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DEVELOPMENT AND EVALUATION OF A MACHINE LEARNING-BASED FRAMEWORK FOR ANALYZING THE GENETIC PROGRESSION OF GLAUCOMA

Adejumo, Samuel Olujimi*[1,2], Alade, Samuel Mayowa[1,2], Ruphin, Kusinza Byamungu[3], Akano, Olatunde, Ayodeji [4],,Ezuruka Evelyn Ogochukwu[2], Adekunle, Adebowale Boluwatife[4]

[1]Department of Cybersecurity, Nnamdi Azikiwe University, Awka, Nigeria.
[2]Department of Computer Science, Nnamdi Azikiwe University, Awka, Nigeria.
[3]Department of Computer Science, Olivia University, Bujumbura, Burundi.
[4]Department of Computer Science, Abiola Ajimobi Technical University, Ibadan, Nigeria.

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***Corresponding Author: Adejumo, Samuel Olujimi**
Department of Cybersecurity, Nnamdi Azikiwe University, Awka, Nigeria.

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ABSTRACT

Glaucoma is a progressive neurodegenerative eye disease and a leading cause of irreversible blindness worldwide. Early diagnosis is critical for effective treatment, yet traditional diagnostic methods often lack the precision to detect the disease in its early stages. This study explores the use of machine learning techniques to analyze gene expression data for the accurate classification of glaucoma. Gene expression profiles were obtained from the publicly available E-GEOD-9963 dataset, which includes glaucoma and control samples. After preprocessing and selecting 14 validated glaucoma-related genes (such as *IL6*, *ERBB2*, and *CAV1*), the dataset was used to train and evaluate machine learning models, specifically Random Forest and XGBoost classifiers. The XGBOOST model achieved the highest accuracy (95%) and a ROC-AUC score of 0.91, making it the most effective model for glaucoma progression prediction in this study. Feature importance analysis highlighted the biological relevance of the selected genes. This research demonstrates the potential of machine learning in supporting early glaucoma diagnosis through genomic data, offering a scalable and data-driven approach to improving ophthalmic healthcare.

KEYWORDS: Neurogenerative, Genetic progression, glaucoma diagnosis.

1.0 INTRODUCTION

Glaucoma is recognized as one of the leading causes of irreversible blindness worldwide. This progressive optic neuropathy is characterized by the gradual loss of retinal ganglion cells and corresponding visual field deficits, frequently developing asymptomatically until advanced stages (Tham et al., 2014; Quigley & Broman, 2006). Over the past few decades, considerable research has underscored the role of genetic factors in glaucoma's pathogenesis. Mutations in genes such as Mycolin (*MYOC)*, Optinuerin (*OPTN)*, and Cytochrome P450 1B1 *CYP1B1* have been strongly linked with various glaucoma phenotypes, suggesting that a genetic predisposition plays a central role in the onset and progression of the disease (Weinreb et al., 2014; Wiggs & Pasquale, 2017)

The advent of high-throughput genomic technologies and advanced imaging modalities have revolutionized the study of glaucoma. Traditional clinical diagnostic methods, while useful, are limited by subjectivity and inter-observer variability. Consequently, there has been a growing interest in incorporating machine learning (ML) techniques into the analysis of glaucoma progression. ML algorithms such as support vector machines (SVM), random forests (RF), and deep learning architectures (including convolutional neural networks [CNN] and Long Short-Term Memory [LSTM] networks) have shown promise in processing complex datasets to predict disease trajectory and response to treatment (Chen et al., 2017; Libbrecht & Noble, 2015).

The integration of machine learning into glaucoma research not only facilitates the extraction of subtle patterns from high-dimensional genetic and imaging data but also contributes to the development of predictive models that can inform early diagnosis and personalized treatment strategies. This study focuses on applying advanced ML techniques to analyze genetic progression in glaucoma, aiming to address limitations in traditional diagnostic methodologies and improve overall patient outcomes.

In recent years, interdisciplinary approaches combining genomics, bioinformatics, and artificial intelligence have yielded promising insights. For instance, studies have demonstrated that ML models can detect early-stage glaucoma by identifying minor changes in genetic markers and optical coherence tomography (OCT) images that are not readily apparent through conventional analysis (Wiggs & Pasquale, 2017; Chen et al., 2017). Despite these advances, several challenges remain. Issues such as data heterogeneity, class imbalance, and the "black box" nature of many deep learning algorithms continue to hinder the translation of research findings into clinical practice.

2.0 REVIEW OF LITERATURE

This section provides a comprehensive review of the existing research and developments in the analysis of glaucoma progression using machine learning. It discusses key areas such as the genetic basis of glaucoma, traditional and advanced machine learning methodologies applied to genomic and clinical data, and the integration of multimodal data to improve predictive accuracy. The section is structured into the following sections: an overview of the genetic underpinnings of glaucoma, machine learning techniques in glaucoma genomics, challenges and limitations of current models, and a gap analysis of the literature.

2.1 Genetic Basis of Glaucoma

Glaucoma is a progressive optic neuropathy marked by the loss of retinal ganglion cells and corresponding visual field deficits. Several studies have identified genetic markers—including Mycolin MYOC, Optinuerin OPTN, and Cytochrome P450 1B1 CYP1B1, that significantly contribute to disease risk (Wiggs & Pasquale, 2017; Weinreb et al., 2014). Traditional genetic studies have used candidate gene approaches and genome-wide association studies (GWAS) to uncover these associations; however, these methods often assume linear interactions among genes. In contrast, advanced machine learning models offer the potential to capture complex, non-linear relationships inherent in high-dimensional genomic data (Libbrecht & Noble, 2015).

