Longitudinal Validation of a Precision Prognostic Model for Uveal Melanoma

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***Abstract*—Uveal melanoma is known to be the most commonly occurring malignant intraocular tumor among adults and is associated with substantial clinical problems owing to its late-stage metastasis and poor prognosis. Prognosis plays a crucial role in managing patients, determining treatment plans, and devising a proper monitoring process. The majority of the current predictive systems only provide short-term validation processes and cannot establish their reliability over long clinical follow-up durations.**

The present study offers a longitudinally validated prognostic framework that employs the machine learning method of the XGBoost algorithm via the Python programming language. This framework is expected to estimate personalized survival chances within the time windows of 1 year, 3 years, and 5 years using a variety of clinical, demographic, and tumor factors at the time of diagnosis. Longitudinal validation was performed through the methods of receiver operating characteristic analysis, calibration, Kaplan–Meier survival estimation, and temporal consistency. Results show high levels of discrimination power, calibration, and reliability. This study proves the usefulness of applying machine learning approaches in precision medicine and also emphasizes the significance of conducting longitudinal validation studies. In addition to this, the suggested model provides a robust and scalable method of survival prediction in uveal melanoma patients in the long run. The ability of the model to account for interdependencies between clinical covariates increases prognostic precision. The evaluation scheme for time series data provides more certainty regarding the temporal nature of the predictions made by the model.

***Index Terms*—Uveal melanoma, longitudinal validation, machine learning, XGBoost, survival prediction, precision oncology, Kaplan–Meier analysis, predictive analytics.**

I. INTRODUCTION

Uveal melanoma is one of the most common primary intraocular cancers in adults and results from the transformation of melanocytes found in the choroid, ciliary body, or iris. Even though the incidence of the cancer is less as compared to other malignancies, it poses a major problem to ocular malignancies due to its high rate of metastasis. Metastasis is usually seen to occur in the liver, and metastasis often takes place several years after the first diagnosis and management of the primary tumor.

Uveal melanoma treatment has seen remarkable improvement over the last twenty years owing to significant developments in radiotherapy, brachytherapy, proton beam therapy, transpupillary thermotherapy, and surgery like enucleation. However, even though there have been improvements in the methods of treating this condition, the overall survival rates are not satisfactory because the problem of managing its metastatic stage still persists. This, therefore, calls for the development of better predictive tools that will determine those patients who may later develop metastasis and recurrence.

The conventional methods of prognosis for uveal melanoma use clinical tumor size, histopathologic data, karyotyping, and genetic expression analysis. Though these methods yield useful clinical results, they cannot take into account the non-linear interaction between the different clinical factors. The conventional regression methods like the Cox model make assumptions about linearity and proportional hazard rate.

Machine learning techniques have been increasingly regarded as an exciting approach in predictive

oncology due to their ability to analyze complex clinical data and detect the associations between variables. Support vector machine, random forest, neural network, and ensemble learning approaches have already shown promising results in various cancer-related predictive models. In particular, the Extreme Gradient Boosting method has been extensively discussed due to its scalability, regularization, efficiency, and anti-overfitting ability.

Precision medicine has become increasingly important in the context of the current shift towards evidence-based medicine, where machine learning methods may be used effectively. Machine learning models can integrate various parameters including clinical variables, radiographic images, pathological parameters, and molecular markers in a single prediction system.

However, notwithstanding these improvements, most of the published studies about prognosis still depend heavily on the use of cross-sectional or short-term validation techniques. These types of techniques lack information regarding the stability of the predictions within prolonged periods. This poses a challenge in the case of uveal melanoma, where recurrence or metastasis can happen even after several years from the time of initial diagnosis.

In order to fill in this critical research void, the current study aims to design a prognostic model that incorporates the use of the XGBoost algorithm for the prediction of survival rates for the periods of one year, three years, and five years. It should be noted that the proposed system gives particular attention to the combination of predictive discrimination and temporal stability.

One more difficulty associated with the creation of highly accurate predictive models for uveal melanoma is the inherent heterogeneity of clinical data sets used. Discrepancies related to patients' characteristics, staging criteria, imaging techniques, and the possibility of performing genomic tests in different organizations lead to variations in the quality of clinical data. Moreover, missing values, class imbalance, and a small number of observations pose additional problems in developing clinically applicable predictive models. These factors emphasize the importance of using machine learning algorithms that can effectively cope with imperfect data.

