF dataset and validated it using both the MLOF and CHAMP datasets.



(A) (B)

- To provide an overview of the MLOF dataset with respect to disease severity we plotted the fraction of the disease severity for each of the variables. These variables have been ranked based on the fraction of individuals with highest severity.



MACHINE LEARNING & EXPLAINABLE AI

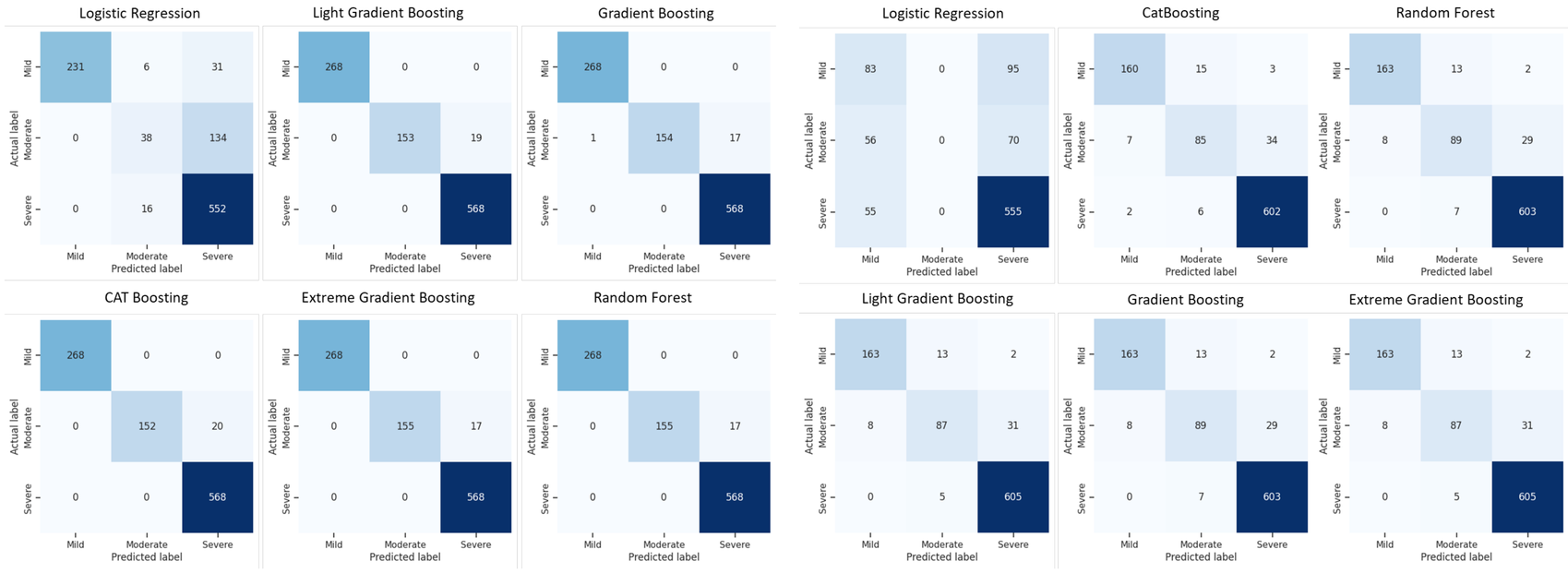
- Six Machine Learning (ML) models based on multi-class classification problem of whether a patient has severe, moderate or mild disease.
- Performance metrices of Accuracy, Precision, Recall and F1-Score.
  - F1 score of 0.99 when trained + validated on the MLOF dataset.
  - F1 score of 0.94 when trained on the MLOF dataset & validated on the CHAMP dataset.
- Confusion matrices for both the MLOF & CHAMP validation datasets highlight the model performance.

MLOF – Training & Validation

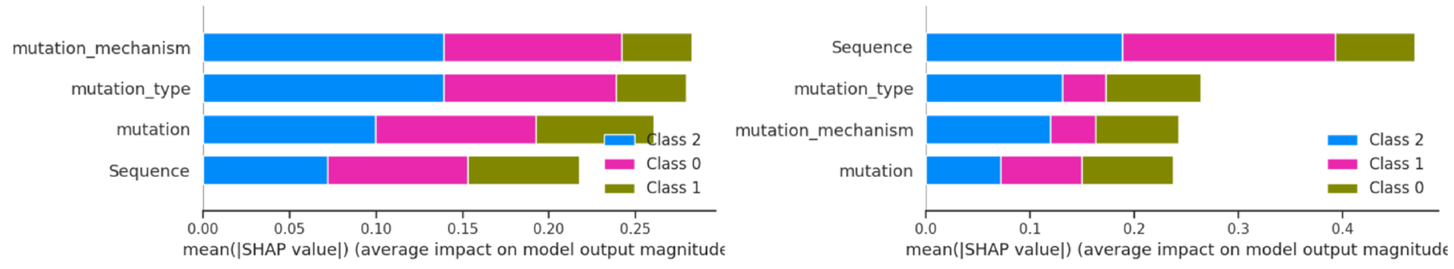
Model	Accuracy	Precision	Recall	F1-Score	Total
Random Forest	0.9694	0.99	0.99	0.99	3.93
Extreme Gradient Boosting	0.9694	0.99	0.99	0.99	3.93
Cat Boosting	0.9711	0.98	0.98	0.98	3.91
Gradient Boosting	0.9707	0.98	0.98	0.98	3.91
Light Gradient Boosting	0.9702	0.98	0.98	0.98	3.91
Logistic Regression	0.8576	0.81	0.81	0.79	3.26

MLOF Training - CHAMP Validation

Model	Accuracy	Precision	Recall	F1-Score	Total
Extreme Gradient Boosting	0.7515	0.94	0.94	0.94	3.57
Gradient Boosting	0.7488	0.94	0.94	0.94	3.56
Light Gradient Boosting	0.7408	0.94	0.94	0.94	3.56
Random Forest	0.7030	0.94	0.94	0.94	3.52
Cat Boosting	0.7443	0.93	0.93	0.93	3.53
Logistic Regression	0.5339	0.60	0.70	0.64	2.47



- We utilized Explainable AI (XAI) via SHAP (SHapley Additive exPlanations) to rank the variables associated with disease severity



CONCLUSION

- Machine learning based analysis of MLOF and CHAMP datasets demonstrates the successful predictive features of FVIII protein mutations for disease severity in HA patients.
- Severity prediction can aide in the treatment and prevention of hemophilia related complications such as bleeding in female carriers.
- These results can be valuable for future studies in achieving better treatment and clinical outcomes for patients.
  - Severity prediction from genotyped information can also further aid in the prediction of inhibitor development during treatment.
- We employed a “hypothesis free” approach to identify which variables would have a larger impact on the disease severity.