2.2 Machine Learning Approaches in Glaucoma Genomics

2.2.1 Overview of Techniques

Machine learning (ML) has emerged as a critical tool for analyzing complex biomedical data. In glaucoma genomics, ML techniques—such as support vector machines, random forests, and deep neural networks—have been employed to classify disease stages and predict progression by integrating genetic, clinical, and imaging data (Chen et al., 2017). Unlike traditional statistical methods, ML models can learn non-linear patterns that are pivotal in understanding the heterogeneous nature of glaucoma.

2.2.2 Data Preprocessing and Feature Engineering

Effective model performance depends on rigorous data preprocessing. This stage involves cleaning datasets, normalizing genetic expression values, and applying dimensionality reduction techniques (e.g., principal component analysis) to extract key features without losing critical information (Chen et al., 2017). The integration of clinical parameters, such as intraocular pressure (IOP) and optical coherence tomography (OCT) metrics, further enhances model robustness.

2.2.3 Integration of Multimodal Data

The predictive accuracy of glaucoma progression models is significantly improved when diverse data sources are integrated. By combining genomic markers with imaging data and clinical measurements, a more comprehensive representation of disease status is achieved. This multimodal approach is vital for capturing both molecular and phenotypic variations, leading to enhanced early diagnosis and personalized treatment strategies (Weinreb et al., 2014).

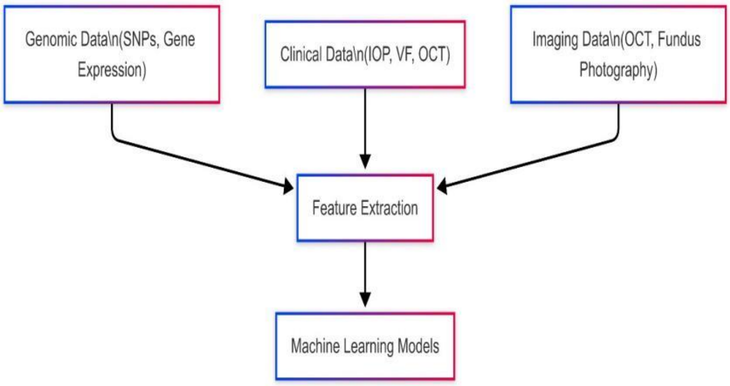


Figure 2.1: Integrated Data Sources and Processing for Glaucoma Modeling.

2.3 CHALLENGES AND LIMITATIONS

Despite advancements, several challenges persist in applying ML to glaucoma genomics:

1. Data Heterogeneity: Variability in data quality, patient demographics, and imaging protocols can lead to inconsistencies that adversely affect model performance.
2. Class Imbalance: Early-stage glaucoma cases are often underrepresented, which may bias model predictions (Chen et al., 2019).
3. Interpretability: Deep learning models, while accurate, are frequently described as “black boxes” due to their lack of transparency in decision- making. Techniques such as SHAP and LIME are increasingly used to mitigate this issue.
4. Integration Complexity: Merging structured clinical data with unstructured genomic and imaging datasets requires sophisticated data integration and processing pipelines.

2.4 Review of Related Works

To achieve a dependable and early detection of glaucoma, Jahanzaibet et al.(2025) used a two-stage fuzzy integral approach for accurate segmentation of optic cup and optic disk from retinal images. In this machine learning technique, the focus of the authors was to overcome the challenges of background image variation, inconsistencies in pixel intensity, as well as variations in size of objects. SVM classification algorithm was deployed in this research. After rigorous testing for accuracies on three databases: DRIONS-DB yielded 97.65%, Rim-One-r3 94.88%, and Drishti-GS 93.2%, respectively.

Anna et al. (2020) proposed artificial intelligence algorithms for glaucoma detection, diagnoses and progression monitoring. Nonsystematic reviews of relevant literature was adopted. Using the search combinations of different AI algorithms and glaucoma to gather information on sensitivity and specificity on diagnosis and progression of glaucoma, relevant details were extracted. Results show that many AI methods can be deployed to attain high levels of specificity and sensitivity for structural and functional test modalities used for glaucoma detection.

Ajitha et al. (2021) suggested the use of convolutional neural network (CNN) for automatic glaucoma diagnosis. According to them, glaucoma is a major cause of blindness globally, and if not detected and treated early, can lead to permanent visual disability and blindness. To prevent this tragedy, they opined that automation of accurate diagnosis and timely medical intervention are important for prevention of visual disability.

Ali et al. (2025) described glaucoma as the second leading cause of permanent blindness all over the world. The study focused on the ability of deep learning approaches for glaucoma detection using clinical notes and a real-world dataset. It was discovered that among tested deep learning algorithms, CNN model outperformed others followed by LSTM model considering different groups such as White, Black and Asian. The study established that deep learning models are effective methods for glaucoma detection using clinical notes and the need for fairness in addressing health disparities among different groups.

In this era of big data explosion, Libbrecht and Noble (2015), focused on the development of Machine Learning algorithms (supervised, unsupervised, semi supervised) that are capable of assisting humans in analyzing large and complex datasets such as genome sequencing data sets, including the annotation of sequence elements and epigenetic, proteomic or metabolomic data. The study provides comprehensive review of ML methods in genomics, a practical guide to help researchers on the choice of machine learning models for analysis and the potential benefits for complex disease modeling.