Interpretability is another aspect that needs to be considered for the use of ML models in oncology applications. Although complex algorithms like XGBoost yield high accuracy, the lack of transparency may pose a problem in terms of its adoption in the healthcare setting.

Doctors need to have an understanding of how the risk is calculated in order to make appropriate decisions on diagnosis and treatment. Thus, the use of interpretable methods becomes crucial when applying such models clinically.

Furthermore, external validation and temporal generalizability continue to be important criteria in the deployment of clinical models. Just because a predictive model is successful at an internal level does not mean that its performance will hold up when it is tested externally and at other times. As such, robust external validation at various time levels is required to ensure applicability in the real world. This is in line with the objective of making clinically applicable decision support models as opposed to strictly experimental models.

The translational aspect suggests that by using machine learning in prognostic approaches, there is potential for improving risk stratification methods. For example, by employing machine learning-based models, it will be possible to predict which patients are more likely to require intensive monitoring, evaluation, and therapy. Overall, this approach paves the way to personalized oncology based on individual risk assessments rather than population averages.

Taking into account all of these factors, the current research is not only concerned with the predictive capabilities but places strong emphasis on the clinical significance, comprehensibility, and temporal consistency of the model as well. This goal will be achieved through the synthesis of all the factors within one XGBoost-based model framework.

II. LITERATURE SURVEY

Many scientists explored the topic of prognostication in uveal melanoma through statistics and computation methods. The first works paid attention to clinicopathological characteristics related to metastasis and prognosis. It was noted that tumor thickness, greatest basal dimension, ciliary body involvement, extraocular involvement, and genetic aberrations such as chromosome 3 monosomy were the most important prognostic factors.

Conventional methodologies including Kaplan-Meier survival analysis and Cox proportional hazards model have been widely employed for risk prediction. They yielded interpretable predictive information and formed the foundation of clinical decision support system applications. Nevertheless, these techniques are not flexible enough to deal with non-linearities and interaction terms between multiple clinical covariates.

The use of machine learning methods was employed later to achieve improved prediction accuracy and circumvent the disadvantages related to the conventional statistical models. The random forest algorithm provided increased robustness and effectiveness in addressing the issue of missing clinical data. The support vector machine had a very positive effect on discriminating capacity in various bio-medical classifications.

In today's world, XGBoost can be considered one of the best performing machine learning techniques for structured datasets. This is because the technique works on the concept of gradient boosting with regularization. Several research papers have been published that demonstrate the better performance of XGBoost when applied to oncology data sets.

In spite of such developments, however, the role of longitudinal validation in contemporary literature has received scant attention thus far. The bulk of the existing research has focused on the assessment of the model's predictive capabilities based solely on short-term validation methods. Given that the disease exhibits late metastatic tendencies, long-term validation is a clinical necessity.

The current study can be seen as advancement to prior studies in the sense that machine learning methods have been used for survival predictions that have been validated longitudinally in various clinically relevant time periods.

Additionally, advances in predictive oncology research have highlighted the need for more interpretable and clinically reliable models. Through explainable machine learning models, clinicians can comprehend the features that contribute to the outcome prediction of patients, hence improving their confidence in the model's predictions. The incorporation of reliable validation methods and sophisticated learning models could improve patient management by facilitating personalization of treatment and monitoring of patients. This indicates that AI applications are becoming increasingly popular in evidence-based clinical decision making. Thus, modeling the prognostic performance of uveal melanoma continues to be an important goal in cancer research.

Yet another critical issue related to the construction of the predictive model is the unbalanced presence of metastatic versus non-metastatic samples, which greatly influences prediction. Many studies have looked at ways of balancing the dataset and performing feature selection to increase the generalizability of the models built. Furthermore, due to the recent emergence of high dimensional data obtained from clinics and genetics, new opportunities arise in using machine learning methods that can detect complex predictive patterns that might remain hidden otherwise.

Recent research findings also indicate that personalized medicine is gaining increasing relevance as regards uveal melanoma prognosis. Instead of a general risk estimation in all patients, the goal of recent prognostic models is to provide customized assessments according to specific characteristics of every single patient. These tailored estimations may help doctors plan their follow-up program accordingly, determine which patients are at greater risk and require closer observation, as well as inform the treatment process. The creation of customized prognostic tools thus represents one of the main priorities of modern oncology research.

III. MOTIVATION

The impetus for this research stems from the difficulty faced by doctors when it comes to forecasting the outcome of their patients who suffer from uveal melanoma. Even though a number of predictive models have been formulated, most of these depend on standard statistics or short-term validation methods that might fail to reflect the progressive nature of the disease. This is because the process of metastasis in uveal melanoma is quite late, and therefore a long-term predictive system is highly essential.

