INDIAN INSTITUTE OF TECHNOLOGY DELHI

CERTIFICATE PAGE

REPORT OF PROJECT AWARDED SURA 2021

Machine Learning for Breast Cancer Risk Prediction in Indian Patients

Submitted by: **Yukti Makhija** (2019BB10067) and **Samarth Bhatia** (2019CH10124)

Name and Signature of the Facilitator:	Prof. Ishaan Gupta
Department of the Facilitator:	School of Artificial Intelligence, Biochemical Engineering and Biotechnology

Table of Contents

Introduction

According to WHO experts, breast cancer is the most common cancer among women, accounting for 12% of total cancer cases annually [1]. Researchers have found a legion of factors including hormonal, genetic, environmental, and lifestyle, which can increase the risk of developing breast cancer. About 5 to 10 percent of breast cancers cluster in families and are linked to gene mutations passed through generations. [2]

In developing countries, healthcare resources are limited and most of the population depends on public facilities. This constraints developing countries to use different ways to diagnose cancer which take fewer resources, thus preventing us from making direct comparisons between the indicators of breast cancer in developed countries and those in developing countries. [3] There has been an upsurge of breast cancer patients in India, with it occurring as often as 1 in 29 women. [4]

The survival rate for breast cancer patients in India is 34%, which is 24% less than in high-income countries like the US [5]. The high mortality observed in India is attributed to the limited cancer screening facilities, delayed diagnosis, and poor disease management strategies. This warrants the need for the development of some predictive methods for risk-stratification tailored to the Indian population. Recent advances in digital health and the widespread use of Electronic Medical Records (EMRs) systems have made the use of data-driven approaches feasible. Machine Learning is the preferred tool for analyzing and identifying patterns in large datasets.

The Role of Prediction Models

In recent years, the field of Oncology has taken a new direction towards preventive and predictive medicine. The widespread deployment of prediction and risk models in clinical practice will assist in decision-making, performing a risk assessment to help establish preventive measures, thereby permitting early diagnosis and improving the quality of patient care. In breast and ovarian cancer, timely diagnosis followed by proper treatment and care significantly enhances prognosis and patient survival. Such models have been developed for Western populations such as BOADICEA and BCRAT but are yet to be implemented and optimized for the Indian population.

Challenges in Risk Prediction in Breast Cancer

Currently, in labs, National Comprehensive Cancer Network (NCCN) guidelines are being used to advise genetic testing, but they have been shown by multiple studies to be ineffective and miss out on many potential high-risk patients with mutations.

In India, we neither have reliable estimates about the prevalence of these mutations, nor any reliable fixed criteria (which needs to be adapted to India) regarding who is to be tested and who is not.

Literature Review

Presently, two major tools are used for predicting the risk of breast and ovarian cancer. These are Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and Breast Cancer Risk Assessment Tool (BCRAT).

BOADICEA

Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm or BOADICEA is a piece of polygenic software used to calculate the risks of breast and ovarian cancer in women based on their family history. It does so by computing the probability of a patient being a carrier of mutations in the susceptible ovarian and breast cancer genes and the age-specific risk of cancer. [6]
It takes into account both pathology data and population-specific cancer incidence history. BOADICEA uses features such as family pedigree (beyond second-degree relatives), age, gender, deceased status, ancestry (such as Ashkenazi Jewish), ovary cancer onset age, prostate cancer onset age(males), pancreatic cancer, pancreatic cancer onset age, breast cancer onset age, contralateral breast cancer onset age, estrogen receptor, progesterone receptor, genetic mutations in BRCA1, BRCA2, PALB2, CHEK2, and ATM. BOADICEA is based on the genetic model presented below, taking into account measured genotypes, as well as family history related to breast cancer. [7]

$$\lambda^{(i)}(t) = \lambda_0(t)$$
$$\exp\left(\sum_{\mu=1}^{6}\left(\beta_{MG\mu}(t) + \sum_{\rho}\boldsymbol{\beta}_{RF\rho\mu}(t)\cdot \boldsymbol{z}_{RF\rho}^{(i)}\right)\prod_{\nu=1}^{\mu-1}\left(1-G_{\nu}^{(i)}\right)G_{\mu}^{(i)} + \beta_{PG}(t)\,x_{P}^{(i)}\right).$$

Where,

$\boldsymbol{\lambda^{(i)}(t)}$ = Breast Cancer Incidence
$\boldsymbol{\lambda_0(t)}$ = Baseline Incidence
$\boldsymbol{G_{\mu}}$ = Indicator variables for the presence/absence of a pathogenic variant in a major gene
$\boldsymbol{\beta_{RF\rho\mu}(t)}$ = vector of the log-RRs associated with RF ρ at age t, which may depend on the major genotype, μ
$\boldsymbol{\beta_{MG\mu}(t)}$ = Age-specific log-relative risks associated with the major genes
$\boldsymbol{x_P^{(i)}}$ = Polygenotype for individual i
$\boldsymbol{z^{(i)}_{RF\rho}}$ = Corresponding vector of indicator variables (0 or 1) that indicate the category of RF ρ for individual i
$\boldsymbol{\beta_{PG}(t)}$ = Age-specific log-RR associated with the polygene

BCRAT

The Breast Cancer Risk Assessment Tool allows health professionals to estimate a woman's risk of developing invasive breast cancer over the next five years and up to age 90 (lifetime risk). BCRAT uses a woman's personal medical and reproductive history and the history of breast cancer among her first-degree relatives (mother, sisters, daughters) to estimate absolute breast cancer risk—her chance or probability of developing invasive breast cancer in a defined age interval. [8]

BCRAT uses eight features, namely: age, age of menarche, age of first live birth, number of previous biopsies, benign disease, BRCA mutations, race, and number of first-degree relatives affected with breast cancer.

Limitations of these Models

Both models assume a linear relationship between risk factors and cancer development [9], thereby overlooking complex relationships between various risk factors and cancer. This simplistic approach reduces the efficacy of the models.

