Genetic Variant Classifications

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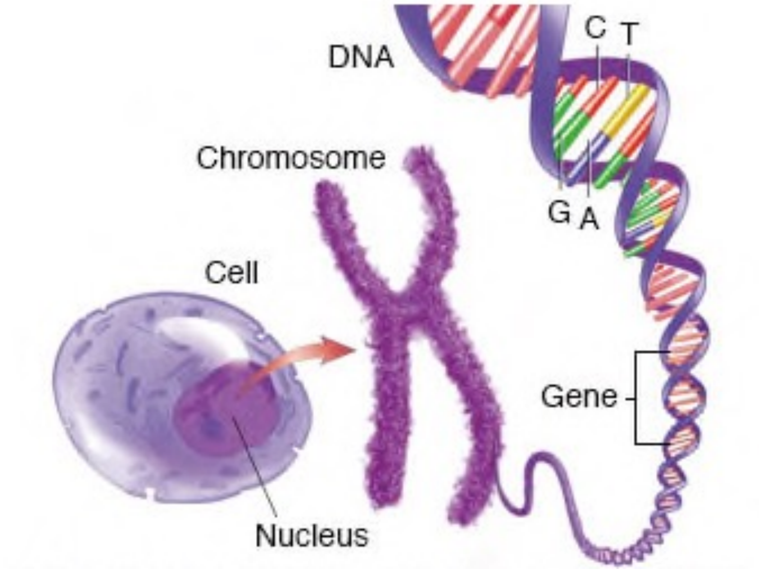
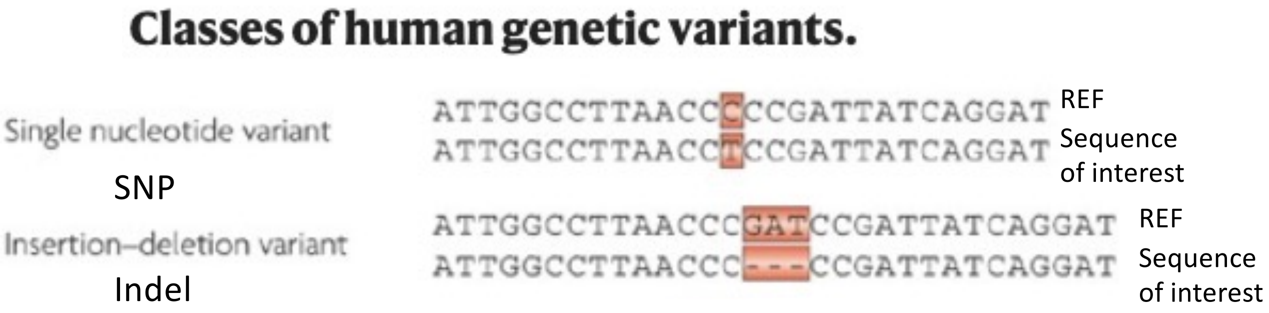
Genetic variants come from the changes of DNA sequences





Classes of human genetic variants.