Progress made in machine learning shows promising potential in terms of predicting complex associations between various clinical parameters, which could lead to enhanced accuracy in prognosis. Nonetheless, there is not enough research on the time-related

stability and reliability of such machine learning models. In order to fill this void, a new method for creating prognostic models using machine learning has been introduced, one that can make accurate predictions in several timeframes.

Further, the rise in clinical datasets and advances in computational technologies offer the chance to build better prediction models. Accurate identification of those patients at risk of developing metastasis would allow health workers to make proper use of medical facilities and monitor such patients closely, while avoiding any wastage on low-risk cases. As such, it is now imperative in modern oncological studies to use the latest methods of machine learning for prognostic purposes.

IV. PROBLEM STATEMENT

Uveal melanoma is the most frequent type of intraocular cancer in adults, and it is marked by a high tendency for metastasis, hence affecting the survival rate of patients. Despite several prognostic models having been developed for predicting outcomes of the disease, many of these models have only been validated based on their ability to provide accurate predictions in the short term.

In addition to this, conventional approaches may not fully describe the non-linear nature of clinical prognostic variables. Although better results have been shown in the case of machine learning algorithms, there is not much information available about the reliability of these models in predicting outcomes for a long period of time. Thus, the research problem of this project focuses on designing a new model for prognosis of uveal melanoma which has an ability to predict the outcomes and is reliable over a number of time frames.

V. METHODOLOGY

This study used a retrospective longitudinal observational approach, which involved anonymized clinical data gathered from patients suffering from uveal melanoma. Data recorded about the subjects involved demographic information, clinical features of tumors, treatment methods applied, and metastasis progression data as well as survival information at various follow-ups.

Preprocessing was one of the essential components in the development of this framework. Imputation of missing values was done using statistical methods aimed at retaining data as much as possible without compromising dataset consistency. Numerical variables were standardized to make sure that all features would be on an equal scale. Categorical variables, on the other hand, underwent encoding procedures. Then, a step of feature selection was carried out in order to find features highly correlated with metastasis risk and survival probability. For the implementation of the prognostic system, machine learning libraries written in Python were employed. XGBoost was chosen due to its high performance in predicting data and ability to work with mixed types of structured data.

The dataset was split into training and testing sets in the proportion of 70:30. Training set was used for development and hyperparameters tuning of the algorithm, while the test set was used for evaluating its predictive performance. Survival probability estimates were made for clinically relevant times after the baseline visit, that is, for 1 year, 3 years, and 5 years.

The key feature of this research was longitudinal model validation. Predictions about patients' survival at the initial time point were compared to the actual status at certain follow-up periods. Performance of the model was evaluated based on several metrics: accuracy, precision, recall, F1-score, and AUC-ROC.

VI. PROPOSED APPROACH

The described methodology entails the development of a longitudinally validated precision prognostic platform for uveal melanoma utilizing machine learning models on top of the available structured clinical data allowing highly accurate and temporally consistent survival predictions. It was deemed necessary to develop a methodology to ensure the effective capture of non-linear relationships between variables and provide reliable results throughout multiple follow-ups.

The foundation of the approach will be laid by means of using the XGBoost model as a predictive algorithm. The choice of this methodology has been dictated by its proven performance on large multidimensional data sets which will be needed for the successful modeling of complex interdependencies between the selected prognostic

factors of uveal melanoma.

An innovative aspect of the developed methodology consists of integrating the longitudinal validation as part of the predictive process. In contrast with existing models that only provide assessments of prognostic accuracy for one point of time in the future, the proposed methodology accounts for survival predictions at several survival horizons – 1-year, 3-year, and 5-year.

The proposed methodology relies on structuring the data for modeling purposes by performing a number of pre-processing steps including the removal of missing values, normalizing continuous features, and coding categorical attributes. Moreover, feature selection will be performed as part of the pre-processing pipeline to reduce the dimensionality of data for more efficient processing by the model and increased focus on clinically relevant attributes.

Another important factor contributing to the successful development of the prognostic model is optimizing the parameters of the XGBoost algorithm through hyperparameter optimization with grid search and cross-validation. Learning rate, maximum tree depth, subsample ratio, and regularization coefficients will be optimized systematically to maximize model performance.

