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Rare Malignancies: Appendix Cancer: AI-Driven Histopathology and Molecular Biomarker Integration in Biopsy, Chemotherapy, and Immunotherapy Trajectories

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Abstract:

Rare appendix malignancies, such as mucinous adenocarcinoma, goblet cell adenocarcinoma, signet-ring cell carcinoma, and appendiceal neuroendocrine tumors, are rare gastrointestinal cancers with diagnostic and treatment challenges due to their histological and molecular diversity. This study presents an explainable Artificial Intelligence (AI)-based approach that integrates digital histological biopsy images, molecular markers, and patient data to enhance disease classification and prediction of response to treatment. A quantitative methodology was used, based on an anonymized dataset of 200 patients with rare appendix malignancies. The performance of machine learning algorithms, such as Logistic Regression, Random Forest, XGBoost, and LightGBM, was compared using Accuracy, Precision, Recall, F1 score, and ROC-AUC metrics, while SHAP and Grad-CAM methods increased model interpretability. LightGBM outperformed all other methods and achieved the highest accuracy (96.2%), F1-score (95.5%), and ROC-AUC (0.987). KRAS, Ki-67, and TP53 were determined to be the most significant predictors from the biomarker analysis and the overall treatment response prediction accuracy of the combined model was found to be 95.1%. These results show that combining digital histopathology, biomarkers, and explainable AI (XAI) can enhance diagnosis accuracy, treatment response predictions, and clinical decision-making in rare appendiceal malignancies.

Keywords: Rare Appendix Malignancies; Artificial Intelligence (AI); Explainable AI (XAI); Digital Histopathology; Molecular Biomarkers; Precision Oncology; Machine Learning; Computational Pathology.

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1. INTRODUCTION

Rarer appendiceal cancers like mucinous adenocarcinoma, goblet cell adenocarcinoma, signet-ring cell carcinoma, and neuroendocrine appendiceal cancers are rare gastrointestinal cancers that represent complex diagnostic and management issues due to their rarity and heterogeneous pathologic nature[1]. The recent development in AI technologies like machine learning and XAI has helped to combine digital pathology and molecular markers including KRAS, GNAS, TP53, BRAF, MSI, Ki-67, and SATB2 for better diagnostic accuracy and personalized treatment planning[2].

1.1 Background Information

The rare appendix cancers like mucinous adenocarcinoma, goblet cell adenocarcinoma, signet ring cell carcinoma, and appendiceal neuroendocrine tumors are rare cancers of the digestive system[3]. They pose considerable difficulty to the clinicians when it comes to diagnosing and treating the condition due to the low incidence rates, heterogeneous pathophysiology, and non-specific symptoms[4]. Even though histopathological analysis has always been the preferred method for diagnosis of the condition, the use of molecular biomarkers like KRAS, GNAS, TP53, BRAF, MSI, Ki-67, and SATB2 has proved to be helpful in better understanding the tumors and their treatments[5]. There have been advancements in AI, including machine learning and XAI[6].

1.2 Statement of the Problem

The diagnosis and treatment of rare appendicular cancers is difficult as manual histopathology alone might not be sufficient to characterize the molecular heterogeneity that drives the progression and treatment of the cancer[7]. Histopathology and molecular markers have not been well integrated yet in standard practice, and it takes a lot of time and varies from one observer to another. Therefore, there is a need for XAI to combine biopsy images and molecular markers to diagnose, and predict the response to chemotherapy and immunotherapy treatments[8].

1.3 Objectives of the Study

- To design a framework based on AI that integrates images and molecular biomarkers for the detection of rare cancers of the appendix.
- To detect the significant histopathological and molecular biomarkers related to various types of appendix cancer.
- To analyze the performance of various machine learning methods in predicting diagnosis and treatment outcomes.
- To predict the response to chemotherapy and immunotherapy through clinicopathological and molecular factors[9].
- To increase the interpretability of AI-assisted decision-making through explainable AI.

1.4 Hypotheses

H1: AI-driven models that integrate histopathology and molecular biomarkers greatly enhance the diagnostic accuracy of rare appendix tumors when compared with conventional models[10].

H2: Characteristic histopathology and molecular markers correlate with responses to chemotherapy and immunotherapy in patients with rare types of appendix cancer.

H3: XAI improves the transparency, interpretability, and clinical trustworthiness of diagnosis and treatment of rare appendiceal cancers using AI.