Single nucleotide variant

SNP

ATTGGCCTTAACCCCCGATTATCAGGAT REF

ATTGGCCTTAACCTCCGATTATCAGGAT Sequence of interest

Insertion–deletion variant

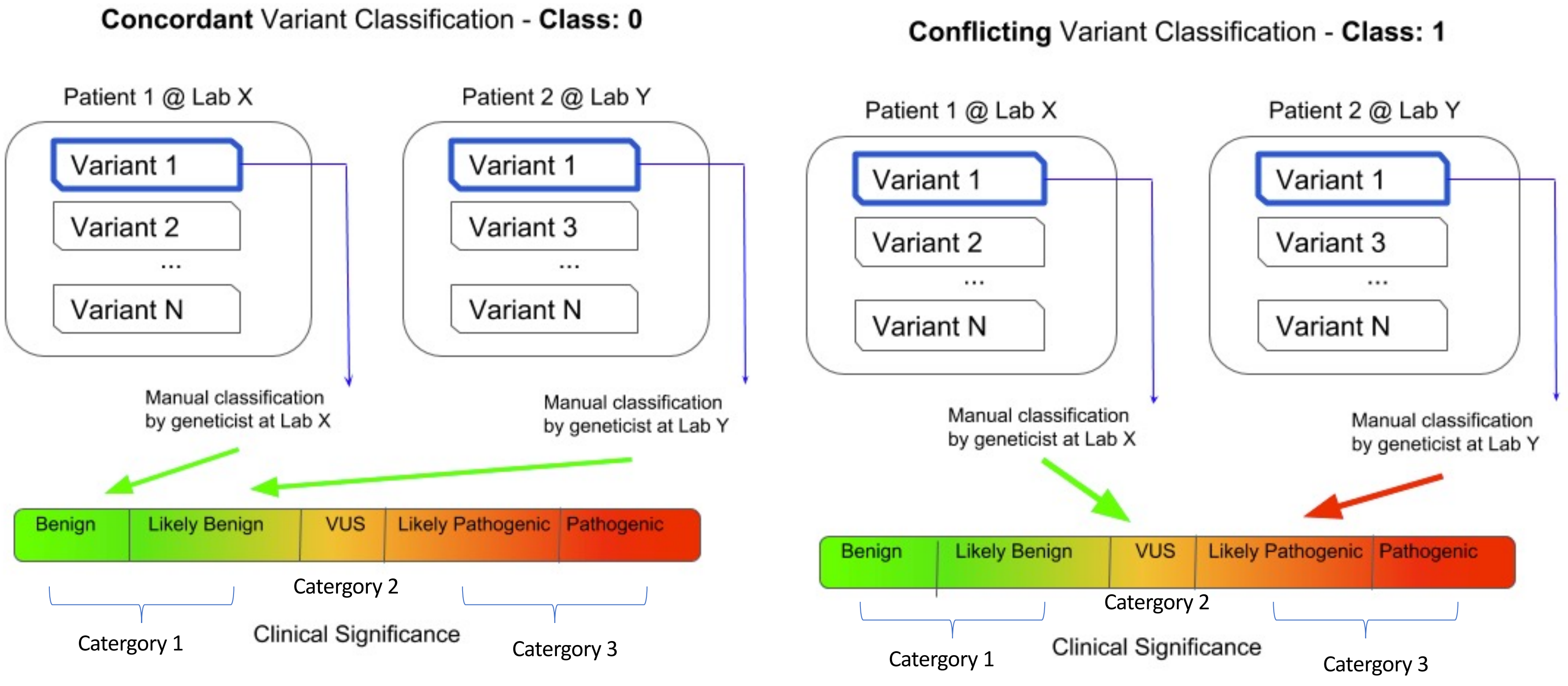
Indel

ATTGGCCTTAACCCGATCCGATTATCAGGAT REF

ATTGGCCTTAACCC---CCGATTATCAGGAT Sequence of interest

- Variants might have negative, little or no effect to diseases

Genetic variants are classified manually which resulting in conflicting classification



Concordant Variant Classification - **Class: 0**

Patient 1 @ Lab X

Variant 1

Variant 2

...

Variant N

Patient 2 @ Lab Y

Variant 1

Variant 3

...

Variant N

Manual classification by geneticist at Lab X

Manual classification by geneticist at Lab Y

Benign | Likely Benign | VUS | Likely Pathogenic | Pathogenic

Catergory 1

Catergory 2

Catergory 3

Clinical Significance

Conflicting Variant Classification - **Class: 1**

Patient 1 @ Lab X

Variant 1

Variant 2

...

Variant N

Patient 2 @ Lab Y

Variant 1

Variant 3

...