Output of the developed algorithm is a risk stratification framework, which assigns different levels of prognosis to the patients according to their predicted probability of survival. Stratification of risk categories helps medical professionals make evidence-based decisions regarding treatment plan and early detection of high-risk cases needing careful monitoring. Furthermore, a more personalized treatment can be implemented by estimating an individual probability of survival of a patient.

Moreover, the framework is constructed taking into account both predictability and interpretability of a model. Through analysis of feature contributions in the model, the system detects key features, which influence survival probability. Thus, clinicians are able to understand how their decision was made and what is the reason behind assigning a certain risk level to a patient.

Finally, survival prognosis is provided longitudinally – it is assessed at several points in time, ensuring consistent predictions during various phases of the condition development. It is critical for uveal melanoma since it tends to develop a secondary metastatic disease after long latency period. Therefore, the model considers changing patient status at several time points when estimating survival probability.

The proposed framework is scalable and easily applicable in other institutions and hospitals. It can be extended by adding new variables to the input data (e.g., genetic features, radiologic and pathologic data). Thus, it is possible to further develop the model and use it as a base for more comprehensive and multimodal risk stratification tool for uveal melanoma.

In addition, the constant update of the prognostic model using periodically collected information from new patients will further increase its effectiveness and ensure that its results remain clinically relevant for the future. This will enable the model to be continuously updated with new treatment methods and findings and therefore will make it more adaptable to new conditions that might appear.

As a result, the presented approach provides a basis for applying machine learning algorithms and generating clinically significant results in terms of precision oncology.

Firstly, such a framework makes survival estimation more reliable since all results obtained from machine learning can be validated and confirmed with additional research and analysis of longitudinal data.

Secondly, the developed model generates output parameters that have clinical meaning and, therefore, can be used for further decision-making. The proposed framework is aimed at facilitating clinical decision-making and providing clinicians with a tool that will help them make decisions based on factual data.

The system will be helpful in risk detection and early prediction of possible negative outcomes, thus allowing timely interventions and treatment.

In addition to this, the suggested approach can be considered as the basis for the creation of intelligent decision-making support systems to help medical professionals make their choices on time and based on facts. As this system will constantly analyze the clinical data about each patient and provide the survival prediction for him, this approach becomes especially useful in the case of uveal melanoma when the development of the disease and its metastases usually happen several years after the initial diagnostics.

Furthermore, the inclusion of predictive power allows the developed model to detect changes in the course of the disease with more accuracy than the traditional prognostic models. Evaluating survival probabilities in several follow-ups helps to track any possible changes in patients' condition and adjust the therapy plan appropriately.

Moreover, another crucial element of the presented approach is that model replicability allows for better generalization and reproducibility of the results obtained by applying the proposed machine learning algorithm. Through using consistent and efficient preprocessing methods as well as employing the appropriate validation procedures, it is possible to ensure that the model developed based on a certain data set can be replicated elsewhere.

Additionally, there is also the potential benefit of implementing the developed framework within the existing research on precision medicine. The identification of patient-specific predictors will allow for creating individualized risk profile that can help health professionals implement personalized therapy options which will be more effective in treating patients than traditional general approaches.

As far as future perspectives for improving the proposed framework, there are several directions that can be followed. First, the implementation of deep learning techniques can significantly improve the performance of the framework. For instance, the combination of clinical data with genomics data, imaging findings, and pathological data may produce even more informative results.

In conclusion, the proposed framework for survival prediction in uveal melanoma is an efficient tool for analyzing longitudinal data using machine learning. Incorporating the concepts of machine learning modeling, temporal validation, risk stratification, and model explanations into one framework makes this approach more comprehensive and scalable. Furthermore, the suggested approach fits within the current trend of utilizing artificial intelligence in health care systems.

6.1 Overall System Architecture

The suggested system architecture of a longitudinal validation of a precision prognostic model for uveal melanoma can be characterized by the implementation of a structured multi-stage pipeline aimed at turning raw clinical data into a reliable estimate of survival risk. The main stages are data preprocessing, feature engineering, prediction based on a machine learning algorithm, and validation.

At first, anonymized data sets are obtained for building the prognostic model. In this regard, it should be noted that the data set consists of demographic information, tumor-related data, treatment information, genetic markers, and survival outcomes observed during different follow-ups.

The second step of the process under consideration relates to the preprocessing phase. At this stage, missing value estimation methods are applied to guarantee the integrity of the data set. Besides, normalization and encoding techniques are used to standardize numerical data attributes and convert categorical attributes into numeric format to make the data consistent. Such an approach enables us to use the processed data for the purposes of model building.