Another issue that remains unattended: all the work and the training of models has been done on foreign patients' data. In our recent work [10] on COVID-19, we found that the validation results were poor when the machine learning model trained on data of Wuhan patients was used on a cohort of Indian patients, and how much improvement can be made by making the model keeping in mind the demographic differences. These variations arise due to genetic differences and alter the ranges of the measured parameters.

Machine Learning models compared to BOADICEA and BCRAT

In a recent paper by Ming et al. [9], the authors have tested how machine learning models perform

in comparison to the two state-of-the-art tools and found that machine learning models consistently performed better than them, getting AU-ROC(Area Under Receiver Operating Characteristic) scores of ~90% after 10-fold cross-validation to even out the effects of imbalances. In contrast, BOADICEA and BCRAT got only 59.31% and 62.40%, respectively. Of course, this is the trade-off between an interpretable statistical model and a black-box decision tree machine learning model like AdaBoost (Adaptive Boosting) or RF (Random Forests). In their paper, Ming et al. had trained two sets of machine learning models, one with features common to BOADICEA, and the other with BCRAT.

Materials and Methods

Data Collection

The data used for this study was collected in collaboration with the Oncology Department at All India Institute of Medical Sciences (AIIMS), New Delhi. All the subjects had a confirmed diagnosis of breast cancer and were receiving treatment at AIIMS. The data for 236 patients admitted in the year 2019-2020 was curated. All the information used for analysis was obtained at the time of diagnosis.

The features were divided into five broad categories as Clinical features (including Age, TNBC, Estrogen/Progesterone Levels), Reproductive History (including Age at Menarche, Age at first childbirth, Number and Gender of children), Psychological Factors (including Occupation, Marital Status, Alcohol use), Family History (including No. of affected first and second-degree relatives), and Genetic Mutations.

Genetic Mutations can be categorized into two categories:

- Pathogenic Gene Mutations: There is plenty of literature available that validates the role played by these genes in Breast Cancer. The following genes belong to this category. *BRCA1, BRCA2, PALB2, RAD51d, RAD50, FANCI, ATM, TP53, MSH2, MUTYH*
- VUS (Variants of Uncertain Significance): Not much is known about these mutations and it is not known if they affect the risk of breast cancer either.

There were a total of 115 features in the raw dataset after this step was over.

Preprocessing

We started with a total of 115 features distributed in five categories. The data was cleaned up by deleting any feature columns with more than 10% of missing data and imputing the remaining missing data using mode for the categorical features and there were no missing values for continuous features.
With this and some manual cleanup of misentered/wrongly-formatted values, we ended up with a dataset of 236 patients and 44 features. Out of these 236 patients, 98 (41.52%) didn't have any genetic mutations while the remaining 138 (58.47%) had mutations in pathogenic genes or unknown genes or even both. Mutations in one or more pathogenic genes were observed in 44 (31.88%) patients out of 138 patients. VUS mutations were present in 115 (48.72%) patients out of the total 236 patients. We then used this data for analysis and training purposes.

Clinical Data	Reproductive History	Psychological Factors	Family History
• Age • Weight • Height • T-stage • N-stage • M-stage • TNBC • Estrogen and Progesterone Levels • Clinical Stage of cancer • Two Breast Primaries • RRSO Surgery Advised/Done • RRM Surgery Advised/Done • Type of cancer - Metachronous or Synchronous • History of Hysterectomy	• Age at Menarche • Number of Children • Gender of Children • Duration of Breastfeeding • Age at first Childbirth • Usage of Oral Contraceptive Pill (OCP) • Tubal Ligation	• Occupation • Marital Status • Any PTSD • Distress levels • Anxiety levels • Alcohol use **The following scores were calculated on the basis of the stress/anxiety and depression levels and PTSD:** **- DASS-21(Depression, Anxiety and Stress Scale) score** **- IES-R (Impact of Event Scale) score**	• Ethnicity • Number of first-degree relatives • Number of affected first-degree relatives • Number of Family Members Tested • Number of second-degree relatives • Number of affected second-degree relatives

Table 1: List of features present in the preprocessed dataset

Dimensionality Reduction and Visualisation

The preliminary analysis focused on visualizing the data and plotting the distributions of various features present in the dataset to identify patterns in the data.
Various state-of-the-art methods were used to visualize the trends in data and whether it clustered easily and the different classes (based on Genetic Mutations) were distinguishable.
We compare the results for the following algorithms:

1. Principal Component Analysis (PCA)
2. t-Distributed Stochastic Neighbor Embedding (tSNE)
3. Linear Discriminant Analysis (LDA)
4. Neighborhood Component Analysis (NCA)
5. Uniform Manifold Approximation and Projection (UMAP)