Variant N

Manual classification by geneticist at Lab X

Manual classification by geneticist at Lab Y

Benign | Likely Benign | VUS | Likely Pathogenic | Pathogenic

Catergory 1

Catergory 2

Catergory 3

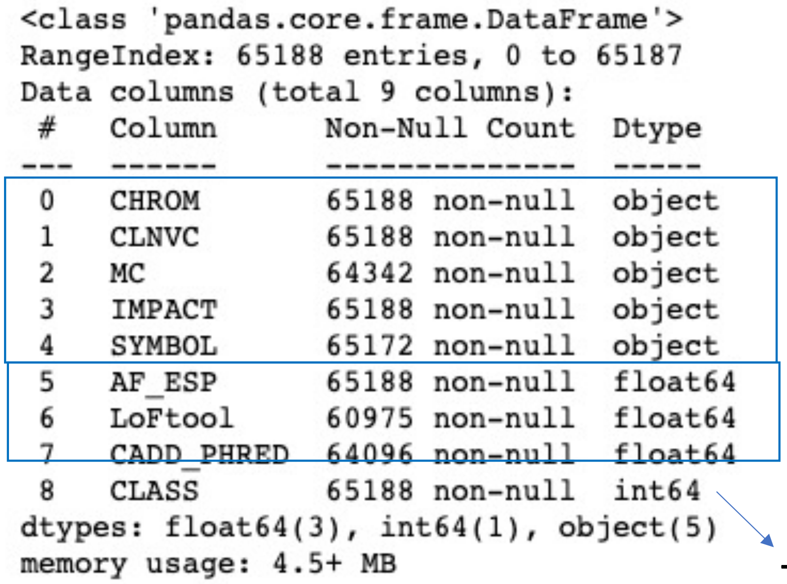
Clinical Significance

Data exploration analysis

clinvar_conflicting.csv (Kaggle)
(46 features)

Remove features

1. Redundant
2. Not correlated
3. Have > 90% nan



```
<class 'pandas.core.frame.DataFrame'>
RangeIndex: 65188 entries, 0 to 65187
Data columns (total 9 columns):
 #   Column      Non-Null Count  Dtype
---  ------      --------------  -----
 0   CHROM       65188 non-null  object
 1   CLNVC       65188 non-null  object
 2   MC          64342 non-null  object
 3   IMPACT      65188 non-null  object
 4   SYMBOL      65172 non-null  object
 5   AF_ESP      65188 non-null  float64
 6   LoFtool     60975 non-null  float64
 7   CADD_PHRED  64096 non-null  float64
 8   CLASS       65188 non-null  int64
dtypes: float64(3), int64(1), object(5)
memory usage: 4.5+ MB
```

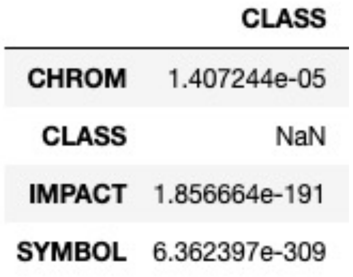
Categorical features :
CHROM- chromosome
CLNVC - Variant Type
MC - Molecular consequence
IMPACT - the impact of the variants
SYMBOL - Gene Name

Numerical features:
AF_ESP - Allele frequencies of variants
LoFtool - Loss of Function tolerance score
CADD_PHRED - Scoring the deleteriousness of the variants

Target:
class 0 (concordant variant classification)
class 1 (conflicting variant classification)

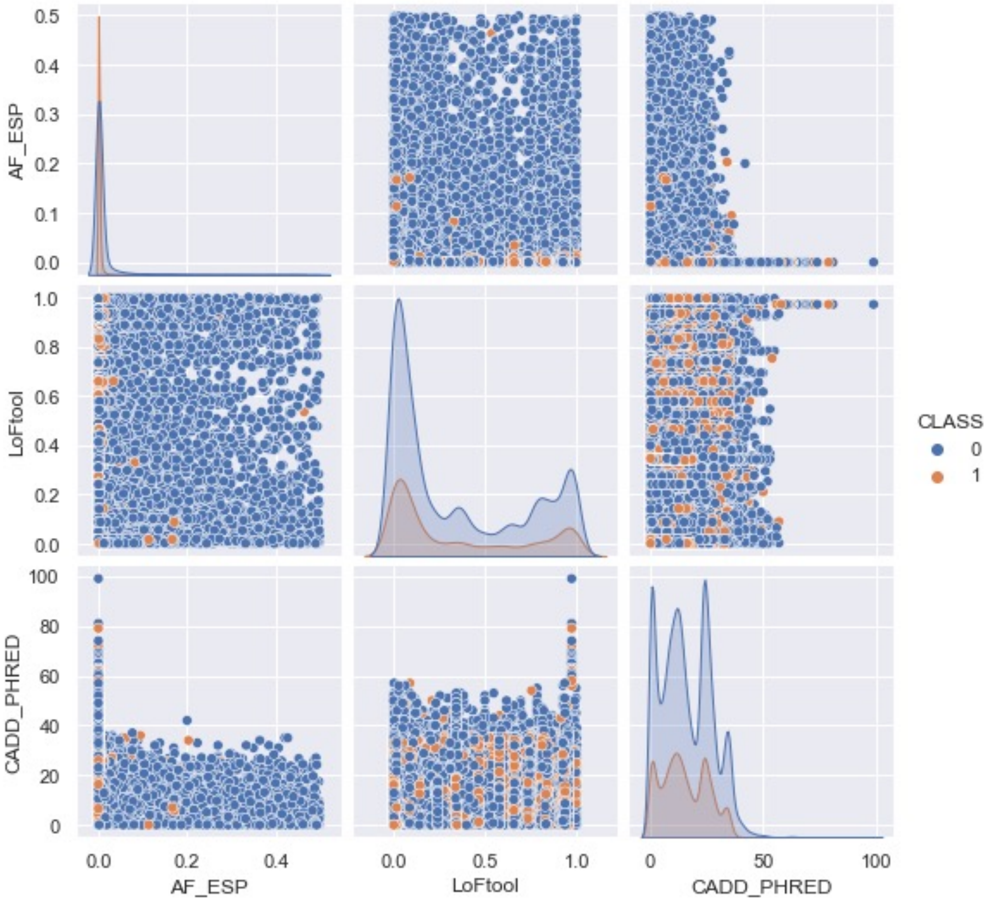
AF_ESP and SYMBOL are more distinguishable among 2 classes

