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Application of explainable artificial intelligence in the identification of Non-Small Cell Lung Cancer biomarkers

A DISSERTATION

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CANDIDATE'S DECLARATION

I, Palak Gupta, Roll Number: 2K21/BIO/02, student of M.Tech. Bioinformatics, hereby declare that the work which is presented in the Major Project entitled- **Application of explainable artificial intelligence in the identification of Non-Small Cell Lung Cancer biomarkers** in the fulfillment of the requirement for the award of the degree of Master of Technology in Bioinformatics and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is an authentic record of my own carried out during the period from January-May 2023, under the supervision of Prof. Yasha Hasija. The matter presented in this report has not been submitted by me for the award for any other degree of this or any other Institute/University.

Palak Gupta

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Place: Delhi

Date: 13-06-2023

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CERTIFICATE

I hereby certify that the Project Dissertation titled "**Application of explainable artificial intelligence in the identification of Non-Small Cell Lung Cancer biomarkers**" which is submitted by Palak Gupta, Roll No. 2K21/BIO/02, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Technology, is a record of the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any Degree or any Diploma to this University or elsewhere.

Place: Delhi

Date: 13-06-2023

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Abstract

Worldwide, lung cancer is the second most commonly diagnosed cancer. NSCLC is the most common type of lung cancer in the United States, accounting for 85% of all lung cancer diagnoses. The purpose of this study was to find potential diagnostic biomarkers for NSCLC by application of eXplainable Artificial Intelligence (XAI) on XGBoost machine learning (ML) models trained on binary classification datasets comprising the expression data of 60 non-small cell lung cancer tissue samples and 60 normal healthy tissue samples. After successfully incorporating SHAP values into the ML models, 20 significant genes were identified and were found to be associated with the progression of NSCLC. These identified genes may serve as diagnostic and prognostic biomarkers in patients with NSCLC.

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CHAPTER 1

INTRODUCTION

Currently, machine learning and deep learning algorithms are at the forefront of technological advancements. The application of deep neural networks (DNNs) and machine learning (ML) algorithms in artificial intelligence (AI) systems has become prevalent in addressing significant issues in the fields of bioinformatics, biomedical informatics, and precision medicine. These algorithms not only yield remarkable results but also eliminate the need for human intervention in the handling, storage, and processing of data. The primary objective of these models is to enhance accuracy, expedite processes, and execute decision-making tasks, thereby augmenting the reliance of individuals on them [1].

However, the intricate nature of Deep Neural Networks (DNNs) or Machine Learning (ML) models can pose a challenge in comprehending the rationale behind their decision-making process, as they are frequently regarded as obscure and enigmatic. It has been noted that these models lack transparency, impartiality, and explanation, rendering them inadequate for practical problem-solving applications. The absence of transparency poses a difficulty for end-users, decision-makers, and AI developers alike. In domains that are sensitive such as healthcare, AI systems that can have a substantial influence on human lives are mandated by law to possess not only desirability but also explainability and accountability [2]. Explainable Artificial Intelligence (XAI) offers a solution to enable transparency and comprehensibility of the internal mechanisms of the layers within these models, thereby enhancing their reliability [3]. Explainable Artificial Intelligence (XAI) is engineered to furnish substantiated evidence that corroborates its output and identifies salient features that may influence the ultimate decision.

Moreover, the issue of fairness is increasingly becoming a matter of concern, given that algorithmic decision-making ought to be devoid of any form of partiality or prejudicial treatment towards specific groups or individuals on the basis of sensitive attributes. The objective of explainable artificial intelligence (XAI) is to address the lack of transparency in black-box models and enable elucidation of the decision-making process of AI systems. Machine learning models that are interpretable possess the ability to elucidate the reasoning behind their predictions and the variables that impact their results. However, the majority of

current interpretable machine learning techniques are not tailored to specific domains and have originated from fields such as computer vision, automated reasoning, and statistics. This can pose difficulties when attempting to directly apply these methods to bioinformatics unsolved questions without altering processes and 'scientific body'-specific adjustment. Therefore, further exploration is warranted across various domains, such as forecasting, healthcare, and industry, to fully realize the potential applications of explainable AI [4].

To examine the significance of explainability within the realm of bioinformatics, a comprehensive report of interpretable machine learning (ML) techniques and tools specific to certain models or model-agnostic is being presented. The aim is to highlight the potential limitations and disadvantages of these methods while exploring the process of adapting interpretable machine learning techniques to address bioinformatics challenges [5]. It is crucial to recognize the vast potential of XAI techniques in enhancing transparency in various domains such as bioimaging, cancer genomics, and text mining through the use of illustrative case studies. By incorporating explainable AI in bioinformatics, we can not only improve the reliability of AI systems but also ensure their fairness and accountability, leading to more trustworthy and effective solutions the objective if this in-silico analysis to identify potential biomarkers for NSCLC with the application of SHAP tool.

CHAPTER 2

XAI TAXONOMY

The reviewed research articles establish that procedures under XAI can be classified on the following bases: (i) Global Interpretability versus Local Interpretability, (ii) Post-hoc versus Intrinsic and (iii) Model-Agnostic versus Model-Specific.

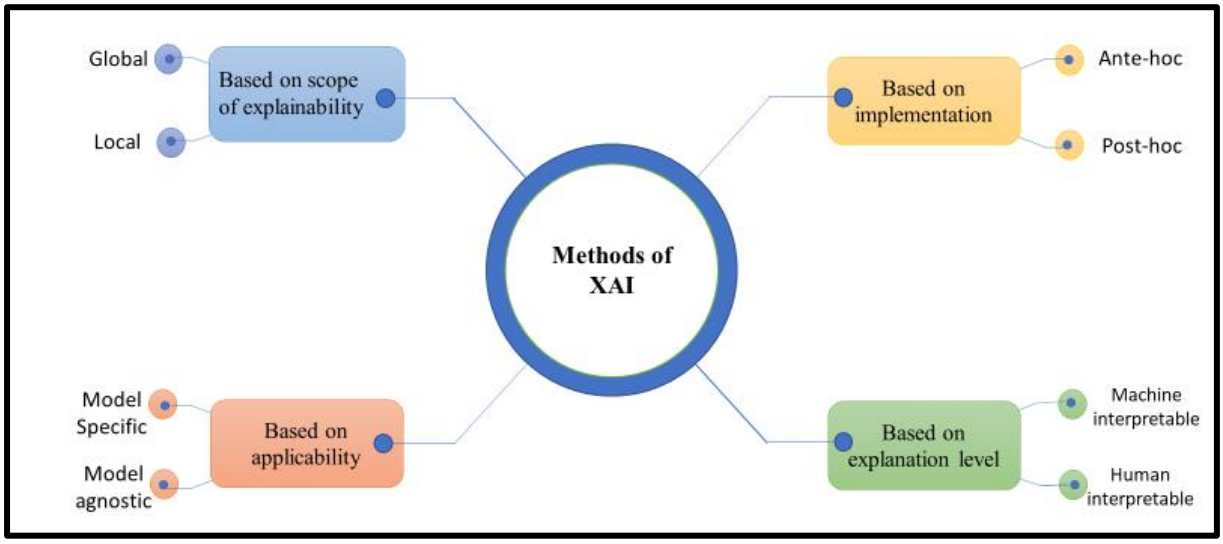

Fig.1 Classification methods of XAI

2.1 GLOBAL AND LOCAL EXPLAINABILITY

The incorporation of explainability in AI models can be beneficial as it facilitates the disclosure of the underlying cognitive mechanisms employed by such models. Apart from being perceived from the standpoint of the end user, the local interpretability of models encompasses the provision of exhaustive justifications for the acquisition of a specific decision. Local explainability is a technique that aims to address the issue of explainability in machine learning models [6]. This is achieved by dividing the feature subset into smaller subsets and providing explanations for these simpler subsets that are crucial to the development of an accurate model. The utilisation of techniques that distinguish the functioning of a specific component of a model while elucidating only a portion of the system's comprehensive operation is referred to as a local explanation.