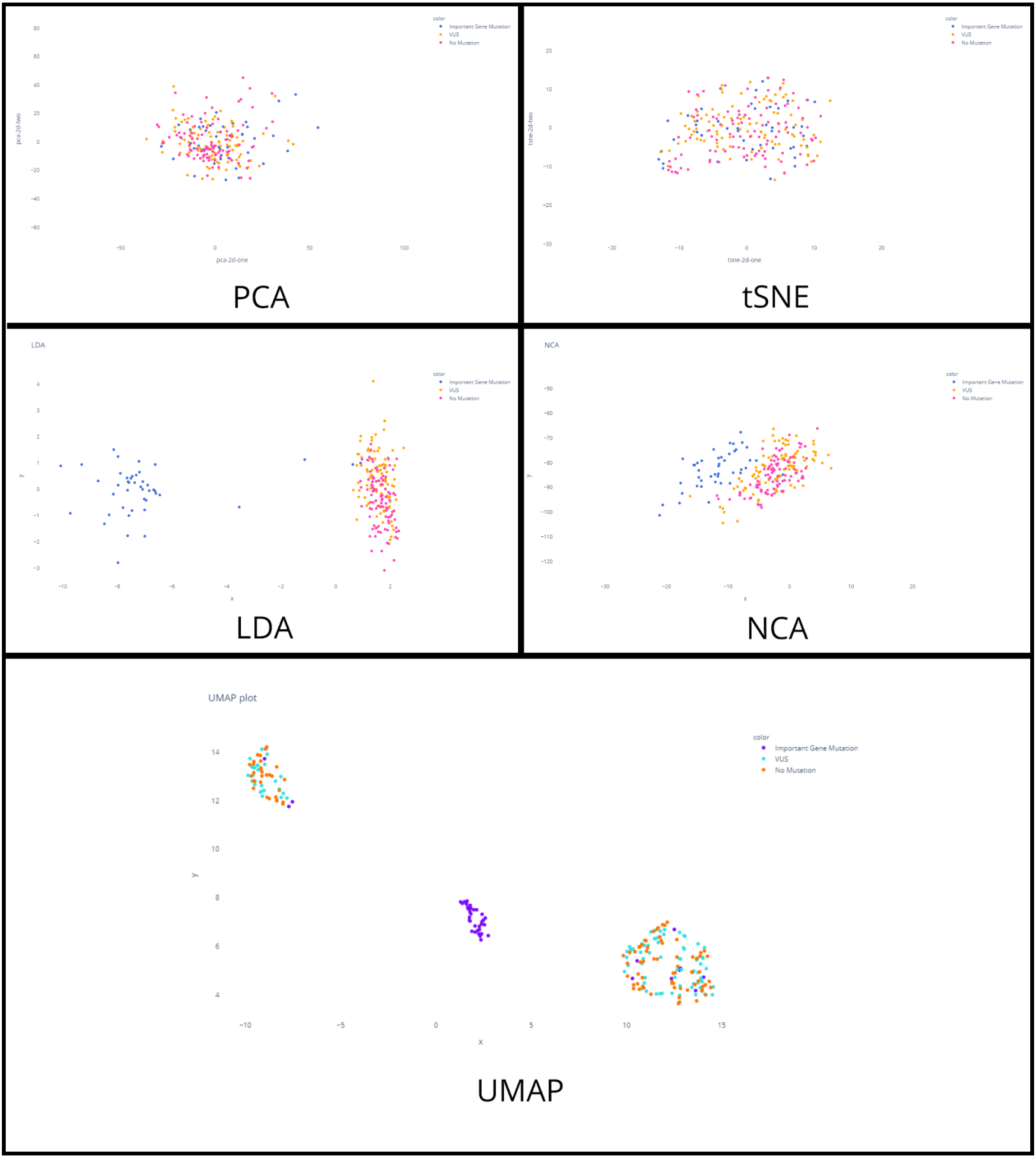

Figure 1: Comparison of different dimensionality reduction techniques

We tried 10 values for randomly chosen random seeds for all algorithms and picked the best plot (in which the clusters can be clearly seen).
As is evident from the figure, PCA and tSNE fail to properly cluster the data, whereas LDA, NCA, and UMAP work very well to cluster the data. We even tried first using PCA and tSNE for a variable high number of dimensions (n>2) and then further reducing dimensionality to 2 using UMAP, however, no improvements in the clusters were seen.
In all of these, only the pathogenic gene mutation cluster is significantly distinct compared to the no gene mutation and VUS clusters, which appear to be mixed. It is safe to assume that the data for no gene mutation and VUS cannot be differentiated in any high dimension. This means that these two act in the same way, as is affirmed by the name itself - Variant of Uncertain Significance. A VUS mutation's significance cannot be determined by any effects and thus acts the same way as if there was no gene mutation.
This also goes to affirm that an ML model would be able to differentiate between the different classes and our approach is valid.

Modeling Strategy

The goal of our project was to make a model which will assist in predicting what type of gene mutations are present in Indian breast cancer patients. Hence, we decided to keep genetic mutations as the outcome/target variable.
After performing a broad survey of different ML models, we decided to focus on CARTs (Classification and Regression Trees), and specifically the XGBoost algorithm.

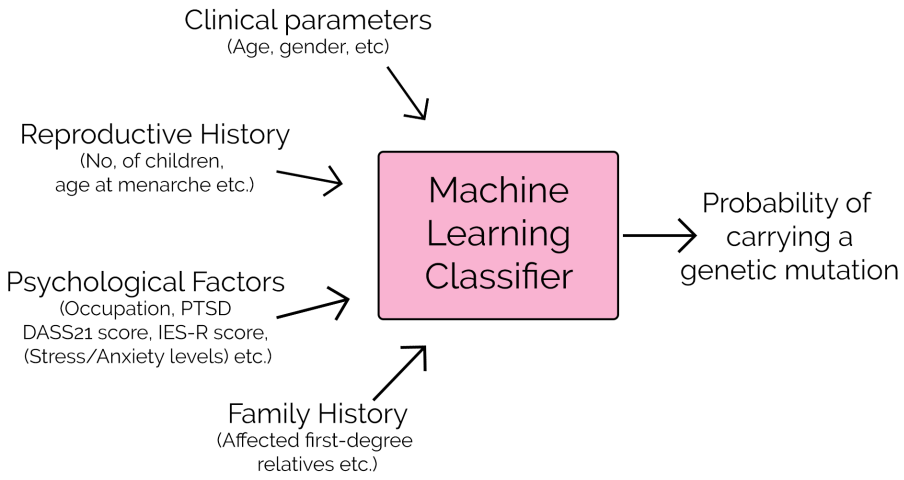

Figure 2: Effective Disease Management

Since the size of the dataset was small, instead of solving a multi-class classification problem, we decided to break the problem into 3 binary classification problems. To maintain uniformity in our analysis, the modeling strategy was kept the same for all three models. In the following sub-sections, we will describe the datasets for each model.

1. Any (Pathogenic or VUS) gene mutations prediction

Out of the 236 patients, 138 (58.47%) patients had gene mutations and were assigned class 1. The remaining patients were assigned class 0. In the next step, we split the dataset into training (75%) and validation (25%) datasets using stratified sampling to maintain the ratio of patients with and without mutations in both datasets. The validation set was kept held out from the training process in order to test the generalizability of the final model.
The final training dataset contained 179 patients (105 have mutations and 74 don't have any mutations) and the validation set had 57 patients (33 have mutations + 24 don't have any mutations).