Chi2 test for **categorical features** (p-value)



	CLASS
CHROM	1.407244e-05
CLASS	NaN
IMPACT	1.856664e-191
SYMBOL	6.362397e-309

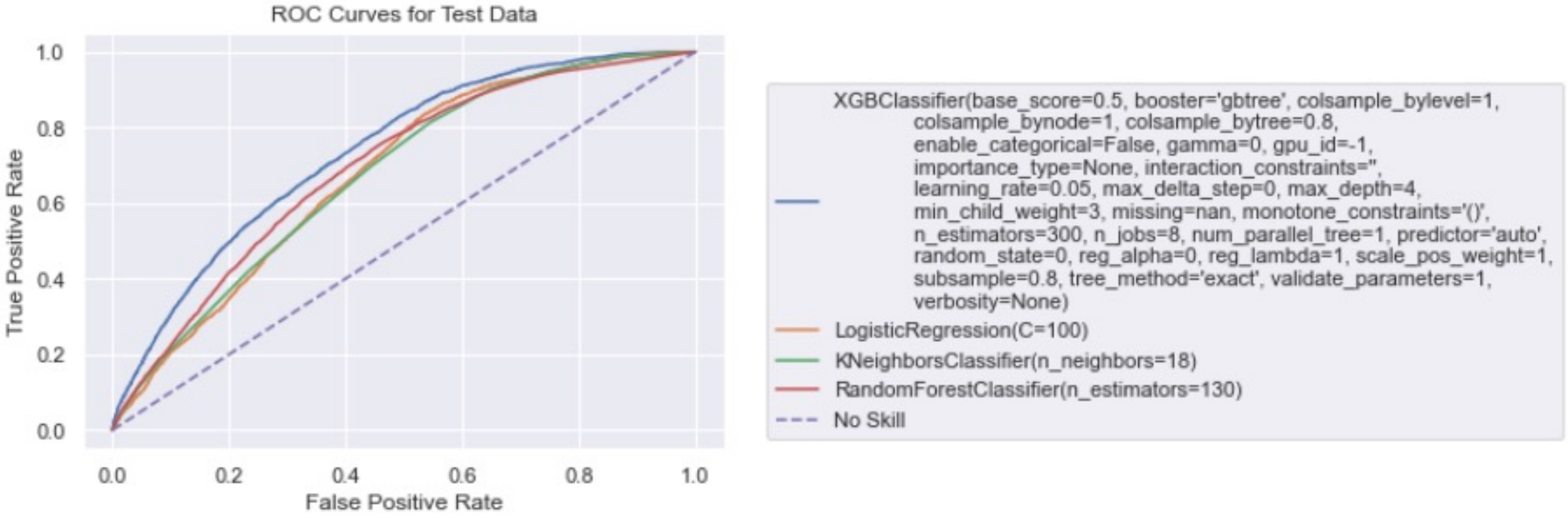
Pairplot for **numerical features**