The utilisation of a global model improves the determination of the overall distribution of the intended outcome. The initial step in understanding the classification of "good" or "bad" in a multiclass model involves the utilisation of the partial dependence model [7]. It is imperative

to comprehend the methodology and data when utilising the real-time explainable global model for training purposes. The degree of interpretability that facilitates comprehension of the model is achieved by considering the model's choices in a holistic manner, encompassing the feature set and each learned element such as weights, biases, parameters, and structures.

2.2 INTRINSIC AND POST-HOC EXPLAINABILITY

The distinction between intrinsic and post-hoc explainable artificial intelligence (AI) pertains to the temporal and integrative aspects of the explainability techniques employed in the AI system. The term "intrinsic explainable AI" pertains to the process of creating and constructing AI models that possess inherent interpretability and transparency. The models are designed in a manner that facilitates comprehension and explanation of their decision-making procedures and underlying mechanisms. The concept of intrinsically explainable artificial intelligence (AI) places emphasis on the clarity and comprehensibility of the model right from the beginning. This approach guarantees that the rationale behind the model's predictions or decisions can be easily accessed and scrutinised [8].

The achievement of intrinsic explainability necessitates meticulous model design and feature selection to guarantee lucidity. The representatives of intrinsically explainable models are linear regression, logistic regression, and decision tree models.

Conversely, post-hoc explainable AI centres on furnishing justifications for the determinations rendered by opaque models subsequent to the generation of their results. The explanations are produced extrinsically to the AI system, utilising methodologies and approaches that endeavour to elucidate the inner mechanisms of the model. Retrospective post-hoc explainability techniques are utilised to interpret the results of the artificial intelligence model and reveal the factors or characteristics that impacted its decision-making process. This involves approximating deep-learning black-box models with more straightforward, interpretable models that can be scrutinised to provide explanations for the black-box models [9].
Post-hoc explainability entails the utilisation of methodologies such as feature importance analysis, rule extraction, or surrogate models to acquire comprehension of the decision-making mechanism.

Some examples of AI models that can be made post-hoc explainable include Deep Neural Networks (DNNs), Random Forests, Support Vector Machines (SVM) and Gradient Boosting Machines (GBMs) [10].

2.3 MODEL-SPECIFIC AND MODEL-AGNOSTIC MODELS

The comparison between model-agnostic and model-specific approach is critical to present a more adaptable technology, allowing the implementation of explainability methodologies to a diverse array of pre-existing models. One key aspect that sets apart interpretability methodologies is their level of inclusivity with respect to the range of models to which they can be employed. Model-agnostic techniques have the ability to provide explanations for models without being constrained by a particular model structure. In contrast, techniques that are specific to a particular model are limited to a particular model structure, necessitating access to the model's internal data [11].

CHAPTER 3

METHODS OF INTERPRETIBILTY

Interpretable machine learning (ML) helps troubleshoot, discover new insights, and build confidence in ML model predictions. Latter aids in comprehending the model's forecasting abilities, discover errors or predisposed notions, and identify structurally impacting imagery [12]. Influence of explainable methods is not be undermined when it comes to ML algorithms' outputs. Probing, perturbing, and surrogate methods help in elaborating machine learning models [13]. Probing the model's internal representations discloses its extraction of information. Perturbation techniques manipulate input data to discover model output fluctuations, highlighting salient features which makes it more reliable. Surrogate techniques reform a simpler model to approximately evaluate the rendition of the convoluted machine learning model belonging to the black-box list. Interpretable machine learning uses correlation rather than causality. These procedures should be used to create experimental hypotheses. These methods may reveal the opaque mechanics of machine learning models and exploit their power while retaining transparency and dependability.

3.1 PROBING METHODS

Training machine learning (ML) models requires finding the optimum label prediction parameters. Probe the parameters after training to see what the model learns. Although limited, probing techniques enable global interpretations of ML models. Probing tactics vary per ML algorithm.

SVM models may be investigated by obtaining the hyperplane coefficient weights. Higher absolute weights suggest stronger label links and higher prediction significance. Linear SVM model probing is simple. Nonlinear SVM models employ the "kernel trick" to project data into higher dimensions, necessitating kernel-specific probing procedures [14]. These methods examine label-sequence motif relationships.

Random Forest and gradient tree boosting models are hierarchical. These models are probed by assessing feature significance in labelling instances [15]. Decision tree true/false questions' informativeness is measured by the mean reduction in node impurity. Ensemble decision-tree models reveal intricate feature interactions.

However, probing findings must be interpreted with caution. Correlated traits may dilute their relevance. Continuous and categorical qualities with more categories or a greater numeric range may score higher [16]. Interpreting non-uniform feature spaces requires care.

Succinctly put, probing strategies partially disintegrate them to comprehend the interior framework of ML models by extracting important parameters or evaluating the significance of features and their interrelationships. They provide insights into what the model has learned and help understand the reasoning behind its predictions.

3.2 PERTURBING METHODS

Perturbing techniques adjust input data and observe model output to comprehend machine learning (ML) models. These model-agnostic methodologies use sensitivity analysis and what-if approaches.

Sensitivity analysis includes changing one feature and assessing the model's performance. When features are eliminated or permuted, model performance decreases, indicating feature relevance. If correlations exist, sensitivity analysis may overlook crucial characteristics. Permutation-based methods assess the ML model's performance after randomizing features. This computation-efficient method calculates feature significance repeatedly. Genetics and image analysis use it [17, 18].

What-if analysis examines how feature input values affect predictions [19]. It localizes ML models. PDPs demonstrate how altering one feature's value affects others. Individual conditional expectation (ICE) plots reveal interactions and group-specific effects. These approaches read deep learning models effectively [20].

PDPs and ICE graphs reveal feature-model output connections. They are only visualized for a few characteristics and may need domain expertise or other interpretation procedures to discover relevant elements [21]. Perturbing tactics help comprehend ML models and learn how characteristics affect predictions.

3.3 SURROGATE MODELS

Surrogate techniques may understand machine learning (ML) models. Consider an opaque machine learning model that resists probing and perturbation methods that fail to give significant insights. To approximate the black box model, train a more interpretable model [22]. Linear models, where coefficients reflect feature relevance, and decision trees, where node impurity may be determined, are examples of interpretable models.

Surrogate models are interpretable. For instance, to create a surrogate model for a black box model that predicts gene upregulation using regulatory elements as characteristics, apply the model to a collection of genes, G. The black box model's projected label (up- or down-regulated) for those genes was retrieved [23]. The same set of genes, G, would be used as examples, and the black box's anticipated labels would be surrogate training labels.