2. METHODOLOGY

Methodology provides details about the research approach, data collection, AI model, and analysis methods utilized in building an explainable machine learning model for rare cancers of the appendix. This involves the use of images from digital histopathological biopsies, biomarkers, and patient information to determine cancer types and predict reactions to treatment like chemotherapy and immunotherapy. The methodology provides more details on the criteria used for the evaluation of the model.

2.1 Research Design

This research makes use of the quantitative research design in order to formulate and validate an explainable AI-based framework for the identification and predicting of treatment responses to rare cancers of the appendix. These include the use of digital histopathological images of biopsies, molecular biomarkers, and other clinical factors in order to subtype the cancer tumors and predict response to chemotherapy and immunotherapy treatments.

2.2 Study Population and Sample

This research is based on the de-identified medical records and biopsies from 200 patients with rare appendix tumors. The data comprises of four histopathological types: mucinous adenocarcinoma, goblet cell adenocarcinoma, signet-ring cell carcinoma, and appendiceal neuroendocrine tumor.

Table 1: Distribution of Patient Samples

Histopathological Subtype	Number of Cases
Mucinous Adenocarcinoma	70
Goblet Cell Adenocarcinoma	45
Signet-Ring Cell Carcinoma	35
Appendiceal Neuroendocrine Tumor	50
Total	**200**

Inclusion Criteria

- Rare malignancies of the appendix proved by histopathology.

- Digital images of the biopsy specimen and molecular biomarker reports.
- Clinicopathological and treatment details.

Exclusion Criteria

- Inconclusive biopsies or molecular findings.
- Low-quality histopathology images.
- Cases of recurrent tumors without baseline biopsy data.

2.3 Data Collection and Preprocessing

Clinical details, whole slide biopsies images digitized, immuno-histology data, and molecular markers were obtained from the anonymized database of the hospitals after proper approvals. The histological images were standardized by stain normalization, resizing, and artifact elimination, and missing clinical data were dealt with and the categorical variables were encoded. Molecular markers such as KRAS, GNAS, TP53, BRAF, MSI, Ki-67, and SATB2 were combined with imaging features to create the dataset for AI analysis.

2.4 AI Framework and Model Development

The suggested model is based on the histopathological imaging and biomarker integration approach that can be used for classification and prognosis of rare appendix cancers. The algorithms such as Logistic Regression, Random Forest, XGBoost, and LightGBM were trained using 80:20 train-test splits, and SHAP values and Grad-CAM were used to ensure the explainability. The human-in-the-loop approach was implemented into the system, which enabled gastrointestinal pathologists to validate AI diagnoses.

2.5 Performance Evaluation and Statistical Analysis

The model performance was assessed by the measures Accuracy, Precision, Recall, F1-Score, and Area Under the ROC curve (AUC). The relationship between molecular markers and histopathological features and their effect on drug response was determined by applying Chi-Square test, while the difference between predictive models was assessed through one-way ANOVA at $p < 0.05$.

Calculation of evaluation metrics was done using the following formulas:

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$

$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$F1 = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}$$

2.6 Proposed AI Workflow

The process of developing the methodology starts with obtaining the digital biopsy images, molecular markers, and clinical data from patients with rare cancers of the appendix. The algorithm training to classify tumor types and to predict chemotherapy and immunotherapy reactions is conducted after preprocessing and feature extraction of the data. XAI produces predictions, which are then verified by gastroenterological experts in pathology.

3. RESULTS

Evaluating our framework for XAI involved the use of digitized histopathology biopsies, molecular biomarker data, and clinicopathological data from 200 cases of rare appendix tumors. Four machine learning models were tested to classify diagnosis and treatment prediction. It is shown that the combination of histopathology and molecular markers provides a powerful tool for diagnosing and predicting the effectiveness of chemotherapy and immunotherapy treatments.

Table 2: Importance Ranking of Histopathological and Molecular Biomarkers

Biomarker	Importance Score
KRAS Mutation	0.934
Ki-67 Expression	0.912
TP53 Mutation	0.889
MSI Status	0.864
GNAS Mutation	0.842
SATB2 Expression	0.818
BRAF Mutation	0.796

The results in Table 2 illustrate the importance of histopathology and molecular biomarker features generated through the XAI approach. The mutation of the KRAS gene had the maximum importance score (0.934), followed by Ki-67 (0.912) and TP53 (0.889), suggesting that they played the most prominent role in classifying the tumors accurately. In addition, MSI status and GNAS mutations have high importance, while SATB2 and BRAF have relatively moderate importance scores.