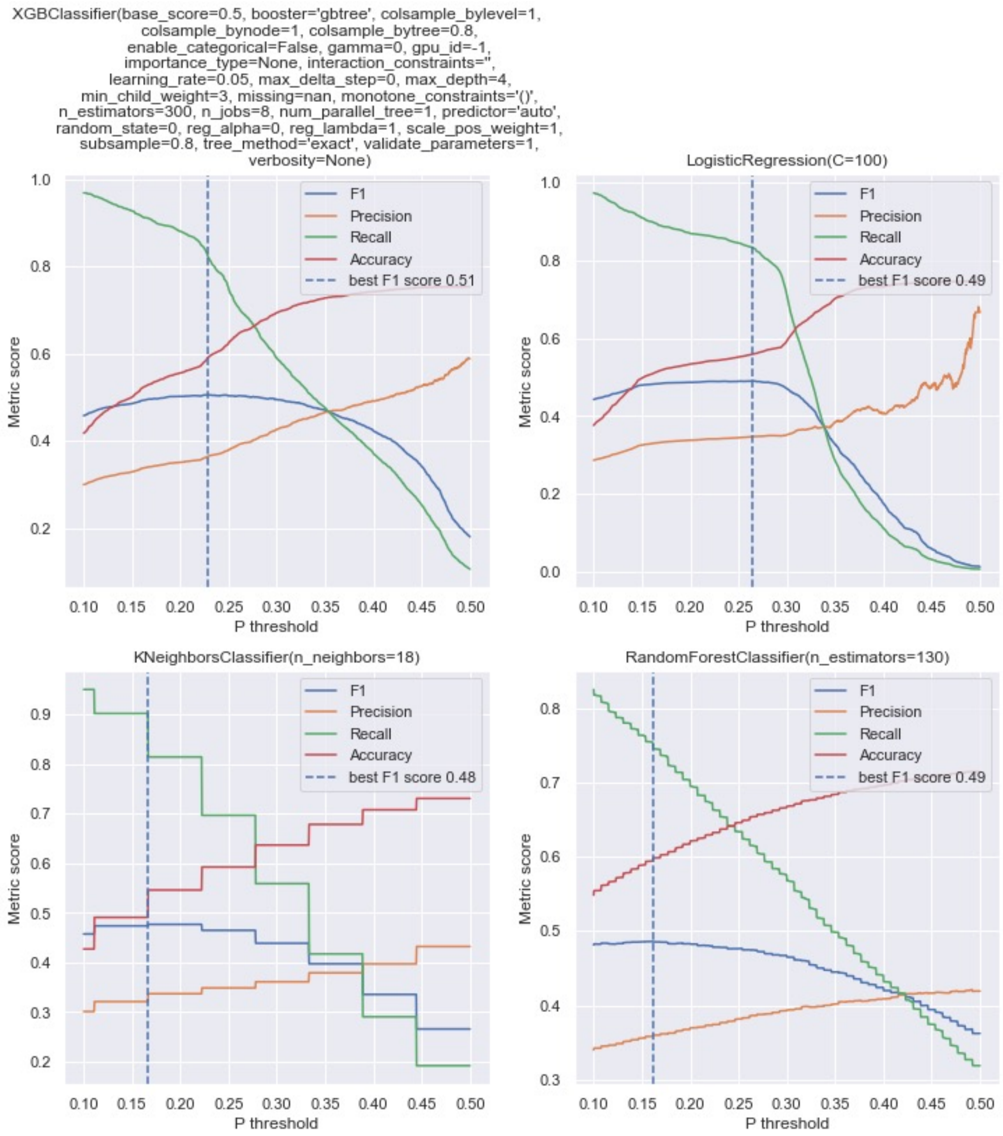


Data preprocessing

- Convert categorical features into dummies variables
- Scale the numerical data
- Class rebalance
- Model fitting (GridSearch for hyperparameter optimalization)