Black box models often have considerable nonlinearity and many higher-order interactions, which limits surrogate models. Interpretable surrogates cannot grasp such models. A surrogate model that learns a piece of the opaque model may solve this problem. LIMEs are local, interpretable, model-agnostic explanations [24]. The logic for a single occurrence or a cluster of like occurrences (such as co-expressed genes) may be simple enough for a surrogate model to absorb. LIME was used to explain how a black box model that predicts cardiac arrest survival rates misclassified certain individuals [25]. A LIME model applied to a patient who was incorrectly projected to live showed that the model was too influenced by neurological health and the lack of chronic respiratory diseases. The model neglected important factors like high creatinine levels and old age.

CHAPTER 4

XAI FRAMEWORK

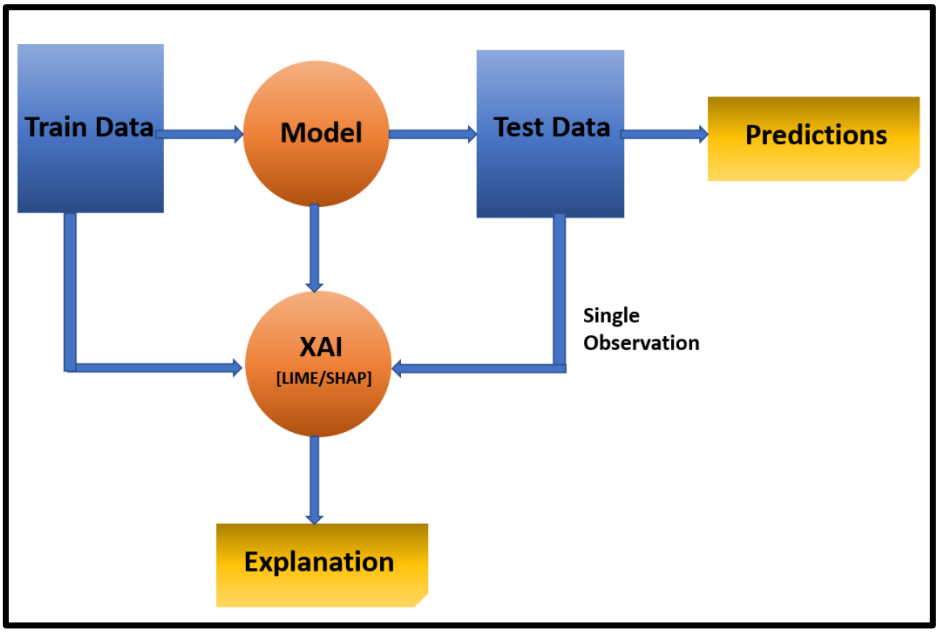

Fig. 2 XAI Workflow

4.1 SHAP

Explainable AI relies heavily on the SHAP (SHapley Additive exPlanations) framework. This technique uses each feature's estimated evaluation to explain machine learning model outcomes. Shapley values and SHAP tool are based on underlying theory called game theory. Quantification of each feature's prediction contribution is carried out [26].

The SHAP tool helps users determine which forecasting characteristics have the most impact on model output by computing their importance. The data above helps understand the model's behaviour and its decision-making factors.

By unifying feature contributions across instances, SHAP provides an elaborative and curated understanding of the model's performance. This method allows global model interpretation. The tool helps understand complex models by examining variable patterns and relationships.

Model-agnostic SHAP may be used with a variety of machine learning models, including opaque ones. Its independence from model structures and assumptions makes this method suitable for many fields [27].

By giving characteristics importance, the SHAP technique helps identify model biases in decision-making. Allows fairness analysis. This method helps identify factors that may be disproportionately affecting forecasts and evaluate fairness and equality issues [28].

The SHAP tool promotes consistency and coherence. The tool's feature importance values are trustworthy and significant. Users trust and verify the tool's reasons using this functionality. SHAP improves machine learning models' interpretability and transparency. It helps consumers understand forecasts, identify biases, and make educated choices based on model outputs [29].

4.2 LIME

The LIME framework, a popular explainable AI tool, aims to provide local interpretability for machine learning models. LIME estimates the decision limits of complex models using interpretable surrogate models to explain unique predictions.

LIME helps consumers understand the reasoning behind single forecasts by providing local explanations. In scenarios where specific cases need explanations rather than model performance, thorough interpretability is beneficial.

Like SHAP, LIME is model-agnostic and is to be operated and executed with numerous machine learning models. This technique is independent of the model architecture, making it versatile and applicable without previous knowledge [30].

LIME uses surrogate models to approximate the decision limits of complicated models, creating interpretable, simpler, and more transparent models. Surrogate models thoroughly reflect the black-box model's behaviours to provide local explanations [31]. LIME weights features based on their local prediction contributions. Weights indicate each feature's importance in the model's decision-making process, helping users identify key aspects that influence predictions.

Supportive text and images have helped LIME forecast textual and visual data. Highlighting key terms or areas in a text or picture might reveal the model output's influences [32]. LIME's explanatory visualisations highlight an instance's most important traits and places that affect prediction. Visualisations enhance explanations and help explain the model's decision-making process.

LIME helps users understand predictions and identify the elements that affect complex model outputs. Local explanations and surrogate models increase machine learning model transparency and interpretability using LIME. This tactic cultivates trust and educated decision-making.

CHAPTER 5

CHALLENGES IN XAI

The protection of data privacy and security- The analysis of both public and private data can offer significant insights for decision-making purposes. However, in certain cases, the use of sensitive data may be necessary to elucidate particular decisions. The utilisation of the aforementioned data necessitates meticulous management to preclude its exposure to potential vulnerabilities and malicious actors. Inadequate management of confidential information poses a potential threat to the confidentiality and integrity of both individuals and entities, thereby resulting in grave ramifications. Hence, it is imperative to establish unambiguous guidelines and protocols for the management and safeguarding of data in XAI systems [33].

The intricacy of artificial intelligence models- Artificial intelligence models undergo evolutionary changes over time to cater to the requirements of various organisations. The pursuit of enhanced decision-making capabilities may prompt the utilisation of progressively intricate artificial intelligence (AI) models that pose challenges in terms of interpretability. The need for ongoing enhancement of eXplainable Artificial Intelligence (XAI) systems is imperative in order to remain current with evolving circumstances and to uphold the capacity to furnish significant justifications for the decisions made by artificial intelligence. Sustained research and development efforts are necessary to ascertain the efficacy of XAI methodologies in tackling the intricacies and dynamic nature of contemporary AI models [34].

The phenomenon of human bias- Although XAI prioritises transparency over conventional AI models, it remains susceptible to biases in both the data and algorithms employed for analysis. The dependence of XAI systems' training and operation data on parameters established by human agents is the underlying cause of this phenomenon. The mitigation of human bias in explainable artificial intelligence (XAI) necessitates meticulous examination of the data sources and algorithms employed in such systems, alongside persistent endeavours to foster diversity and inclusivity in the creation of AI technologies [35].