2. Pathogenic gene mutation prediction

Out of the 236 patients, 44 (18.64%) had pathogenic mutations and were assigned class 1. The remaining were assigned class 0. Then, we split the dataset into training and validation datasets following the same 75-25 split using stratified sampling to represent both the classes in the datasets consistently and hence minimize the bias of the model towards any class.
The final training dataset contained 179 patients (33 have pathogenic mutations + 146 don't have pathogenic mutations) and the validation dataset had 57 patients (11 have pathogenic mutations + 46 don't have any pathogenic mutations).
In ML, the dataset is ideally 1:1 in terms of each class. However, for this model, since there was an imbalance in the number of patients in each class, we used the scale_pos_weight parameter of XGBoost to set the weight of the positive class (class 1) more than the negative class (class 0) and remove skewness.

3. VUS prediction

49.12% of patients were found to have mutations of unknown significance (VUS) and were assigned class 1. The remaining, 121(50.88%) patients, were assigned class 0. The training and validation datasets were generated using a 75-25 split in a similar fashion as before. Since both the classes had roughly 50% patients, there was no need to perform stratified sampling.
The final training dataset contained 179 patients (87 have VUS mutations + 92 don't have VUS mutations) and the validation dataset had 57 patients (28 have VUS mutations + 29 don't have VUS mutations).
As mentioned above, the modeling strategy was common to all three models. After obtaining the final training and validation sets, we started the training of the XGBoost model. We implemented a grid search algorithm that took the model and a matrix of hyperparameter values as input and output the best performing hyperparameters on the basis of the highest validation accuracy.
There is not much information about the role played by these mutations, hence our initial goal was to check if both the classes (0 and 1) are well-separable or not, and also check if the machine learning model can distinguish between the two based on clinical parameters.

Evaluation Methodology

Multiple metrics were used to evaluate the performance of all the models.
We used training and validation accuracy, sensitivity/recall, specificity, precision (PPV), NPV for the validation set, in addition to Area Under Curve of Receiver Operator Characteristics curve (AUC-ROC) and the Precision-Recall curves (AUC-PR) to ensure that the model is generalizable and is not overfitting. We achieved decent scores for these metrics especially for the Pathogenic mutation model and any gene model.
All these are reported in the tables in the Results section. We also plotted the confusion matrix, ROC, and PR curves for the validation set, and performed SHAP analysis on the model to tell which features contributed most to the model's values (and hence were more important). In other words, changing the value of the most important feature will cause the most change in the output of the model.
After completing feature engineering, we had a list of the features which had the greatest influence on the outcome. We also tried training ML models with only the top ten features and compared their performance to the original models. The idea behind this was to check if the top 10 features can capture the same information as the original model which contained 44 parameters and to quantify the role played by the remaining 34.

Results

1) Any Gene Prediction Model

Training Dataset	179 patients (105 have mutations + 74 don't have any mutations)
Validation Dataset	57 patients (33 have mutations + 24 don't have any mutations)
Training Accuracy	75.42%
Validation Accuracy	73.68%
F-score	0.7368
Sensitivity (Recall)	0.6364
Specificity	0.875
PPV (Precision)	0.875
NPV	0.875
AUC-ROC	0.76
AUC-PR	0.85