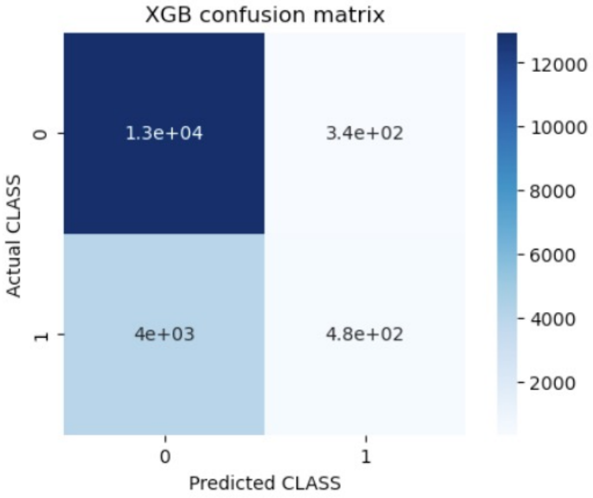
XGBoost tree has better performance for the prediction



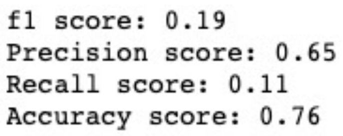


XGB model has the highest F1 scores at the P threshold of 0.22

AF (variant frequency), symbol (gene names) and MC(molecular consequences) are the important features

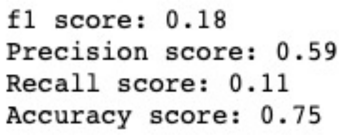


Training set

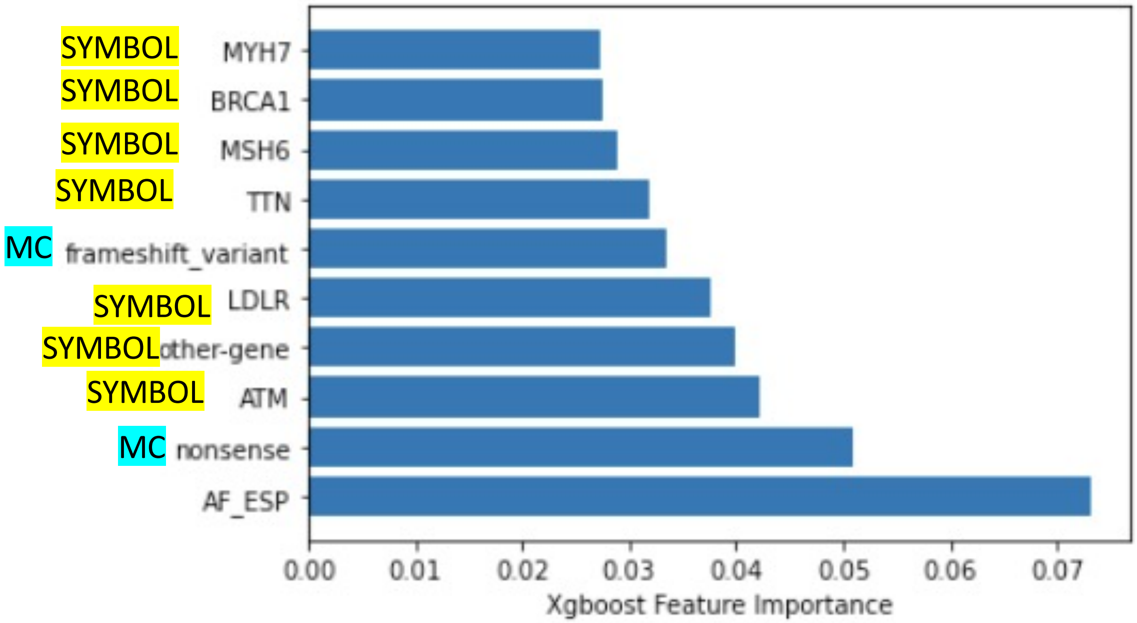


```
f1 score: 0.19
Precision score: 0.65
Recall score: 0.11
Accuracy score: 0.76
```

Test set



```
f1 score: 0.18
Precision score: 0.59
Recall score: 0.11
Accuracy score: 0.75
```



Discussion and future work

- The variants with the low allele frequency (AF), do not have the known deleterious molecular consequence (MC) and located at the cancer genes (SYMBOL) tend to have the conflicting classification.

- The variants within the conflicting classification can be compared with the cancer variant databases to be classified better.