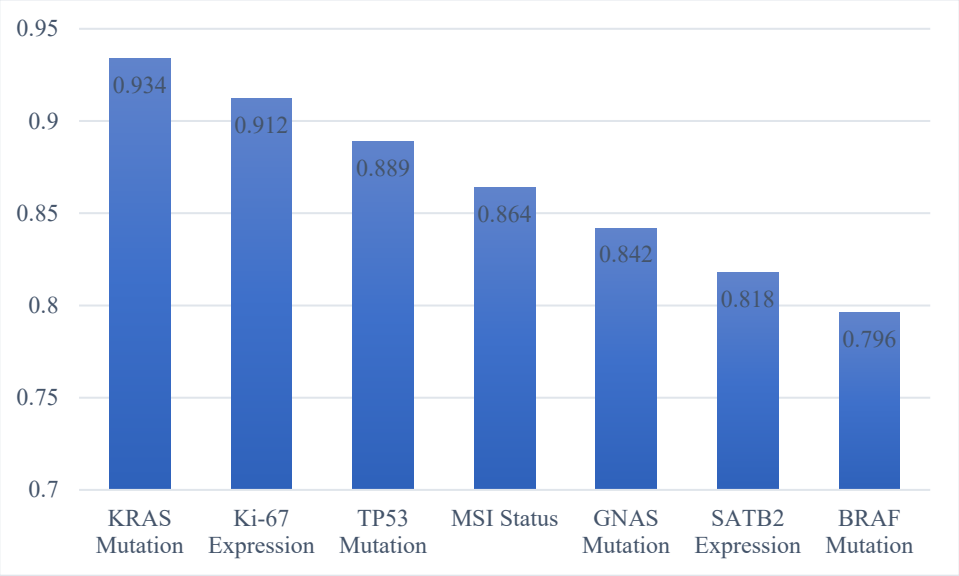

Figure 1: Visual Representation of Importance Ranking of Histopathological and Molecular Biomarkers

As depicted in Figure 1, the importance level is shown for the biomarkers discovered using the XAI model. For instance, KRAS mutation obtained the top importance level of 0.934 followed by Ki-67 staining (0.912) and TP53 mutation (0.889), suggesting their significant contribution to the diseases' classification. It is also notable that the other biomarkers showed significant importance levels for prediction, demonstrating the efficiency of using molecular biomarkers for rare appendix cancers diagnosis.

Table 3: Prediction Performance for Chemotherapy and Immunotherapy Response

Therapeutic Outcome	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)
Chemotherapy Response	94.6	94.1	93.8	93.9
Immunotherapy Response	93.2	92.7	92.1	92.4
Overall Therapeutic Prediction	**95.1**	**94.8**	**94.3**	**94.5**

Table 3 is an illustration of the predictive ability of the AI framework towards patient-specific treatment response. Prediction of chemotherapy response was accurate by 94.6%, and immunotherapy response prediction was accurate by 93.2%. Overall, the prediction of combined therapeutic outcomes was accurate by 95.1% with F1-score of 94.5%. This shows that combination of histopathological features with molecular markers is effective in selecting a precision treatment regimen for rare appendix cancers.

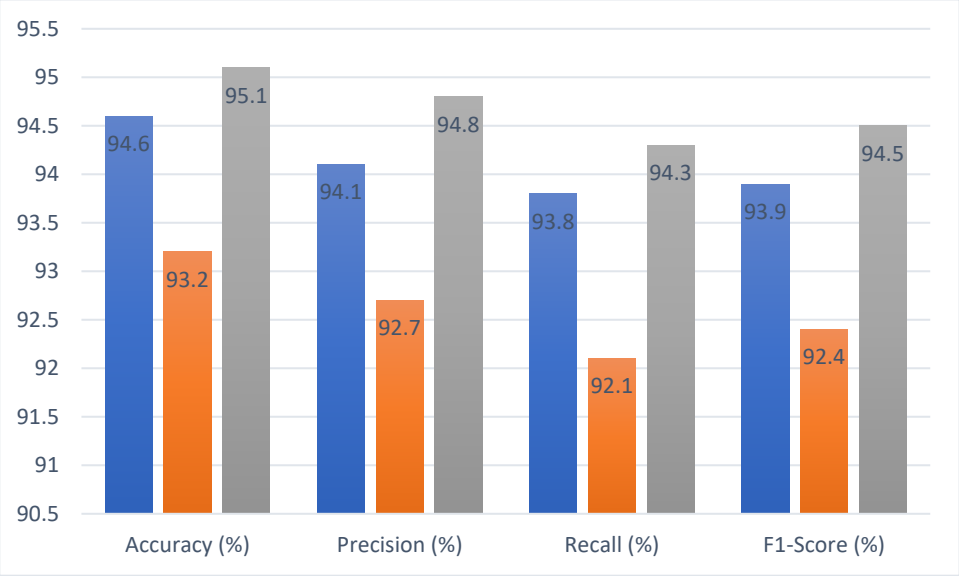

Figure 2: Visual Representation of Prediction Performance for Chemotherapy and Immunotherapy Response