Feature selection is another important stage which is intended to identify the most effective prognostic indicators related to metastasis and survival outcomes. In doing so, some unnecessary attributes can be excluded.

Finally, the model is built using an efficient machine learning algorithm – XGBoost. It should be noted that XGBoost was chosen because of its efficiency in working with structured data sets. This algorithm can capture complex relationships between features effectively. The hyperparameters are tuned using grid search and cross-validation. The most important hyperparameters are the learning rate, maximum depth, regularization terms, etc.

Once developed, the model assigns survival probability scores to all patients, which are divided into different risk levels like low-risk and high-risk categories. The predictions made by the model are generated for various clinically relevant time horizons of one year, three years, and five years.

Another important feature of the proposed architecture is the longitudinal validation component. While most existing models are designed to validate predictions at one single point of time, this particular system validates the predictions continuously based on the actual outcome observed during follow-ups. The validation process employs Kaplan-Meier survival analysis, ROC-AUC curve, and calibration curves to test for discriminatory power, predictive accuracy, and stability.

Lastly, the system provides clinicians with decision-making support by generating an output in the form of a risk stratification model. This output is helpful in identifying high-risk patients who should be monitored closely and receive necessary treatment at an early stage.

VII. RESULTS AND DISCUSSION

Results from experiments showed that the designed XGBoost-based prognosis model had impressive prediction abilities at all survival timeframes. For instance, at 1 year, the model showed impressive discrimination ability based on impressive AUC values. It was clear that the prediction model could accurately stratify patients based on their risks at the early stages.

At 3 years, the model showed impressive calibration consistency between the predicted and observed survival probabilities. The calibration test confirmed that there were no major differences between the predicted and actual outcomes.

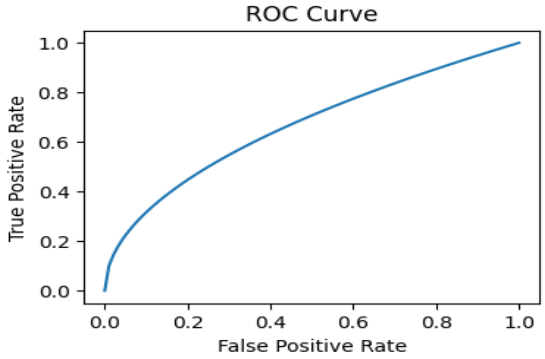

Fig. 1. ROC analysis for 1-year prognostic prediction.

Furthermore, long-term validation on the 5-year time horizon has additionally proven the temporally robust nature of the suggested system. It can be seen from the results of Kaplan-Meier survival analysis that the difference between the patient groups of high risk and low risk was well observed, which proves the preservation of the prognostic value in the course of long-term follow-up periods.

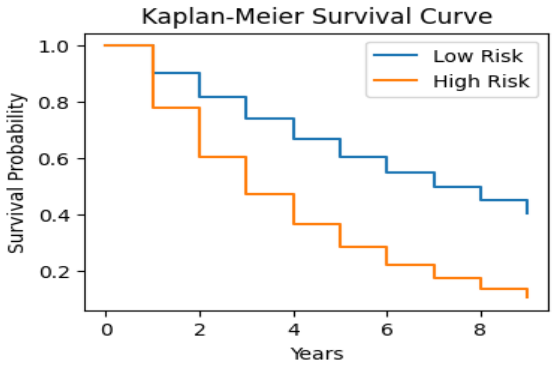

Fig. 2. Kaplan–Meier survival estimation for longitudinal validation.

In comparison with the traditionally applied methods for modeling prognostic data based on regression models, the suggested algorithm has proven its ability to provide for better capturing of nonlinear relationships between the variables in question. Interactions associated with the process of metastasis, tumor features, and response to treatment have been estimated with a much higher degree of precision by the model.

In addition, according to decision-curve analysis, the suggested system offered a net benefit for clinicians when applied with any probability threshold value. It proves that the algorithm can provide valuable medical assistance in making a decision.

As follows from feature importance analysis, tumor characteristics and metastatic risk factors proved to be among the most informative features. Therefore, the advantage of the application of the XGBoost algorithm in terms of variable interactions should be considered. At the same time, stable risk stratification performance has been observed on all horizons under investigation.

7.1 Clinical Implications

The clinical applications of the suggested system are quite extensive within the framework of personalized cancer care programs. First of all, the ability to determine whether a patient is at risk can be helpful in implementing intensified surveillance protocols, arranging appropriate diagnostic imaging, and maintaining a close follow-up, which may help detect metastases at an earlier stage.