Table 2: Evaluation of the Any Gene Prediction Model

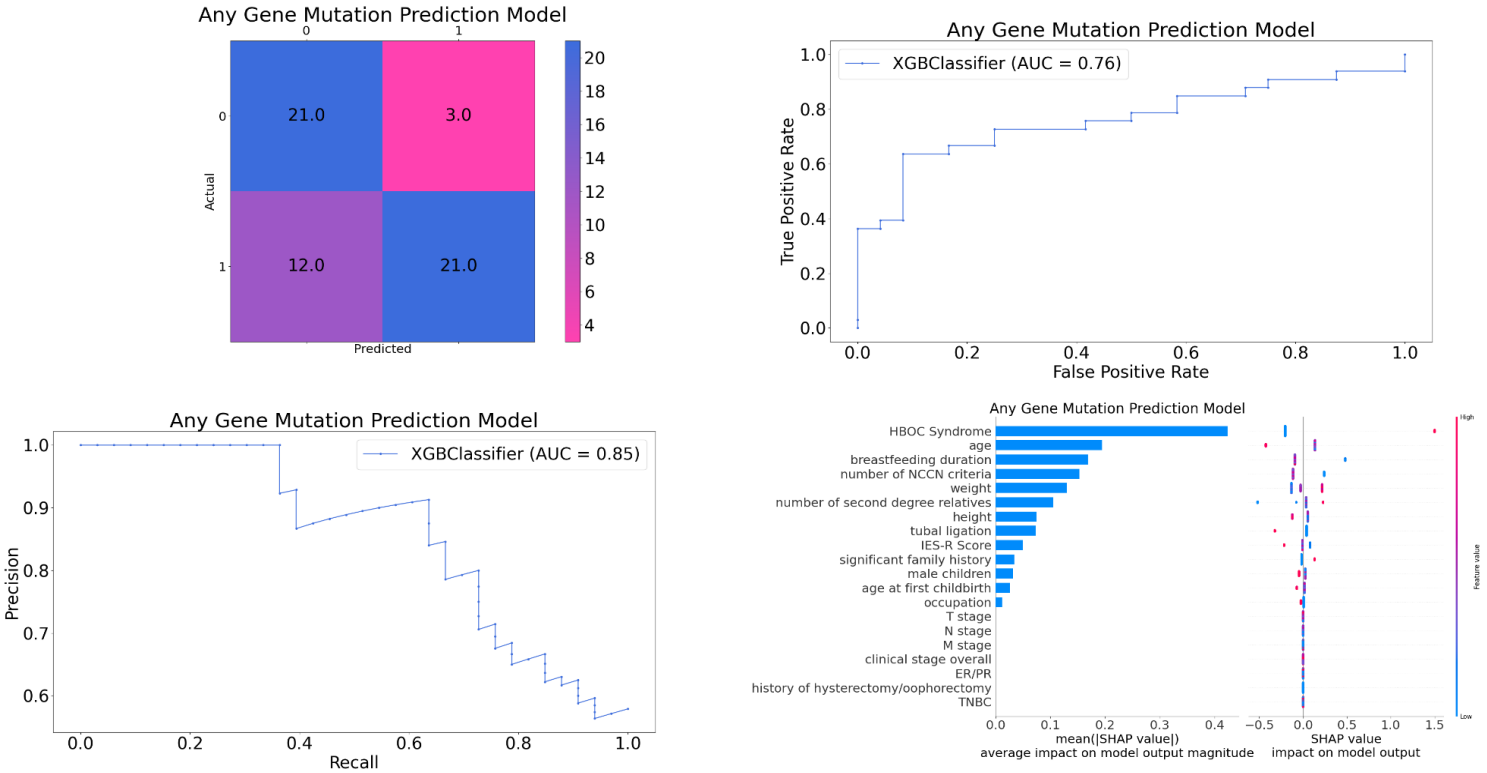

Figure 3: Confusion Matrix and ROC plot for Any Gene Mutation Prediction Model

2) Pathogenic Gene Prediction Model

Training Dataset	179 patients (33 have mutations + 146 don't have any mutations)
Validation Dataset	57 patients (11 have mutations + 46 don't have any mutations)
Training Accuracy	100%
Validation Accuracy	98.25%
F-score	0.95
Sensitivity (Recall)	0.91
Specificity	1.0
PPV (Precision)	1.0
NPV	1.0
AUC-ROC	0.95
AUC-PR	0.96

Table 3: Evaluation of the Pathogenic Gene Mutation Prediction Model

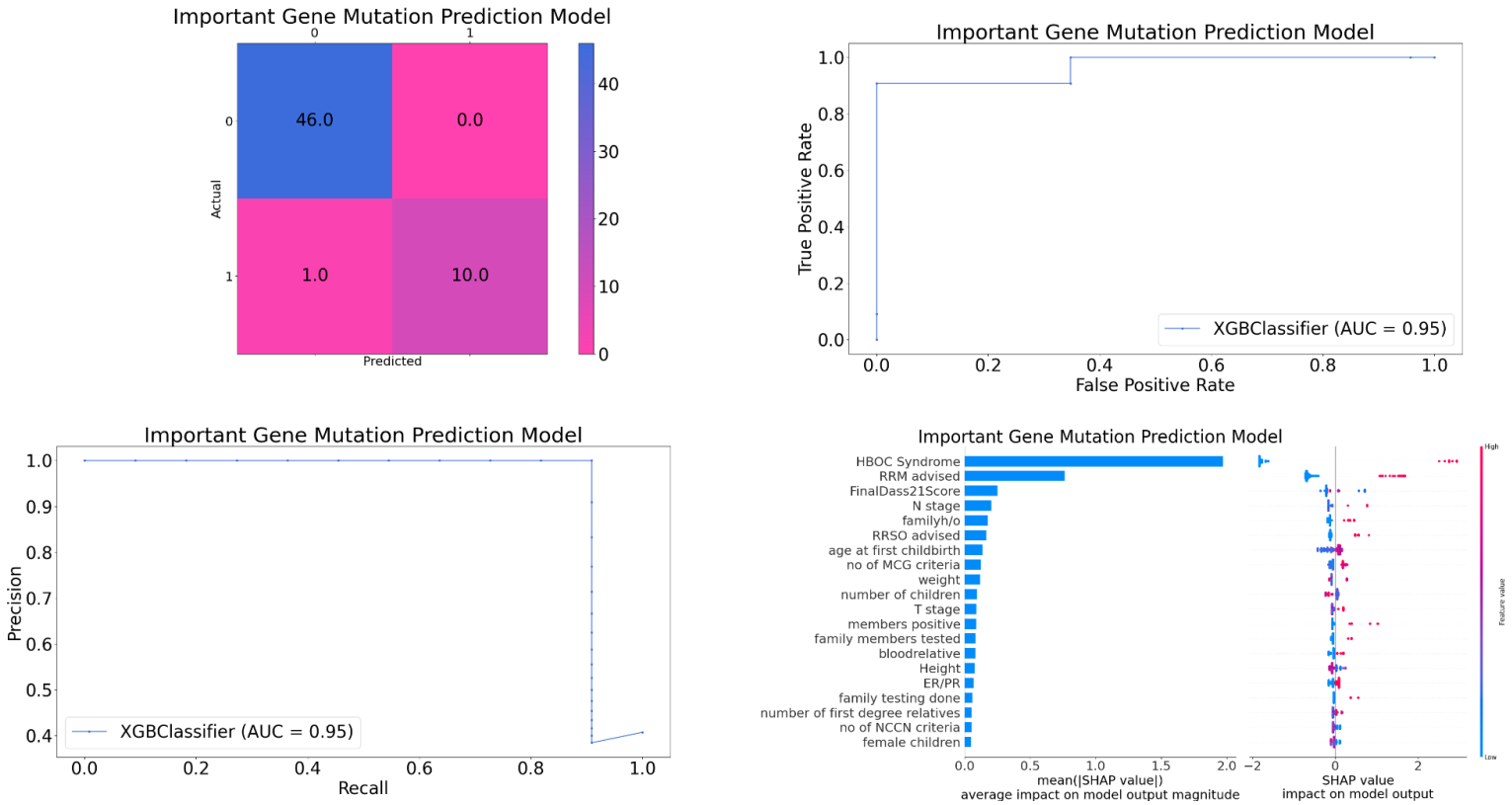

Figure 4: Plots of the Pathogenic Gene Mutation Prediction Model

3) VUS Prediction Model

Training Dataset	179 patients (87 have mutations + 92 don't have any mutations)
Validation Dataset	57 patients (28 have mutations + 29 don't have any mutations)
Training Accuracy	66.48%
Validation Accuracy	59.65%
F-score	0.5306
Sensitivity (Recall)	0.4643
Specificity	0.7241
PPV (Precision)	0.619
NPV	0.5833
AUC-ROC	0.59
AUC-PR	0.52