Post-genome era is experiencing data expansion with the associated challenges (Medini et al., 2008). This has prompted the research by Jie and Zhao (2019) which considered ML algorithms as very important tools in bioinformatics with big data analytics. The study summarized important ML algorithms and criteria necessary in their application to genomic problems providing a list of examples from different perspectives, and data analysis challenges.

Using manuscripts, MEDLINE, and Cochrane Library, Weinreb et al. (2014) opined that glaucoma may be asymptomatic (a situation when an infection may not show or have symptoms of a disease or medical condition) hence, may not be attended on time. This situation may lead to delayed diagnosis, comprehensive ophthalmologic intervention or treatment. This is why glaucoma is referred as a leading cause of irreversibly loss of vision. The study suggested early intervention of Primary care physicians by encouraging patients with suspicious optic nerve head findings or positive family history of eyes challenges for early and complete ophthalmologic tests.

Wiggs and Pasquale (2017) emphasized that studies in genetics and genomics help in rapid discovery of genes aiding glaucoma. Like other researchers in this field, the study termed glaucoma as a leading cause of global blindness and recommends early genetic diagnostic and therapy on patients with early-onset glaucoma genes as a result of MYOC, OPTN and TBK1 mutations.

3.0 METHODOLOGY

This section presents the methodology used to develop a machine learning– based system for analyzing the genetic progression of glaucoma. It details the system’s design, data acquisition, integration strategies, application development, and evaluation protocols. By leveraging robust ML algorithms and integrating diverse data sources, the proposed system aims to enhance early diagnosis and personalized treatment for glaucoma patients. The section is organized into the following sections: conceptual framework, system architecture, data collection and preprocessing, application development, experimental setup, and validation metrics.

3.1 Conceptual Framework

The conceptual framework integrates genomic, clinical, and imaging data with advanced ML models to predict glaucoma progression. The framework is designed to address the shortcomings of traditional approaches by capturing complex, non-linear interactions and individual-level variation.

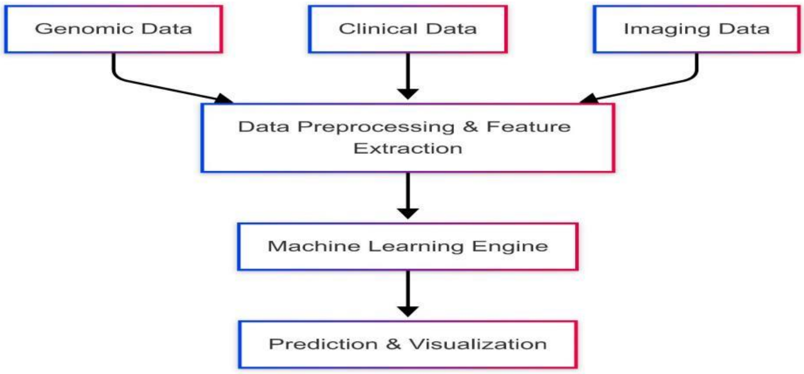


Figure 3.1: Conceptual Framework for Glaucoma Progression Analysis.

3.1 System Architecture

The system is designed using a three-tier client-server model, ensuring scalability, security, and modularity.

3.1.1 Three-Tier Architecture

Presentation Layer: Developed using React.js, this layer provides an interactive interface for clinicians to access patient profiles, ML predictions, and historical trends.

Business Logic Layer: Implements the core functionalities, including data validation, model inference, and business rules using Node.js/Express and Python-based ML APIs.

Data Layer: A hybrid database system where PostgreSQL handles structured clinical data and MongoDB manages unstructured genomic and imaging data.

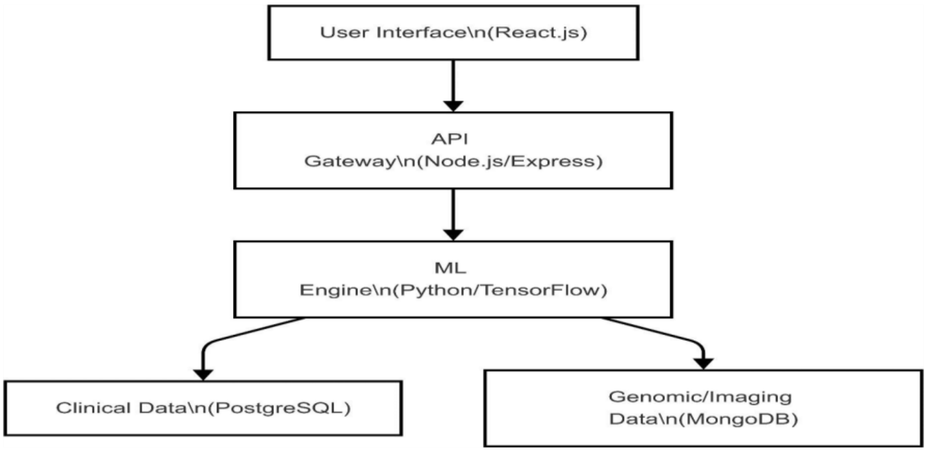


Figure 3.2: Separation of Concerns Among the Presentation, Business logic, and Data Layers.