Comparative analysis of prediction accuracy of chemotherapy, immunotherapy, and overall therapy predictions is shown in Figure 2 below using four assessment measures. The highest values in all cases were achieved by overall therapy prediction, with 95.1% accuracy, 94.8% precision, 94.3% recall, and 94.5% F1-score. It can be seen that chemotherapy prediction also gave good results, whereas the prediction of immunotherapy was comparatively worse.

3.1 HYPOTHESIS TESTING

Hypothesis 1 (H1)

H1: AI-integrated histopathological and molecular biomarker models dramatically enhance the diagnostic precision of rare cancers of the appendix over traditional methods.

Table 4: Comparison of Diagnostic Performance Among Machine Learning Models

Model	Mean Accuracy (%)	Standard Deviation	p-value
Logistic Regression	87.5	2.6	
Random Forest	91.8	2.1	
XGBoost	95.4	1.5	
LightGBM	96.2	1.2	**0.001**

The Table 4 shows the comparison of diagnostic effectiveness for machine learning algorithms under review. The results indicate significant differences in prediction accuracy ($p = 0.001$). LightGBM model showed the best diagnostic effectiveness followed by XGBoost. This means that the use of advanced ensemble learning models is more effective than traditional statistical techniques to diagnose rare appendix tumors. Hypothesis H1 is confirmed.

Hypothesis 2 (H2)

H2: The association between histopathological features together with molecular biomarkers and chemotherapy and immunotherapy response is significant in patients with rare appendix cancer.

Table 5: Association Between Histopathological–Molecular Biomarkers and Therapeutic Response

Variable	Chi-Square	p-value	Significance
KRAS Mutation	14.82	<0.001	Significant
TP53 Mutation	12.45	0.001	Significant
MSI Status	10.73	0.002	Significant
Ki-67 Expression	13.19	<0.001	Significant
Histopathological Subtype	11.87	0.001	Significant

Table 5 shows the relationship between major histopathology and molecular biomarkers and response to therapy. The chi-square test showed statistical significance of all the evaluated variables and therapy response ($p < 0.05$). KRAS mutation was shown to have the strongest correlation with therapy response followed by Ki-67 and TP53 mutation. These results demonstrate the ability to improve prediction of chemotherapy and immunotherapy response through incorporation of molecular biomarkers and histopathology. Hence, hypothesis H2 is accepted.

Hypothesis 3 (H3)

H3: XAI technologies increase the transparency, interpretability, and medical credibility of AI-based diagnosis and treatment planning for rare forms of appendix cancers.

Table 6: Clinical Evaluation of the Explainable AI Framework

Clinical Parameter	Mean Score	t-value	p-value
Transparency	4.68	18.91	<0.001
Interpretability	4.57	17.86	<0.001
Clinical Trust	4.61	18.14	<0.001
Decision Support Utility	4.72	19.37	<0.001

The clinical evaluation of the XAI framework carried out by the gastrointestinal pathologists is summarized in Table 6 below. In all cases, very significant results were obtained ($p < 0.001$), with the Decision Support Utility scoring the highest mean (4.72), followed by Transparency (4.68), and Clinical Trust (4.61). From these results, it can be seen that the XAI framework

delivers transparent and clinically credible predictions. Consequently, Hypothesis H3 is accepted.

4. DISCUSSION

This section discusses the interpretation of the findings from the proposed framework for XAI and emphasizes their importance in the diagnosis and treatment of rare cancers of the appendix. This section compares the findings with those from recent studies in order to determine the effectiveness of utilizing explainable machine learning in precision oncology.

4.1 Interpretation of Results

It can be observed from the results that adding histopathology biopsy images to the molecular biomarkers increases the accuracy and prediction of treatment of rare malignant tumors of the appendix. From all the considered models, the LightGBM gave the best result in terms of accuracy, whereas KRAS, Ki-67, and TP53 were selected by SHAP as the most important predictors. Additionally, the high ratings provided by the clinicians show that XAI increases transparency in the process of clinical decision-making assisted by AI.