The user's comprehension- Despite the objective of explainable artificial intelligence (XAI) to enhance the comprehensibility of AI models, certain users may lack the requisite foundational knowledge to fully grasp the elucidations presented. It is imperative that XAI systems are developed in a manner that facilitates the provision of explanations that are customised to meet

the requirements and comprehension levels of diverse user cohorts. This may involve the use of visual aids, interactive interfaces, or other supplementary mechanisms to aid users in comprehending the rationale behind AI-based determinations [36].

Biomedical data science comprises of and regularly produces a large and varied scope of large-sized data, spread across different subdomains ranging from sequencing data, multidimensional omics data, text input, EMRs, to bioimage data. The challenges highlighted by this big-data, nonlinear, and convoluted category of biological data, combined with the non-homogenous nature of disease-related issues, mostly push AI algorithms to adjust a balance between high-achieving performance and interpretability. High chances are that this high-level performance cannot be successfully accomplished across numerous biomedical data science applications. Henceforth, putting explainability above accurate performance results may not be the foremost concern when approaching problem-solving. There is a possibility that certain AI techniques may possess desired explainability but present us with inhibited performance. However, biomedical data scientists are unlikely to choose such methods since they give precedence to higher efficiency [37].

The focus primarily revolves around the customization of AI methods, handling nonlinear data, addressing complex problem-solving scenarios, and analysing learning biases. Currently, there is a lack of developed techniques for analysing biomedical data. Rather than having a single source, these concepts can be traced back to various fields such as automated reasoning, computer vision, image recognition, cognition, and statistical methods [38].

The task of implementing AI techniques in the field of biomedical data science while ensuring interpretability can present difficulties. It is recommended that AI methodologies be tailored or adapted to specific datasets in order to achieve optimal performance and facilitate accurate interpretation, as opposed to employing a one-size-fits-all approach [39]. The process of customization may prove challenging to accomplish with limited time being devoted, as there is presently a lack of successful and entrenched AI theory to provide further clear path. Additionally, the level of explainability required may differ depending on the specific application domain.

The use of AI or machine learning techniques in biomedical data science may result in learning biases that hinder the provision of basic interpretations by the AI methods. The matter of learning bias pertains to the potential for artificial intelligence outcomes to exhibit bias or

inaccuracies [40]. The kind of learning bias that arises due to uncoordinated interactions between certain AI techniques and specific data types can be due to incorrect parameter configuration or tuning, imbalanced data sets, or other dormant factors. However, detecting such biases may pose a challenge for biomedical data scientists. Bias can be regarded as a learning security issue that generates unpredictable outcomes due to the presence of artefacts in the AI models. The development of explainable AI should be predicated on the premise that AI techniques are capable of producing favourable outcomes and are devoid of any shortcomings related to training. Numerous AI models, including kernel-based learning, ensemble learning, and deep learning, are commonly employed in the biomedical field. However, some of these models may possess or have the potential to possess security issues in terms of learning certain types of biomedical data. In certain application domains, such as translational bioinformatics for disease diagnosis, addressing the security concerns of AI learning or rectifying its learning deficiencies may hold greater significance than ensuring AI explainability. This assertion is supported by existing literature [41].

CHAPTER 6

APPLICATIONS OF XAI

Finance- Artificial intelligence is well applied in the field of finance. AI algorithms are employed to operate different functions, including investment strategies, credit scoring and fraud detection. The allowances of transparency open the door for comprehension of the thesis strengthening crucial financial calculations by customers, auditors, and regulators. XAI smoothens the way for explanation of the variable considered by AI models when catching sight of duplicitous behaviour in the field of finance [42].

Healthcare- In the healthcare domain, execution of XAI is crucial. It eases the job of comprehending and the reliability of AI models' decisions by clinicians and other healthcare professionals. The application of AI-based tools for diagnosis warrants medical professionals to make well versed decisions. In context with medical diagnosis, XAI can come up with the justification for the prognosis of a particular disease or the benefaction of specific symptoms [43].

Customer service- Grasping the theory behind the propositions can help increasing users' faith in the system thereby resulting in the betterment of customer experience. Improvement in customer service can be carried out by the execution of AI bots and virtual assistants by helping in the recommendations to customers and explanations for their responses [44].

Autonomous vehicles- AI plays a major role in the working and implementation of autonomous vehicles and self-driving cars. It helps in ensuring safety and helps in withstanding public's faith. The decisions taken by the autonomous vehicles can be controlled by XAI like the classifying pedestrians or selecting the driving custom. The data ensures accountability, is debugged, and enhances the overall safety of autonomous system [45].

Legal applications- AI plays a vital role in changing the ways of providing information to the lawyers and helping bring justice in the fairest means possible. The advancement in legal affairs is brought mostly by the AI systems and XAI is aiding by smoothening the process of rendering determinations. AI helps in referring and providing explanations in context of legal documents, legal precedents, particular cases. This saves time for the lawyers and the justice system to

come up with the decision and the assessment of potential legal consequences and helps in the construction of arguments [46].

Human Resources- Humans tend to make prejudicial judgements and decisions. XAI promotes unity and takes decisions keeping all the discriminatory and prejudicial factors aside, that a human may have difficulty in doing. It is applied in human resource management for the reasons discussed above. In the professional field AI is used in making decisions during employment and employee evaluation procedures. It is best used during the candidate selection and providing best options for the selected field of work. It helps in withholding the discriminatory practices and helps in ensuring fair conduct in the professional work environment [47].

CHAPTER 7

LITERATURE REVIEW

Non-Small Cell Lung Cancer (NSCLC) is the predominant histological subtype of lung cancer, representing a substantial proportion of lung cancer diagnoses, with an estimated incidence of 85% [48]. Considerable investigation has been carried out to comprehend the biology, molecular pathways, diagnostic approaches, and therapeutic modalities for non-small cell lung cancer (NSCLC).

Various investigations have recognised genetic modifications and molecular pathways that are associated with Non-Small Cell Lung Cancer (NSCLC). These include mutations in genes such as EGFR, ALK, ROS1, KRAS, and BRAF [49].

The scientific inquiry has been directed towards comprehending the function of oncogenic drivers, tumour suppressor genes, and their subsequent signalling pathways in the advancement, progression, and metastasis of non-small cell lung cancer (NSCLC). Studies on the discovery of biomarkers have revealed several potential prognostic and predictive markers, including but not limited to PD-L1 expression, tumour mutational burden, and specific gene alterations, which can be utilised to inform treatment decisions [50].

The accuracy of NSCLC diagnosis and staging has been enhanced by the implementation of advanced imaging techniques such as computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). The utilisation of liquid biopsies and analysis of circulating tumour DNA (ctDNA) has surfaced as a potentially effective approach for identifying genetic mutations and tracking the efficacy of treatment in individuals with non-small cell lung cancer (NSCLC). This method is non-invasive and shows great potential.

The treatment of non-small cell lung cancer (NSCLC) has been significantly transformed by the advent of targeted therapies that are designed to specifically target genetic mutations. The administration of EGFR tyrosine kinase inhibitors (TKIs) and ALK inhibitors has demonstrated notable effectiveness in individuals with corresponding mutations [51].

Immune checkpoint inhibitors (ICIs) are a class of drugs that have been developed to enhance the immune system's ability to fight cancer [52]. The clinical benefits of immune checkpoint

inhibitors, specifically anti-PD-1/PD-L1 antibodies, have been demonstrated to be remarkable in patients with non-small cell lung cancer (NSCLC) by stimulating the immune system's anti-tumour response.