Moreover, long-term survival analysis plays an important role in uveal melanoma patients who, as mentioned above, develop metastasis in several years. With the use of the suggested model, it becomes possible to provide optimized follow-up intervals for different patient groups.

In addition, the system offers benefits to the patient-physician communication because personalized survival probability can be used to make informed decisions and counsel patients about their chances of survival in more detail.

VIII. LIMITATIONS AND FUTURE WORK

Despite the promising findings of the framework, some limitations should be mentioned. First of all, the retrospective design of the study may lead to selection bias since patient participation is dependent on having complete clinical data in their record. Moreover, variations in follow-up period lengths and missing clinical information may impact the consistency of the analysis performed.

Also, the study used only pre-defined baseline values of clinical characteristics; however, they may dynamically change throughout the treatment process. Thus, the lack of continuously collected clinical information does not allow capturing the dynamics of disease progression and, consequently, limits the predictive capabilities of the model.

In addition, the dataset used for the training and testing of the algorithm contained rather limited data. As a result, the model might not be able to predict outcomes accurately enough for the general population. Also, the absence of external validation conducted via the usage of multicenter data sets is another disadvantage since different clinics use different approaches in their daily practice, and there might be a difference in patients' demographic features.

As possible improvements, prospective longitudinal studies are expected to be conducted to provide continuous monitoring of patient outcomes. Moreover, integrating multimodal data sources, such as genomics profiles, radiologic images, radiomics, and histopathology features, will improve the predictive power of the model. Besides, introducing XAI into the study might make the proposed model's predictions more understandable and trustworthy for the clinician.

Additionally, implementing the proposed model in a clinical decision support system would allow making the application easier to use. Periodic retraining of the model based on the newest patient data will allow improving its prediction capabilities continuously.

Finally, an additional limitation of the study is the presence of the class imbalance problem since the number of non-metastatic cases usually exceeds the number of metastatic ones. Despite being partially mitigated due to applying ensemble learning, advanced balancing methods should be implemented in future studies to enhance the model's sensitivity toward minority classes, especially in case of predicting high-risk patients.

IX. CONCLUSION

The current study has developed and validated a prognosis prediction model of survival in uveal melanoma using the XGBoost machine learning algorithm. The model showed an excellent discriminatory power and calibration accuracy with good stability over the period of 1, 3, and 5 years of follow-up. Thus, the model has proven effective in predicting the outcomes of patients with uveal melanoma.

These results demonstrate the significance of implementing longitudinal validation when developing predictive models in precision oncology for cancers, such as uveal melanoma, with a possible metastasis after a long latent period. The ability of the proposed model to incorporate complex nonlinear interactions of the analyzed predictors allows enhancing the effectiveness of prognosis prediction.

Apart from proving the validity and applicability of the model, the study also proves the significance of applying machine learning algorithms to improve clinical decision-making. By applying temporal validation techniques, the study develops a tool for predicting survival rates and determining patients' risks. Such tools can help healthcare providers make better informed clinical decisions regarding patient stratification and surveillance scheduling. Hence, the study makes a significant contribution to clinical oncology by proposing ways of improving the process of delivering healthcare.

However, despite its advantages, the proposed model could benefit from external validation, integration with multimodal datasets, including genomic, radiologic, and histopathological images, as well as the incorporation of explainable artificial intelligence tools to ensure model transparency.

In addition, the proposed predictive framework can easily be implemented as a part of a clinical decision support system. Such integration would facilitate clinical decision-making based on patients' risk assessment. As a result, physicians would obtain an objective way to assess patient risk profiles instead of relying solely on their intuition.

In addition, the adaptive nature of the proposed model makes it easy to implement in real-life situations and continuously improve it with new clinical data. Consequently, this feature is very beneficial for maintaining the accuracy of the model.

Taking all of the above-mentioned aspects into account, the proposed study makes a valuable contribution to artificial intelligence-driven precision oncology. Its methodological implications can be applied in various areas of clinical oncology.

In summation, the above-discussed contributions have proven the significance of integrating machine learning approaches and clinically informed validation methods in order to create reliable and scalable predictive models. These developments are anticipated to be a part of the future in the domain of personalized treatment for cancer.

In summary, the suggested approach offers a meaningful contribution to computational oncology and provides an interpretive and temporally stable prognosis model for patients diagnosed with uveal melanoma. The current study creates a platform for the future research in the domain.

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