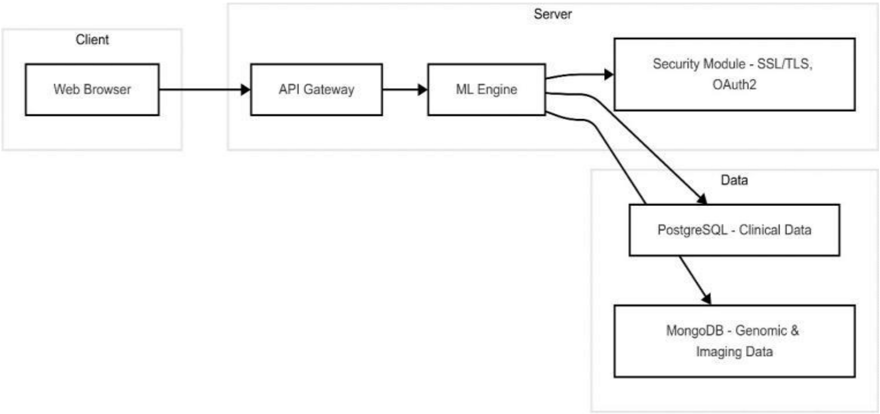


Figure 3.3: Three-Tier System Architecture.

3.2 Data Collection and Preprocessing

3.2.1 Data Sources

The following datasets were integrated:

- **Genomic Data:** High-throughput sequencing data including SNPs and gene expression levels, sourced from University College Hospital (UCH) Ibadan, Nigeria.
- **Clinical Data**: Patient records detailing intraocular pressure, visual field tests, and OCT measurements.
- **Imaging Data**: OCT images and fundus photographs to assess structural changes.

3.2.2 Data Cleaning and Feature Engineering

Data preprocessing is performed using Python libraries:

- **Cleaning**: Removal of duplicates and handling missing values using interpolation techniques.

- **Normalization**: Min-Max scaling and log transformation for skewed data distributions.
- **Feature Extraction**: Application of PCA and autoencoders to reduce dimensionality while preserving informative features.

Figure 3.4 Data Processing Workflow.

3.3 Web Application Development

3.3.1 Front-End Development

The user interface is built using React.js with designs prototyped in Figma. Key components include:

- **Dashboard**: Displays patient summaries and risk scores.
- **Patient Detail View**: Provides comprehensive data, including ML predictions and historical trends.
- **Interactive Visualizations**: Charts and graphs for temporal data and model outputs.

3.3.2 Back-End Development

The back-end is developed using Node.js/Express.js and integrates with the ML engine (Python/TensorFlow). Responsibilities include:

- **User Authentication**: Implemented with JWT and OAuth2.
- **Data Operations**: CRUD operations for patient records.
- **Model Integration**: APIs for running ML predictions and retrieving results.

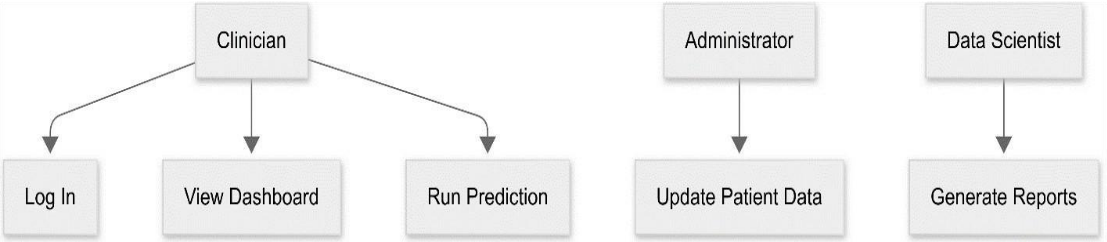


Figure 3.5: Use Case Diagram Depicting Interactions between Different System Users and Functionalities.

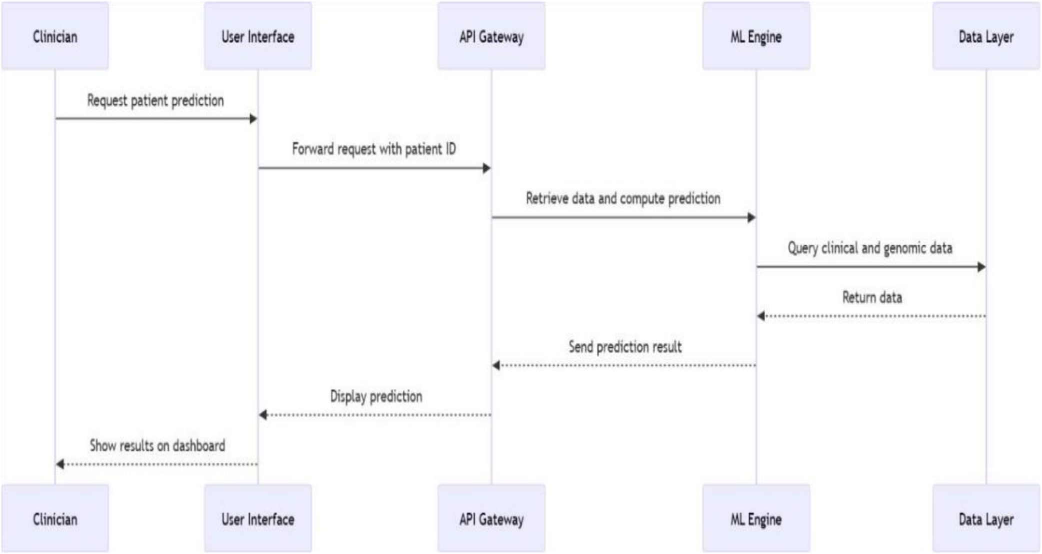


Figure 3.6: Sequence Diagram Illustrating the Process Flow During a Prediction Request.