Biomarkers, including but not limited to PD-L1 expression, tumour mutational burden, and immune gene signatures, are currently under investigation for their potential to forecast the response to ICIs and facilitate the selection of patients [53].

In context of personalised medicine, the combined effect of immunotherapies, targeted therapies and chemotherapy is testing the efficacy of the results of the treatment. The personalised medicine strategies are examined by conducting the processes like liquid biopsies and genomic profiling, and are on their way to favour the selection of options for treatment procedures which are on the basis of the uniqueness of different tumours.

CHAPTER 8

METHODOLOGY

8.1 DATA RETRIEVAL

The data has been acquired from the GEO Datasets database available at NCBI. The dataset chosen after using the terms non-small cell lung cancer and non-smokers was GSE19804. This data was downloaded in the form of full SoFT file. In the dataset, there were 60 samples each of healthy control tissue and of primary tumour.

8.2 DATA PRE-PROCESSING

This process includes removal of gene expression entries with null values and entries having no gene IDs. After pre-processing, 20000 genes remained for a total of 120 samples. This dataset was subjected to PCA using the scikit-learn package of python to assess whether or not the sample groups separated based on the variance of gene expression in two major components, hence determining the dataset's quality [54].

8.3 MACHINE LEARNING ON THE DATASETS

The allocation of datasets followed a random process, resulting in an 80:20 split between training and testing sets. Machine learning techniques, including Support Vector Machines (SVMs), K-Nearest Neighbours (KNNs), and Deep Learning, have become increasingly popular in various fields such as omics data analysis, sequence data analysis, biomedical imaging, and signal processing [55]. Therefore, we opted to employ machine learning methods for our datasets. This decision was based on the aforementioned popularity of these techniques in relevant disciplines [56]. The XGBoost model was trained for classification on the 80 percent of the datasets using training sets. The XGBoost algorithm, also referred to as Extreme Gradient Boosting, is a machine learning methodology that utilises decision trees to enhance performance through a technique called boosting [57]. From its inception, this method has demonstrated a consistent superiority over a majority of other machine learning techniques, such as logistic regression, the random forest model, and traditional decision trees.

The XGBoost frameworks have been developed for multiple programming languages, with Python being a prominent example. Additionally, it exhibits seamless compatibility with the

widely utilised scikit-learn machine learning framework employed by data scientists in Python. Following the utilisation of the XGBoost machine learning classifier through the Scikit-learn library on the given datasets, the models' efficacy was assessed through the application of the testing dataset which accounted for 20 percent of the whole dataset.

The models underwent evaluation through the utilisation of a confusion matrix, and the accuracy of said models was determined by means of the test set.

8.4 XAI ON THE TRAINED ML MODELS

SHAP package in Python was used to carry out the XAI analysis on the previously performed XGBoost models. XAI (Explainable Artificial Intelligence) analysis delves into the decision-making process of machine learning models and aids in the identification of features that hold significant contributions.

The level of confidence in the prediction is made by the model. The analysis of Explainable Artificial Intelligence (XAI) will facilitate the identification of pertinent genes that can be utilised by trained models for the purpose of phenotype/condition identification and classification such as Healthy or Lung_Cancer. Fig 7 shows a SHAP summary plots indicating contribution of the values to the decision confidence. Also, GEO2R tool was used to identify and highlight the statistical significance of the genes which were found to be key after XAI analysis [58]. In this process, genes with $p<0.05$ are considered to be significant. Also, the logFC value is considered to classify up and down-regulated genes. Genes with logFC <-1 are down regulated whereas those with logFC > 1 are up-regulated.

The genes that are significant after Machine Learning of 20000 genes are then fed into another XGBoost model which is new and is to be trained. Finally, the performance (in terms of accuracy and confusion matrix) of newly trained ML model is compared to the prior one which was initially fed with 20000 genes.

Additionally, a literature survey is done of the key genes given as output by the SHAP tool to examine their roles in progression of lung cancer from healthy tissue.

CHAPTER 9

RESULTS

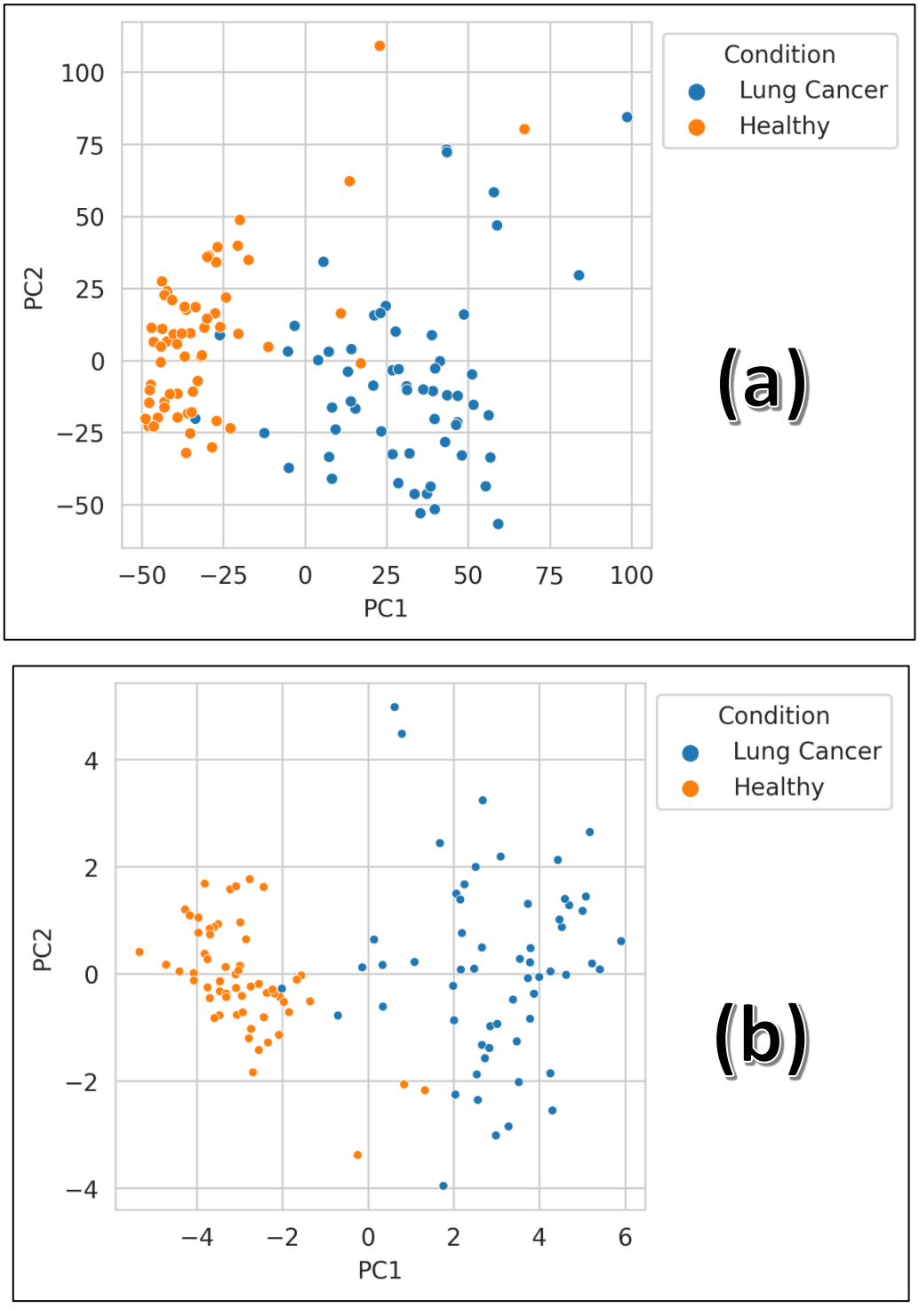

Fig.3: Principal Component Analysis plots for (a) Healthy vs NSCLC dataset of all 20,000 genes (b) Healthy vs NSCLC dataset of 20 key genes. Segregation was observed for both.