Table 4: Evaluation of the VUS Prediction Model

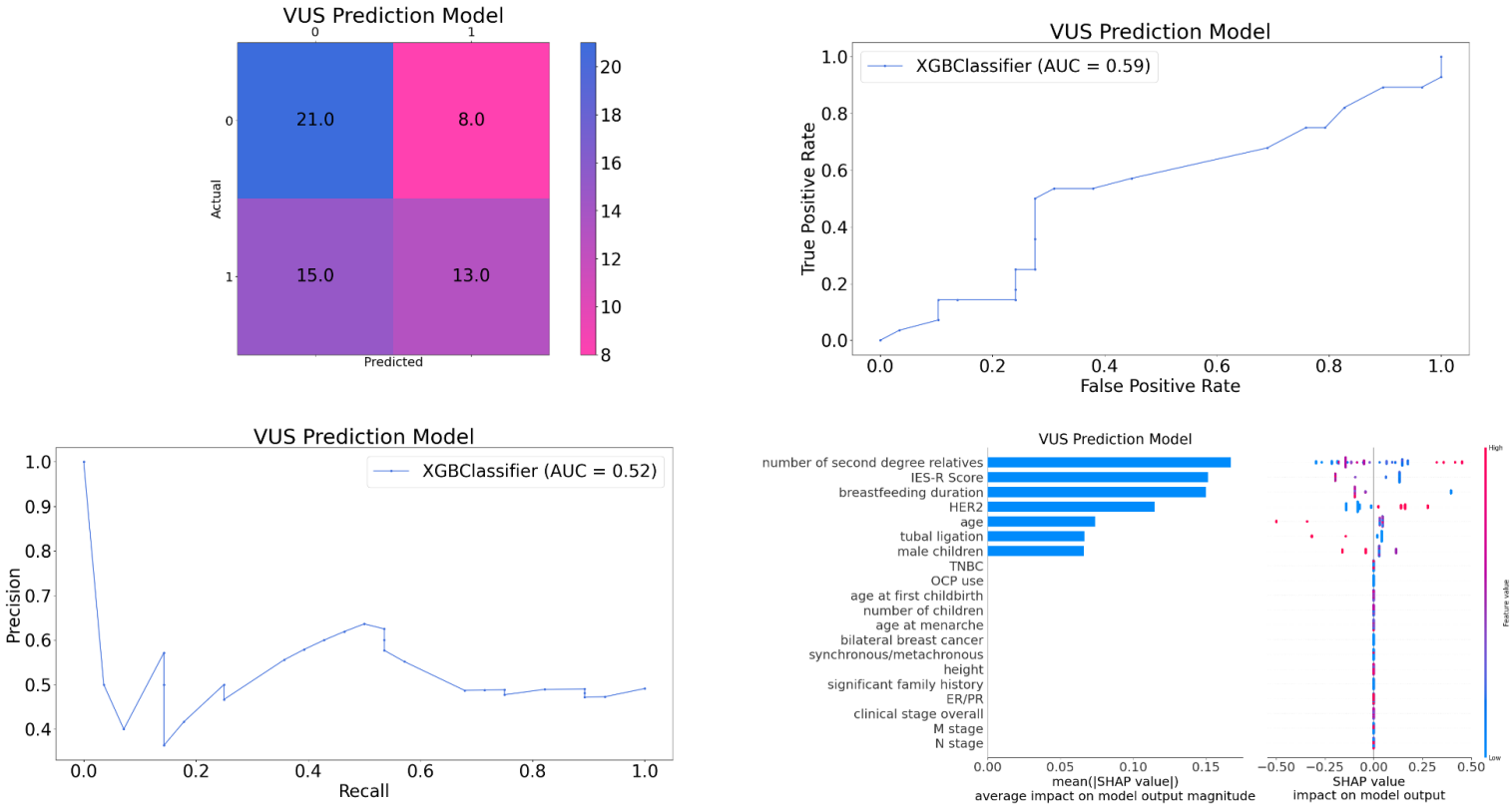

Figure 5: Plots of the VUS Prediction Model

Discussion and Conclusion

There is a lot to unpack from the results of these three models. We will start with the SHAP value plots. These plots detail how much every feature affects the output.

From the SHAP plot of the Any Gene Mutation Prediction model, the feature HBOC Syndrome and age are the 2 most important features which can describe the probability that a patient will have a mutation in any gene.
HBOC (Hereditary Breast and Ovarian Cancer) Syndrome is a "family history" feature; it is an inherited genetic condition that tells us that the patient is at increased risk of having breast/ovarian cancer.[11] This shows that our results are in agreement with the real world - as HBOC testing is considered quite important for breast/ovarian cancer.

In the Important Gene Mutation Prediction model's SHAP plots, we see that HBOC again shows up as the most important feature. We also see the Final DASS21 score as one of the most important features.
The DASS21 test measures three related negative emotional states: depression, anxiety, and tension/stress.[12] This shows that the mental health state of the patient also has some influence on the risk.
Moreover, we see that this model has very high accuracy and AUC-ROC (area under the receiver operator characteristics curve), even on the validation(holdout) dataset. This means that our model generalizes well and is ready to use in a real-world clinical setting to quantify the risks of mutations accurately.

Moving on to the last model, VUS Prediction, we notice that it has an AUC of 0.59, close to 0.5 (random classifier). This implies that the model was unable to learn a distinction between the two classes even after a considerable amount of hyperparameter tuning and optimization. This can be explained as VUS means a Variant of Uncertain Significance. This is because it has not been possible to show (medically) that these variants/mutations have any effect on real-world parameters, and are thus classified as uncertain (some variations might be marginally more important than the majority). [13]
Considering these points, it makes sense to have an AUC of around (bit more than) 0.5 as the majority of variations didn't change the features being observed, so classifying them will be as good as randomly assigning classes to each. However, for the minority that have a slight effect on the observed features, we are able to learn those, making the AUC go up slightly.