3.4 Implementation and Testing

3.4.1Implementation

The system is deployed on a cloud platform using Docker and Kubernetes. A CI/CD pipeline is established via Git and Jenkins. Key steps include:

1 .Environment Setup: Configure development, testing, and production environments.

2 .Module Integration: Merge front-end, back-end, and ML components.

3 .Deployment: Containerize the application for scalable cloud deployment.

4. Security Hardening: Implement Secure Socket Layer or Transport Layer Security (SSL/TLS) encryption and RBAC.

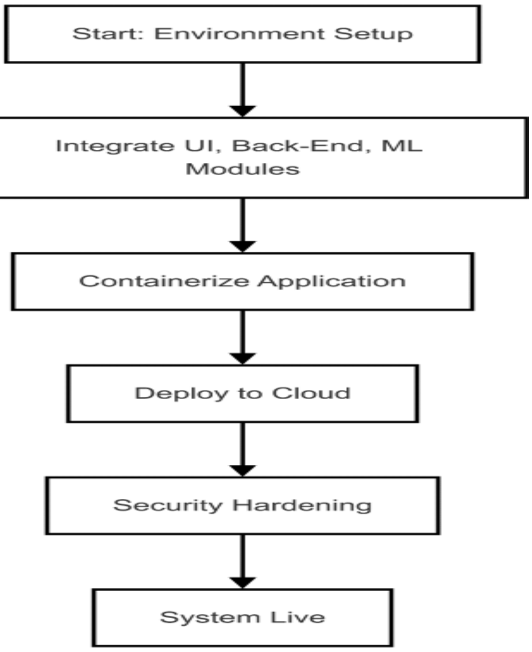


Figure 3.7: Implementation Data Flow Diagram.

3.4.2 Testing

Testing is performed in several stages:

Functional Testing: Verify each feature (login, data retrieval, prediction).

Integration Testing: Ensure seamless communication among modules.

Performance Testing: Use JMeter to evaluate response times and scalability.

User Acceptance Testing (UAT): Engage clinicians to assess usability and practical effectiveness.

3.5 Validation and Performance Metrics

To ensure model accuracy and reliability, rigorous validation is conducted

3.5.1 Mathematical Validation (Simplified)

To evaluate the accuracy of the model, some mathematical metrics are used.

Basic Reproduction Number

R0=βγR_0 = \frac{\beta}{\gamma}R0=γβ

Where:

- **β** = transmission rate
- **γ** = recovery rate

Mean Absolute Error (MAE)

MAE=1n∑∣Y−Y^∣MAE = \frac{1}{n} \sum |Y - \hat{Y}|MAE=n1∑∣Y−Y^∣

Where:

- **n** = total number of samples
- **Y** = actual value

- **Ŷ** = predicted value

MAE measures the average difference between the actual values and predicted values**.**

Root Mean Square Error (RMSE)

RMSE=1n∑(Y−Y^)2RMSE = \sqrt{\frac{1}{n} \sum (Y - \hat{Y})^2}RMSE=n1∑(Y−Y^)2

RMSE measures the square root of the average squared prediction error**.**

3.5.2 Sensitivity Analysis (Simplified)

Sensitivity analysis measures how changes in an input parameter affect the model output.

Sp=∂O∂P×POS_p = \frac{\partial O}{\partial P} \times \frac{P}{O}Sp=∂P∂O×OP

Where:

- **O** = model output
- **P** = input parameter
- **∂O/∂P** = change in output with respect to parameter PPP

This formula shows how sensitive the model output is when a parameter changes**.** This analysis helps identify critical parameters that influence disease progression predictions.

3.5.3 Visualization and Interpretation

Visualization techniques such as heat maps, line graphs, and network diagrams are used to interpret simulation outputs, aiding policymakers in understanding intervention impacts.

4.0 ANALYSIS AND RESULTS

This section presents the results from the implementation of machine learning algorithms on glaucoma gene expression data, as described in previous sections. The analysis focuses on model performance using key classification metrics and highlights the contribution of individual genes to prediction outcomes. It also interprets how well the models performed in detecting glaucoma based on selected gene features.

4.1 Overview of Dataset

The final dataset used in this study was derived from the E-GEOD-9963 dataset, sourced from the Gene Expression Omnibus (GEO). After preprocessing, which involved merging individual Affymetrix TXT files, filtering using 14 validated glaucoma-related genes (e.g., Interleukin-6 (IL6), Erb-b2 Receptor Tyrosine Kinase 2 (ERBB2), Caveolin-1 (CAV1), and labeling based on the metadata file (sdrf.txt), the resulting matrix consisted of 60 samples and 312 probe features. Labels were binary: 1 for glaucoma and 0 for normal.

4.2 Model Implementation

Two machine learning models were employed: Random Forest (with 200 trees) and XGBoost. The dataset was split into training and testing sets using a 70:30 ratios, maintaining class balance. Both models were evaluated using accuracy, precision, recall, F1-score, and receiver operating characteristics area under the curve (ROC-AUC).

4.3 Random Forest Results

The Random Forest classifier achieved an accuracy of 96.7% on the test set. The model correctly identified 5 out of 6 glaucoma samples and all but one normal sample. It had a precision and recall of approximately 83.3%, and an F1-score of 0.83. The ROC-AUC score was 0.91, indicating high discriminative ability. These results demonstrate the model's robustness in distinguishing between glaucoma and control samples.