Scatter plots were created using the data gathered from the PCA analysis as shown in (Fig. 3) in order to test the quality of the data and make sure that our data is well sorted on the basis of variance among the features. PCA was used to combine highly linked factors into a more manageable group of variables that explain the majority of the data variation.

The outcomes of the PC scatter plots here describe the classes as being neatly organised, and machine learning can be used to classify the data.

Fig. 3b shows the PCA scatter plot of 20 key genes across 120 samples. It can be seen there is greater and clearer separation of healthy and diseased principal components when compared to the PCA plot before SHAP application.

After training the ML model on 80% of the dataset (training set), the model's performance is evaluated on the basis of results obtained using the testing set, i.e., 20% of whole dataset. Accuracy is the KPI (Key Performance Indicator) used for ML classifier's performance assessment. Since this is a case of binary classification, accuracy is stated in terms of positives and negatives obtained in confusion matrix results. Accuracy = [(TP + TN)/ (TP + TN + FP + FN)].

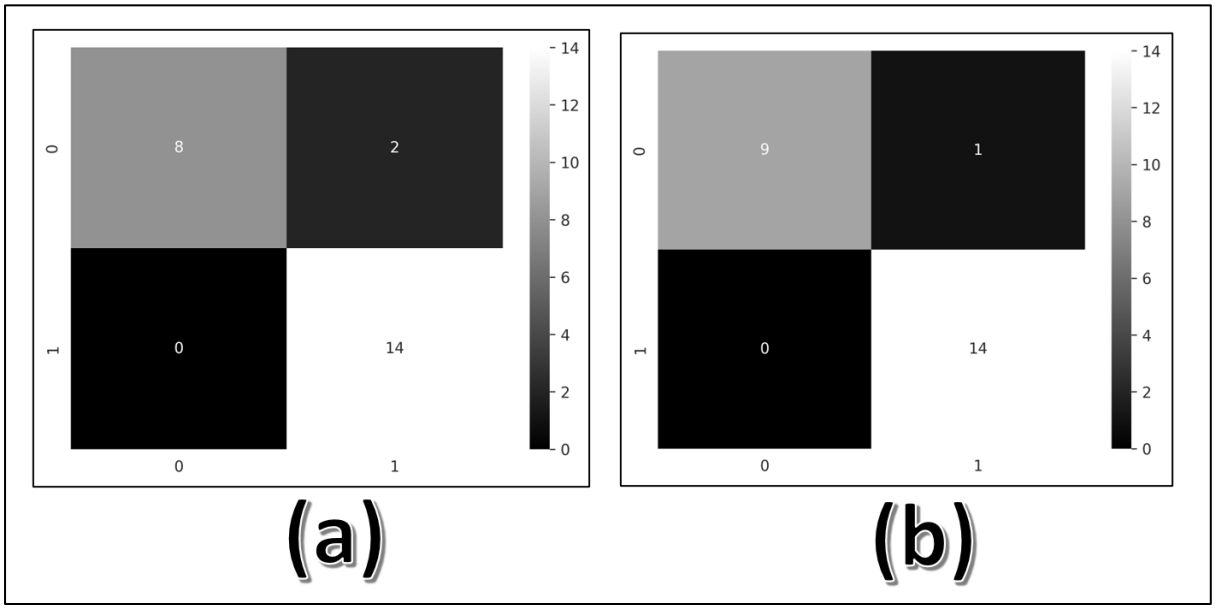

Fig 4: Confusion matrix for Healthy vs NSCLC dataset of (a) 20000 initial genes (b) 20 key genes. Grey squares in the matrix indicate the number of True positive instances (TP), Black squares indicate the number of False positive (FP) and False negative (FN) instances while white squares indicate the number of True negative (TN) instances.

(a)

```
[52] from sklearn.metrics import confusion_matrix, accuracy_score
     cm = confusion_matrix(y_test, y_pred)
     print(cm)
     accuracy_score(y_test, y_pred)
```

```
[[ 8  2]
 [ 0 14]]
0.9166666666666666
```

(b)

```
[14] from sklearn.metrics import confusion_matrix, accuracy_score
     cm = confusion_matrix(y_test, y_pred)
     print(cm)
     accuracy_score(y_test, y_pred)
```

```
[[ 9  1]
 [ 0 14]]
0.9583333333333334
```

Fig 5: (a) shows the accuracy of 91.67% in which the first model selected the key genes (before SHAP), whereas (b) shows the high accuracy of 95.83% when the key genes are again fed to the model as input.

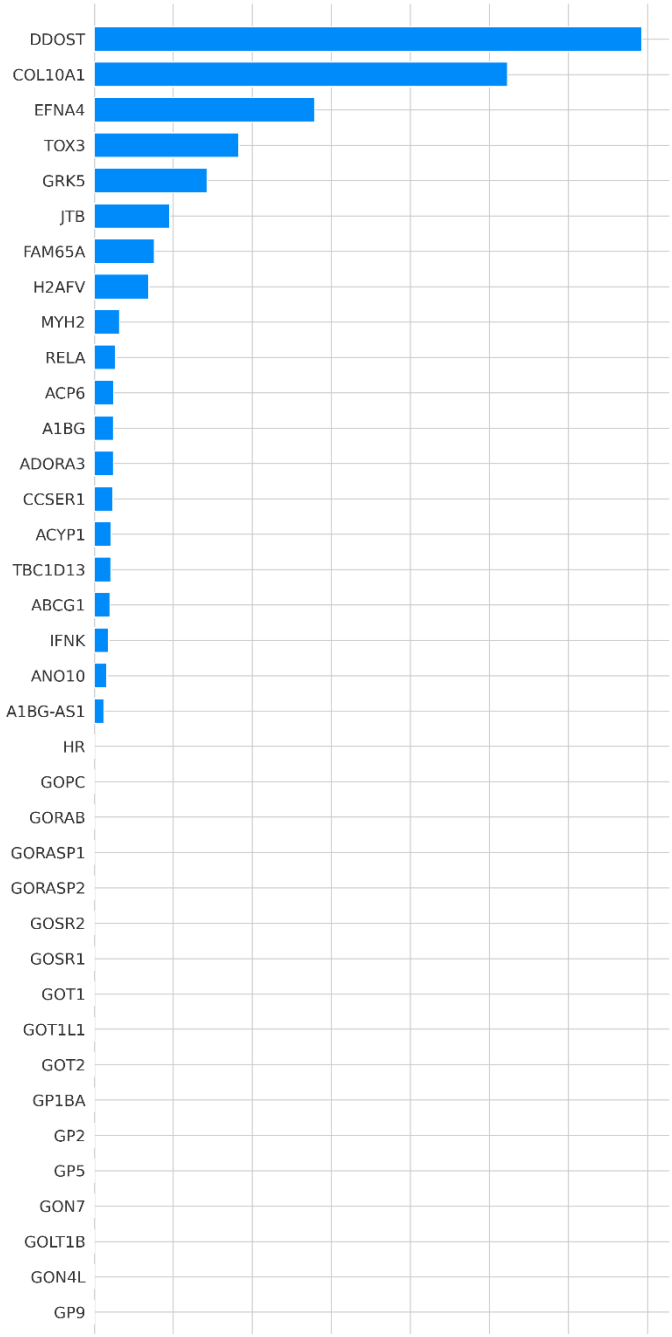

Fig 6: SHAP Barplot depicting the genes of highest relevance on top for Healthy vs NSCLC dataset