We have made a user-friendly web app to provide an easy interface to the models. It is online at: https://bcampred.team1719.repl.co.
The code for our work is available as a github repository at https://github.com/Plutonium-239/bc-risk.

Reduced Models

Since we had a lot of features on which the three models were trained, it would be impractical and inefficient in the real world to expect clinicians to enter all of those features, when the majority of them are not required. So, we decided to make reduced models which make use of only the 10 most important features. (10 was chosen as it seemed to cover most of the variance) We also performed further hyperparameter tuning and optimization for these reduced models. We were able to achieve almost the same levels of accuracy with the reduced models, so we're making a balanced tradeoff between performance and usability.
The results of the reduced models are as follows:

1. Any Gene Mutation Prediction Model (Reduced)

Training Dataset	179 patients (105 have mutations + 74 don't have any mutations)
Validation Dataset	57 patients (33 have mutations + 24 don't have any mutations)
Training Accuracy	78.21%
Test Accuracy	70.18%
F-score	0.7384
Sensitivity (Recall)	0.7273
Specificity	0.6667
PPV (Precision)	0.75
NPV	0.64
AUC-ROC	0.70

Table 5: Metrics of the reduced any gene mutation prediction model

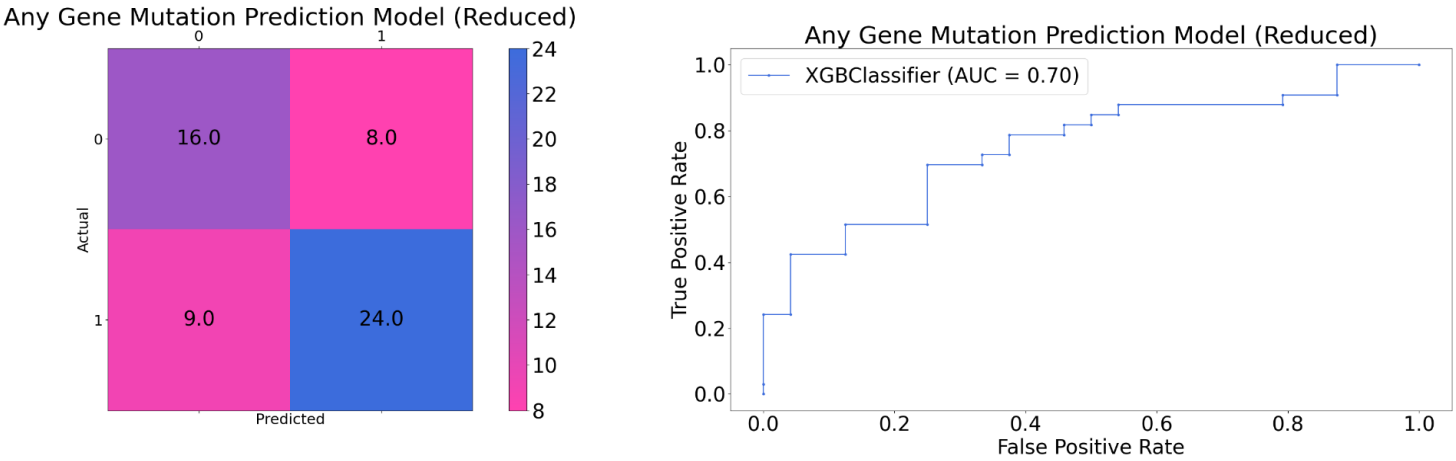

Figure 6: Confusion Matrix and ROC plot for reduced any gene mutation prediction model

2. Important Gene Mutation Prediction Model (Reduced)

Training Dataset	179 patients (33 have mutations + 146 don't have any mutations)
Validation Dataset	57 patients (11 have mutations + 46 don't have any mutations)
Training Accuracy	100%
Test Accuracy	96.49%
F-score	0.9
Sensitivity (Recall)	0.8182
Specificity	1.0
PPV (Precision)	1.0
NPV	0.9583
AUC-ROC	0.91

Table 6: Metrics of the reduced important gene mutation prediction model

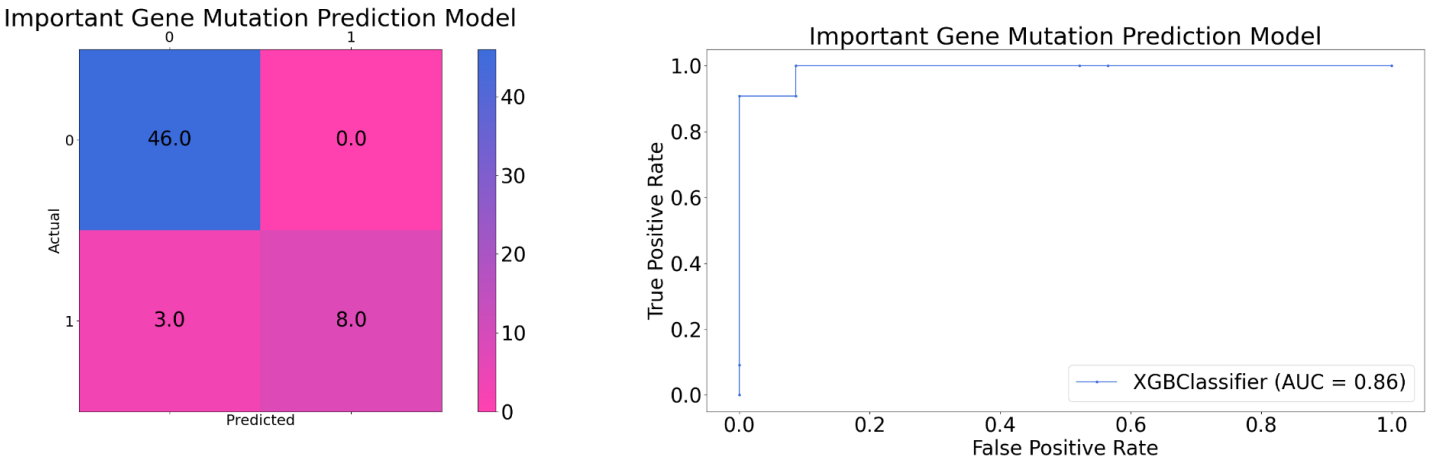

Figure 7: Confusion Matrix and ROC plot for reduced important gene mutation prediction model