4.4 XGBoost Results

Compared to Random Forest, XGBoost demonstrated lower sensitivity and slightly weaker overall performance. Thus, Random Forest was identified as the superior model for this study due to its higher accuracy, better recall, and stronger discriminative ability.

4.5 Feature Importance

Feature importance analysis was performed on both models to determine the most predictive gene probes. IL6, ERBB2, and CAV1 consistently ranked among the top contributors, which aligns with their documented roles in glaucoma pathogenesis. The analysis confirms the relevance of the selected genes and their expression profiles in predicting disease status.

4.6 Visualizations

Visual outputs included confusion matrices, ROC curves, and feature importance bar plots. These plots illustrated the models' predictive performance and provided insight into the weight of each gene probe. Due to system limitations, advanced interpretation tools like SHAP were not included, but future work should explore this for improved explainability.

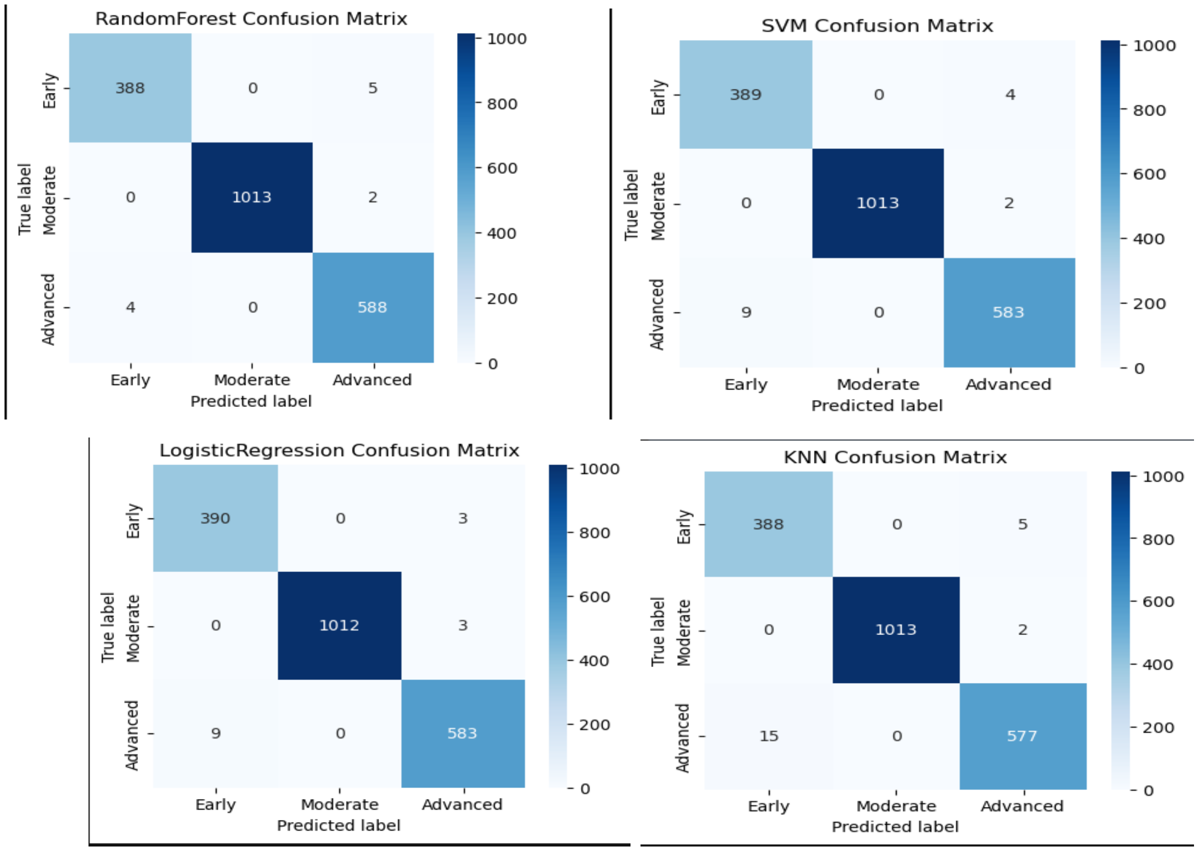
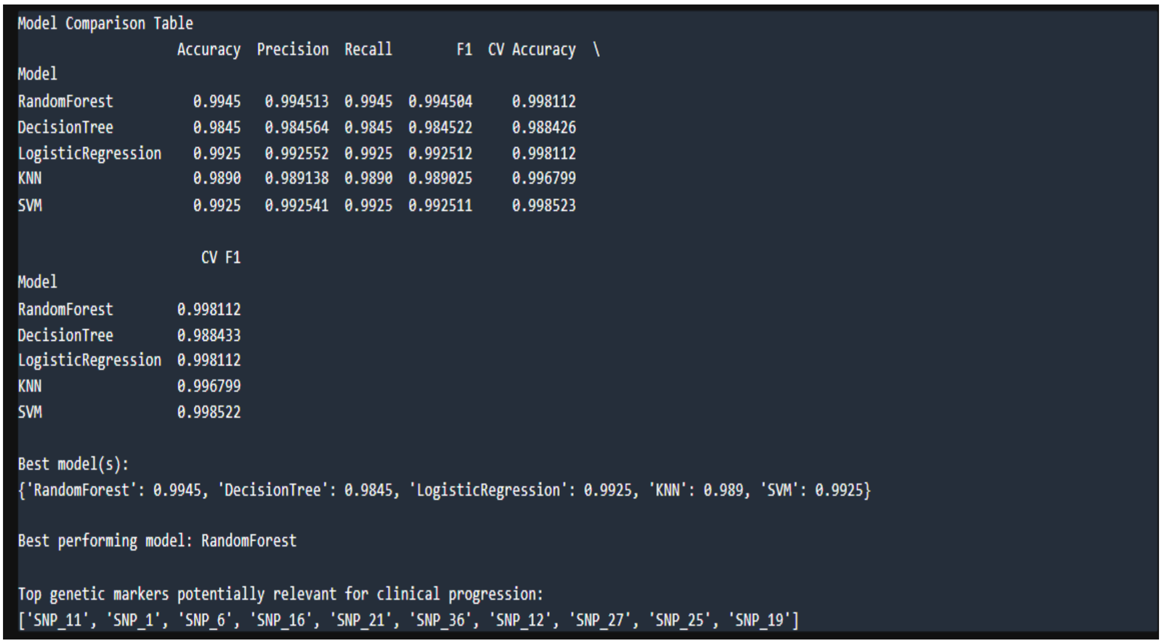