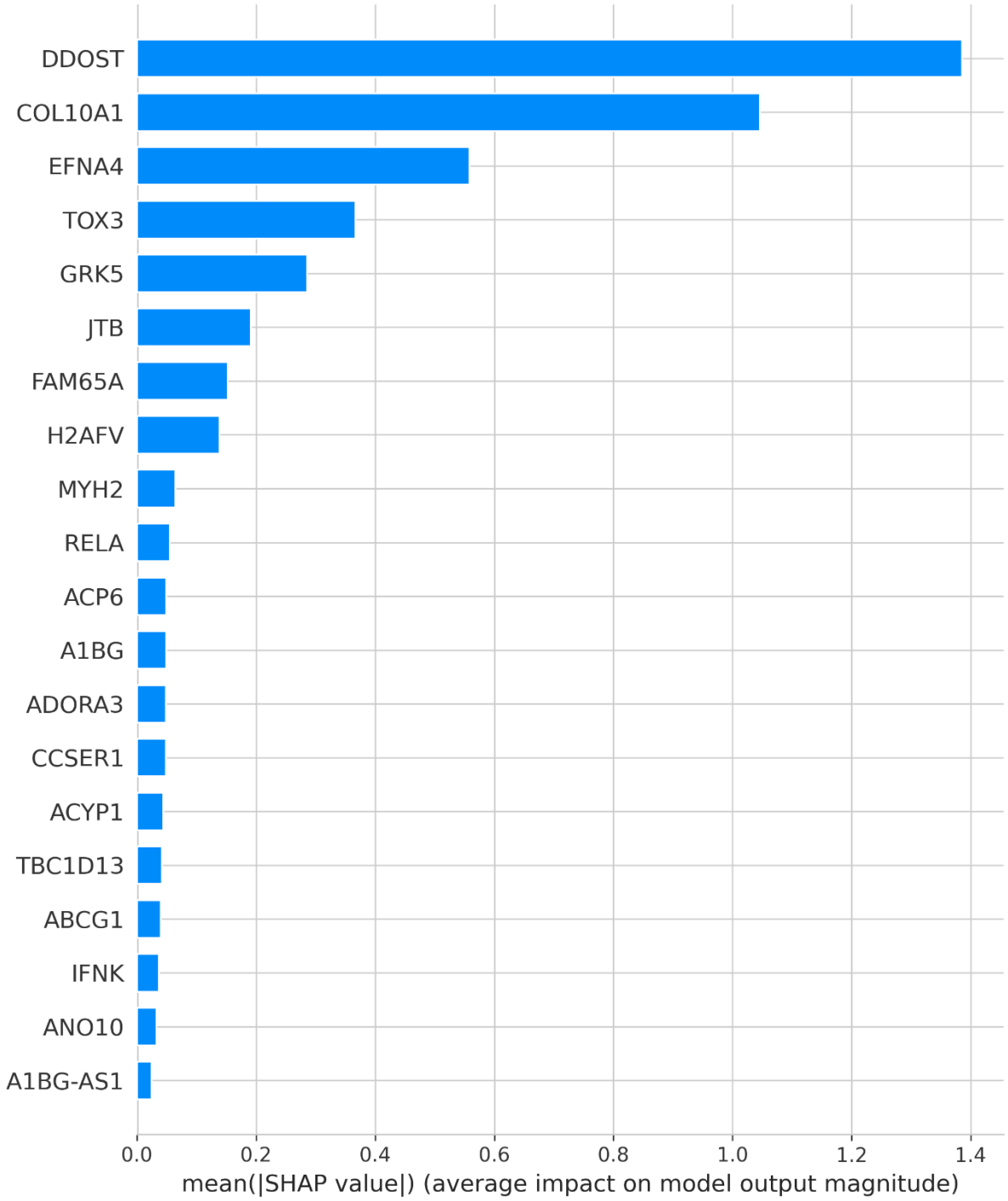

Fig 7: SHAP Bar plot depicting 20 key genes for Healthy vs NSCLC dataset

The bar plot as shown in Fig. 6, depicts the genes of utmost importance placed on the top and the genes of least significance at the bottom. DDOST, COL10A1 and EFNA4 are the genes of high predictive value and are most significant in our ML prediction model.

Fig. 7 shows the bar plot of all key genes which have high predictive value after analysing under new ML model (i.e., after SHAP application).