3. VUS Prediction Model (Reduced)

Training Dataset	179 patients (87 have mutations + 92 don't have any mutations)
Validation Dataset	57 patients (28 have mutations + 29 don't have any mutations)
Training Accuracy	66.48%
Test Accuracy	59.65%
F-score	0.5306
Sensitivity (Recall)	0.4643
Specificity	0.7241
PPV (Precision)	0.619
NPV	0.5833
AUC-ROC	0.59

Table 7: Metrics of the reduced VUS prediction model

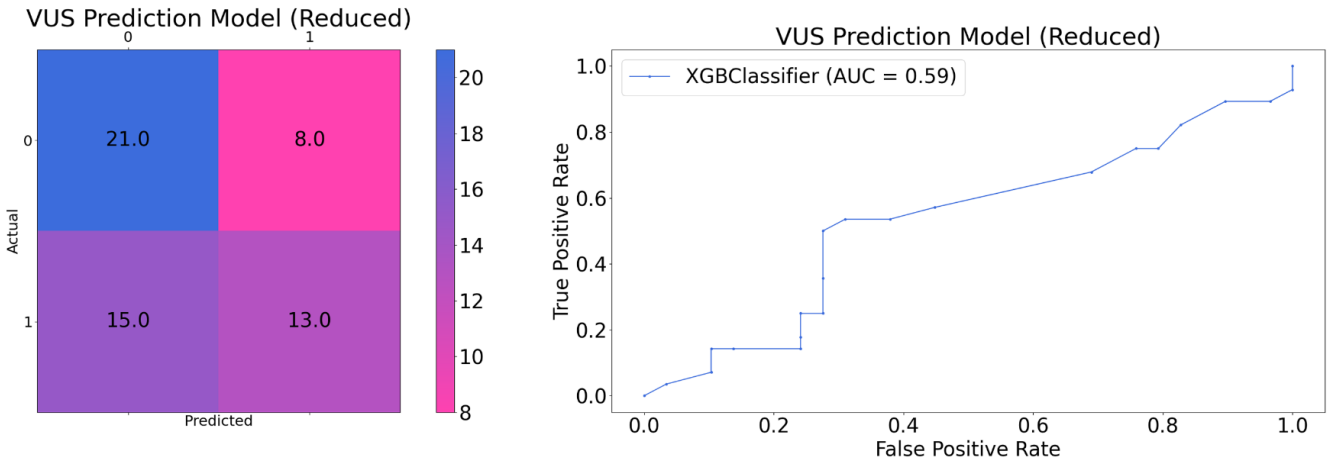

Figure 8: Confusion Matrix and ROC plot for reduced VUS prediction model

References

[1] "Breast cancer now most common form of cancer: WHO taking action." [Online]. Available: https://www.who.int/news/item/03-02-2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action. [Accessed: 19-Oct-2021]

[2] "Genetics," 21-Apr-2021. [Online]. Available: https://www.breastcancer.org/risk/factors/genetics. [Accessed: 19-Oct-2021]

[3] R. A. da Costa Vieira, G. Biller, G. Uemura, C. A. Ruiz, and M. P. Curado, "Breast cancer screening in developing countries," *Clinics* , vol. 72, no. 4, pp. 244–253, Apr. 2017, doi: 10.6061/clinics/2017(04)09. [Online]. Available: http://dx.doi.org/10.6061/clinics/2017(04)09

[4] P. Mathur *et al.*, "Cancer Statistics, 2020: Report From National Cancer Registry Programme, India," *JCO Global Oncology*, Jul. 2020, doi: 10.1200/GO.20.00122. [Online]. Available: http://dx.doi.org/10.1200/GO.20.00122. [Accessed: 19-Oct-2021]

[5] "Breast cancer." [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/breast-cancer. [Accessed: 19-Oct-2021]

[6] "BOADICEA - Centre for Cancer Genetic Epidemiology," 24-Feb-2014. [Online]. Available: https://ccge.medschl.cam.ac.uk/boadicea/. [Accessed: 19-Oct-2021]

[7] A. Lee *et al.*, "BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors," *Genet. Med.*, vol. 21, no. 8, pp. 1708–1718, Jan. 2019, doi: 10.1038/s41436-018-0406-9. [Online]. Available: https://www.nature.com/articles/s41436-018-0406-9. [Accessed: 19-Oct-2021]

[8] "Breast Cancer Risk Assessment Tool." [Online]. Available: https://www.cancer.gov/bcrisktool. [Accessed: 19-Oct-2021]

[9] C. Ming, V. Viassolo, N. Probst-Hensch, P. O. Chappuis, I. D. Dinov, and M. C. Katapodi, "Machine learning techniques for personalized breast cancer risk prediction: comparison with the BCRAT and BOADICEA models," *Breast Cancer Research*, vol. 21, no. 1. 2019 [Online]. Available: http://dx.doi.org/10.1186/s13058-019-1158-4

[10] Y. Makhija *et al.*, "Challenges in the application of a mortality prediction model for COVID-19 patients on an Indian cohort," 15-Jan-2021 [Online]. Available: http://arxiv.org/abs/2101.07215. [Accessed: 28-Oct-2021]

[11] "Hereditary Breast and Ovarian Cancer," 25-Jun-2012. [Online]. Available: https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer. [Accessed: 28-Oct-2021]

[12] "Depression Anxiety Stress Scale-21 (DASS21)." [Online]. Available: https://arc.psych.wisc.edu/self-report/depression-anxiety-stress-scale-21-dass21/. [Accessed: 28-Oct-2021]

[13] "VUS – the most maligned result in genetic testing - Blueprint Genetics," 31-Jan-2019. [Online]. Available: https://blueprintgenetics.com/resources/vus-the-most-maligned-result-in-genetic-testing/. [Accessed: 28-Oct-2021]