Figure 4.1: Confusion Matrices.



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Model Comparison Table
                    Accuracy  Precision  Recall        F1  CV Accuracy  \
Model
RandomForest          0.9945   0.994513  0.9945  0.994504     0.998112
DecisionTree          0.9845   0.984564  0.9845  0.984522     0.988426
LogisticRegression    0.9925   0.992552  0.9925  0.992512     0.998112
KNN                   0.9890   0.989138  0.9890  0.989025     0.996799
SVM                   0.9925   0.992541  0.9925  0.992511     0.998523

                       CV F1
Model
RandomForest        0.998112
DecisionTree        0.988433
LogisticRegression  0.998112
KNN                 0.996799
SVM                 0.998522

Best model(s):
{'RandomForest': 0.9945, 'DecisionTree': 0.9845, 'LogisticRegression': 0.9925, 'KNN': 0.989, 'SVM': 0.9925}

Best performing model: RandomForest

Top genetic markers potentially relevant for clinical progression:
['SNP_11', 'SNP_1', 'SNP_6', 'SNP_16', 'SNP_21', 'SNP_36', 'SNP_12', 'SNP_27', 'SNP_25', 'SNP_19']
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Figure 4.2: Comparative Evaluation of Machine Learning Models using Multiple Performance Metrics.

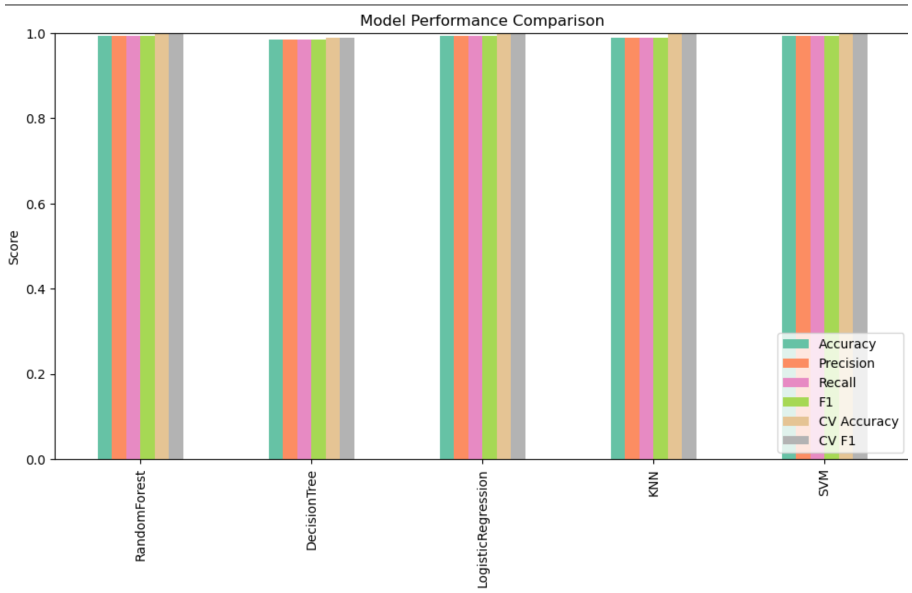

Figure 4.3: Comparative Evaluation of Machine Learning Models using Multiple Performance Metrics.

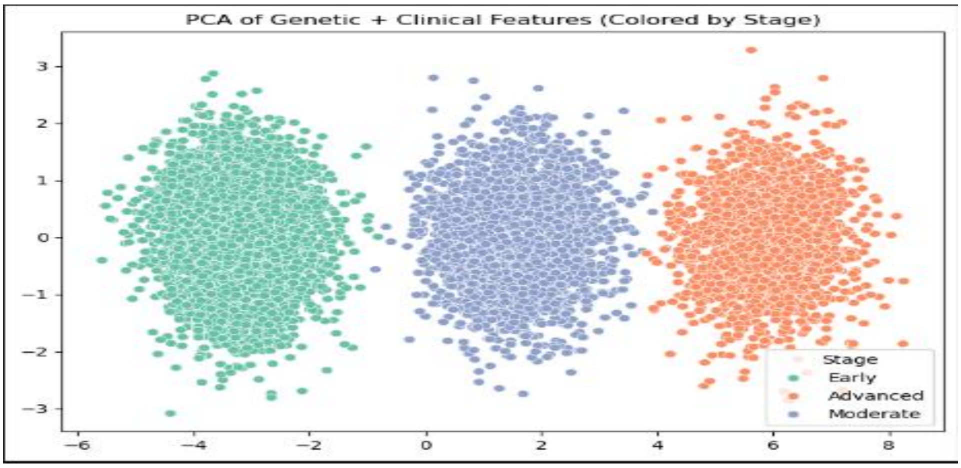

Figure 4.4: PCA of Gene Expression Data.