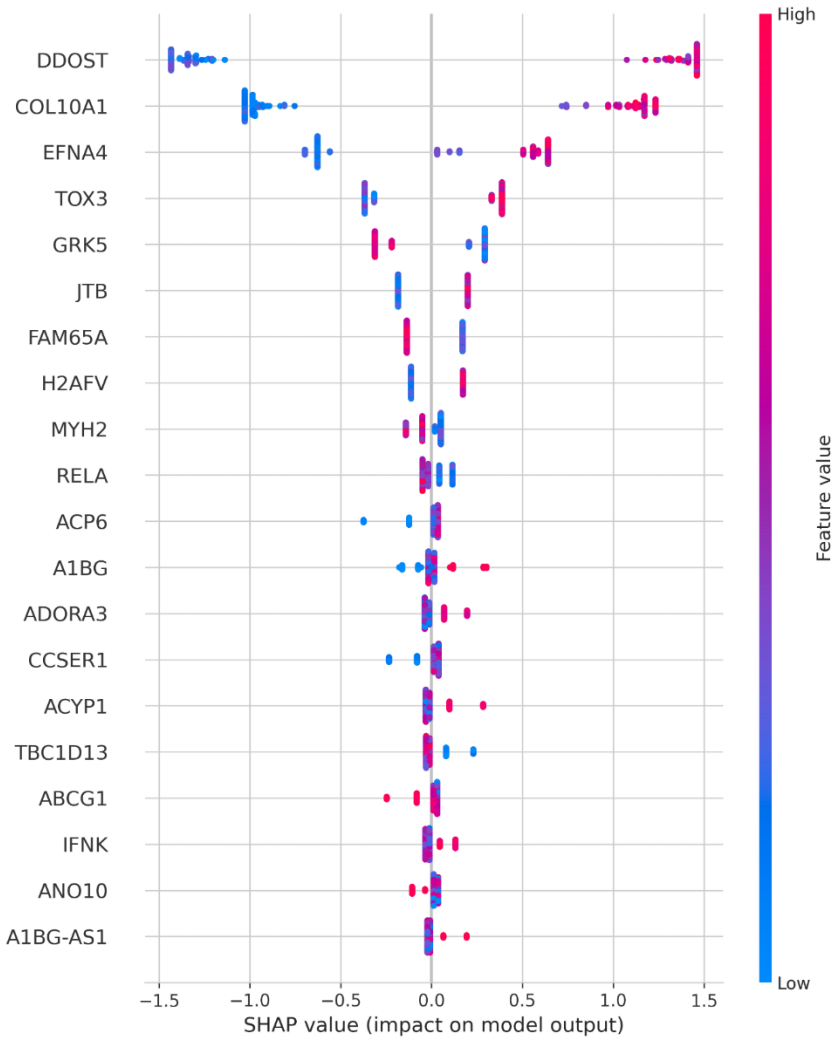

Fig 8: SHAP Summary plot depicting the most important genes and their impact in Healthy vs NSCLC dataset. Identified genes are ranked descendingly according to their feature importance on y-axis. On the x-axis, it is indicated if a gene's effect is associated with greater or reduced prediction, demonstrating the gene's impact on the model output. The colour represents whether the effect of a specific gene is statistically significant (in red) or minimal (in blue) for that observation.

In Fig. 8, the SHAP summary plot illustrates the following points: Genes are ranked descendingly according to their feature importance; the horizontal location indicates whether

the effect of a gene is related with greater or reduced prediction, indicating its impact on the model output; the colour indicates whether the effect of a particular gene is significant (in red) or minimal (in blue) for that observation; a high level of 'DDOST' has a strong positive impact on the quality rating, indicating the correlatedness of that particular gene. The "high" is shown by the red colour, while the "positive" influence is indicated by the X-axis. Similarly, we would state that the "GRK5" is inversely connected to the target variable. From the following SHAP summary plots, we have inferred that DDOST, COL10A1, EFNA4, TOX3, JTB and H2AFV are the most significant genes in all the datasets and have a high and positive impact on models' predictions. While GRK5 and FAM65A are negatively correlated with models' predictions.

We employed the GEO2R computational tool to characterise the relevance of important genes that were differentially expressed during NSCLC development. P-values < 0.05 were considered statistically significant for the identified genes ANO10, A1BG, CCSER1, ACYP1, JTB, DDOST, H2AFV, ACP6, ADORA3, EFNA4, TOX3 and COL10A1 were found to be down-regulated while A1BG-AS1, ABCG1, FAM65A, IFNK, MYH2, GRK5, RELA and TBC1D13 were found to be up-regulated in NSCLC progression (Table 1).

Table 1- Statistical analysis results for identified key genes in the dataset.

S. No	Genes	P-value	logFC
1.	A1BG	3.03E-01	0.070087
2.	A1BG-AS1	7.26E-01	-0.01394
3.	ABCG1	6.13E-11	-0.85556
4.	ACP6	1.76E-15	0.908593
5.	ACYP1	3.38E-02	0.218101
6.	ADORA3	3.18E-08	1.06179
7.	ANO10	4.04E-01	0.047119
8.	CCSER1	9.90E-04	0.111623
9.	COL10A1	3.01E-34	3.798228
10.	DDOST	3.15E-25	0.717216
11.	EFNA4	3.70E-31	1.610928
12.	FAM65A	7.05E-21	-0.91652
13.	GRK5	7.70E-36	-1.77003
14.	H2AFV	4.55E-19	0.879407
15.	IFNK	3.54E-01	-0.01945
16.	JTB	5.44E-24	0.507355
17.	MYH2	4.63E-10	-0.4146
18.	RELA	1.89E-04	-0.19373
19.	TBC1D13	2.44E-02	-0.14988
20.	TOX3	2.54E-22	3.195963

CHAPTER 10

DISCUSSION AND CONCLUSION

A literature survey of the high impact genes identified after SHAP application was done in order to analyze their functionality and significance.

The membrane proteins called as GPCRs are concerned with the physiological pathways which belong to the subclass of neurotransmission signalling and balancing of hormones. GRK5 regulates pathways mediated by GPCRs. When NSCLC is talked about, the up-regulation of this gene presents an inferior survival rate as well as the fact that deteriorating expression of GRK5 weakens the propagation of lung cancerous tissue is crucial in pointing the coherence of its up-regulation as NSCLC progresses [59].

A1BG-AS1 is primarily related to hepatocellular carcinoma. When this gene is deliberately expressed and forced on to the cancer tissue then this results in stifling of hallmark mechanisms of any cancer which are invading the healthy cells and the movement into them and their tumorous propagation. The up-regulation of A1BG-AS1 in NSCLC progression is logical as increase in cancerous tissue warrants the need for the same [60].

RELA up-regulation in case of cancer occurs as it acts as gene regulator for the ones participating in tissue propagation and survival. RELA's higher expression in lung cancer leads to incitement of NF-kB signalling. The latter propagates apoptosis defiance, survival and growth in tumorous tissue [61].

DDOST gene has a crucial role in glycosylation processing in proteins. The down regulation of DDOST gene in lung cancer is coherent with the fact that this may result in improper folding of proteins and their transfer. This transfer can be hindered if anomalous glycosylation adversely affects molecular pathways [62].

EFNA4 has action in cellular signalling specially at development. It denotes Ephrin A-4 and is crucial for homeostasis of healthy tissue. This in-silico analysis showed downregulation of this gene in NSCLC progression. Latter suggests that abnormal tissue propagation occurs as a result of EFNA4's reduced expression. Presently, the role of EFNA4 dysregulation in lung cancer is unclear [63].

COL10A1 symbolizes Collagen α-1 chain and has an important role in maintenance and creation of bone tissue. Its product, Type X collagen is one of the main parts of extracellular

matrix (ECM). Therefore, its mostly associated with ailments involving maturation of cartilage and bone. COL10A1 is an interesting gene in the sense that, although it has a very contained expression in majority of healthy samples of varies diversity, it is downregulated at a large magnitude in case of NSCLC [64].

As a part of the ATP-binding transporter class, ABCG1 regulates lipid homeostasis and efflux. Henceforth, it has critical association with cardiovascular ailments. Comparably, TOX3 regulates gene expression mainly in breast cancer [65, 66].

Further examination of these genes within the context of lung cancer, especially NSCLC, might lead to exploration and ultimately disclosure of some of the genes as markers of therapy and treatment.

CONCLUSION

NSCLC represents around 85% of the total cases of lung cancer. Non-small cell lung cancer (NSCLC) is classified into three major subtypes based on histology: adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma. In this study, we tried the applicability of XAI on transcriptomics data to identify candidate genes namely DDOST, COL10A1, EFNA4, TOX3, GRK5, JTB, FAM65A, H2AFV, MYH2, RELA, ACP6, A1BG, ADORA3, CCSER1, ACYP1, TBC1D13, ABCG1, IFNK, ANO10 and A1BG-AS1 that may be highly associated with the occurrence and progression of NSCLC. However, because these conclusions are based on bioinformatics research, they may require confirmation through wet-lab experiments. This article supports for the use of XAI on ML models to quantify and thoroughly assessing the prediction results specially in the field of biomedicine for discovery of biomarkers relevant in predictive and prognostic purposes.

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