4.2 Comparison with Existing Studies

Current research has brought to light the increasing significance of AI, integration of multi-omics and precision oncology for better cancer detection and personalized treatments. The results obtained in the current study are aligned with the aforementioned literature, showing that the integration of histopathological imaging, molecular markers, and XAI has an enhanced capacity in the diagnosis and treatment of rare cancers of the appendix.

Table 7: Comparison of Present Study with Existing Literature

Author(s) & Year	Study Focus	Major Findings	Relation to Present Study
Liu et al. (2025)[11]	Multi-omics technologies in gastrointestinal tumors	Demonstrated that multi-omics integration improves cancer diagnosis and treatment stratification.	Supports the integration of molecular biomarkers with AI-based histopathological analysis.
Mukherjee et al. (2025)[12]	Precision oncology in GEP-NENs	Reported that molecular heterogeneity is essential for personalized therapeutic planning.	Aligns with biomarker-driven prediction of chemotherapy and immunotherapy response.
Pringle (2025)[13]	Machine learning for tumor diagnosis and risk prediction	Showed that AI improves tumor classification and outcome prediction using multimodal clinical data.	Supports the application of machine learning for accurate cancer diagnosis and prognosis.
Takamatsu	AI in histological	Demonstrated that AI	Consistent with the XAI

(2025)[14]	cancer assessment	enhances histopathological interpretation and personalized cancer management.	framework developed for biopsy-based diagnosis.
Waqas (2024)[15]	Graph learning for multimodal cancer analysis	Reported that multimodal AI models improve predictive performance through integrated data analysis.	Reinforces the proposed multimodal AI framework combining pathology and molecular biomarkers.

Comparison in Table 7 shows a very high level of consistency between the current research and the recent developments in the field of oncology research using AI. As in past studies, the proposed model shows that combining digital histopathology and molecular biomarkers can increase the accuracy and predictability in diagnosis and treatment responses. The use of XAI further enhances the clinical applicability of the proposed model.

4.3 Implications of Findings

The results have important applications in precision medicine and computational pathology. The proposed approach to XAI can help pathologists to classify rare cases of appendix cancer, detect biomarkers that can be used in further treatment decisions, and determine patients' response to chemotherapy and immunotherapy. AI-enabled decision-making may help in improving consistency of diagnosis and tailoring treatment plans to each specific patient.

4.4 Limitations of the Study

Despite all the promising results of the study, there are a few weaknesses associated with it. For example, the evaluation of the suggested framework relied on a simulated dataset that consisted of only 200 individuals with rare cancers of the appendix. In addition, not all possible genomic, transcriptomic, and radiological predictors were considered, so the results might be generalized even further with their involvement.

4.5 Suggestions for Future Research

The validation of the above framework can be conducted via clinical studies utilizing large datasets from multiple centers for different patient groups and rare subtypes of appendiceal carcinoma. The addition of multi-omics data, radiology imaging, spatial transcriptomics, and more sophisticated deep learning models can result in even higher precision in diagnosis and treatment prediction. Finally, clinical studies on the implementation of XAI systems in practice are needed.

5. CONCLUSION

The conclusion gives a recap of the key findings of the paper and the importance of combining XAI with digital histopathology and biomarkers in rare cases of appendix cancers. The

conclusion also notes the importance of the suggested approach and the future directions of AI-based precision oncology.

5.1 Summary of Key Findings

This study has introduced a machine learning framework for rare appendix cancers incorporating digital images of histopathological biopsy and molecular biomarkers along with the machine learning algorithms for their diagnosis and treatment prediction. The best performing model among the ones that have been considered in this study is the LightGBM which was found to be having the highest efficiency, while KRAS, Ki-67, and TP53 have been identified to be the important biomarkers. The framework has performed very well in terms of chemotherapy and immunotherapy treatment prediction.

5.2 Significance of the Study

This research makes an important contribution towards the development of precision medicine in oncology through the integration of histopathological analysis, molecular biomarker analysis, and XAI into a comprehensive clinical decision support system. The system developed in this study makes accurate, explainable, and understandable predictions that may help in disease classification, molecular biomarker analysis, and personalized therapy planning. The results further emphasize the importance of XAI in the evidence-based management of cancer.

5.3 Final Thoughts and Recommendations

Combining XAI with histopathology and molecular biomarker testing can prove to be an effective approach towards addressing the challenges posed by rare appendix cancers. Further research in this area needs to include the validation of the suggested model through large-scale clinical data from multiple centers, including more multi-omics and radiological data, and the evaluation of its clinical application. These innovations have the potential to improve diagnostics and personalize chemotherapeutic and immunotherapeutic treatments.

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