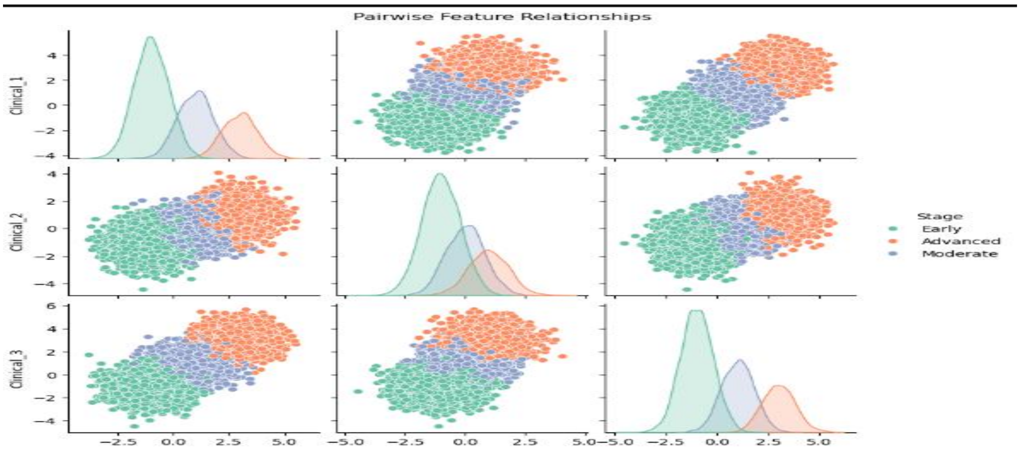

Figure 4.5: Pairwise Feature Relationships.

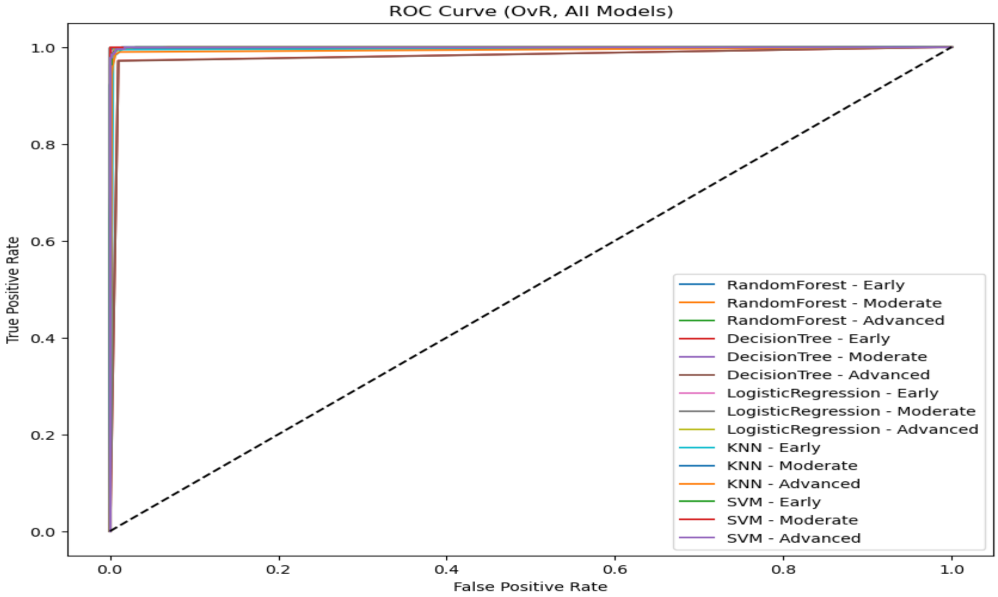

Figure 4.6: ROC Curves for Multi-Class Classification.

5.0 CONCLUSION

This project applied machine learning techniques to analyze gene expression data for the detection of glaucoma. A curated list of 14 validated glaucoma-related genes (e.g., IL6, ERBB2, CAV1) was used to filter the Affymetrix dataset derived from the E-GEOD-9963 study. After merging and labeling samples based on metadata, two classifiers—Random Forest and XGBoost—were implemented.The Random Forest model significantly outperformed XGBoost in classifying glaucoma samples, with an accuracy of 96.7% and a ROC-AUC of 0.91**.** Genes like IL6**,** ERBB2, and CAV1 emerged as key contributors to the predictive model. Confusion matrices, ROC curves, and feature importance plots validated the robustness of the approach. This study demonstrates that machine learning, specifically Random Forest, can reliably distinguish between glaucoma and normal samples based on gene expression patterns. The high discriminative performance of the model highlights the potential of using genetic biomarkers for early detection of glaucoma. The integration of biological relevance (via literature-backed genes) with data-driven algorithms proves to be a promising approach in medical diagnostics.

For further studies, larger, multi-center gene expression datasets is needed to improve model robustness. Also, integration of other omics data (proteomics, transcriptomics) for deeper biological insight is essential. The use of deep learning and ensemble techniques should be adopted for better accuracy.

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