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Machine Learning Integration of Digital Pathology and Genomic Data to Predict Cancer Progression Risk

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Abstract
Aim: *To develop and evaluate machine learning models that integrate digital pathology images and genomic data for accurate prediction of cancer progression risk, thereby improving diagnostic precision and enabling personalized treatment strategies.*
Materials and methods: *Whole-slide images (WSIs) of hematoxylin and eosin (H&E)-stained tissue samples and genomic data (RNA-seq and mutation profiles) were obtained from The Cancer Genome Atlas (TCGA) for three cancer types: breast, lung, and colon. A total of 500 patients were included (approximately 165 from each cancer type). Each patient had both digital pathology images and matched genomic data. Clinical records included progression-free survival (PFS), which was used to classify patients into progression vs. non-progression groups.*
Results: *In our study, the multimodal machine learning model that integrated digital pathology and genomic data outperformed unimodal approaches in predicting cancer progression risk. On a test set of 75 patients, the image-only model achieved an accuracy of 71.5% (AUC: 0.75, F1-score: 0.68), while the genomics-only model showed slightly better performance with 73.5% accuracy (AUC: 0.78, F1-score: 0.71). The multimodal fusion model demonstrated the highest performance, achieving an accuracy of 82.0%, an AUC of 0.88, and an F1-score of 0.80. When analyzed by cancer type, the fusion model yielded strong AUC scores across all three types: 0.89 for breast cancer, 0.86 for lung cancer, and 0.87 for colon cancer, with corresponding 95% confidence intervals indicating consistent robustness.*
Conclusion: *Multimodal AI models hold transformative potential to enhance cancer diagnosis and prognostication, paving the way for more precise and personalized cancer care; however, more large-scale, well-validated studies are required to generate definitive clinical evidence and support widespread implementation.*
Keywords: *cancer, machine, learning*

INTRODUCTION

Cancer remains a major global health burden, with millions of new cases and deaths reported annually. To improve outcomes, advances in diagnostic tools and therapeutic strategies are urgently needed. Modern cancer diagnosis increasingly relies on a variety of clinical data sources, including imaging, molecular profiles, and patient information. Integrating these diverse data types through combined machine learning models has the potential to enhance cancer classification and support the development of more accurate prognostic and predictive biomarkers, advancing the field of precision oncology.[1,2,3]

Traditionally, the gold standard for cancer diagnosis involves microscopic examination of hematoxylin and eosin (H&E)-stained tissue sections by pathologists, which enables assessment of cellular morphology and tissue architecture. The digitization of these slides into high-resolution whole-slide images (WSIs), coupled with advances in deep learning—especially convolutional neural networks (CNNs)—has transformed histopathological image analysis. CNN-based methods have been successfully applied to tasks such as cell segmentation, tissue classification, and cancer subtype prediction, adding significant value to routine diagnostics.[4,5]

While histology provides essential morphological insights, genomic and transcriptomic data offer a molecular-level understanding of tumors, enabling personalized treatment strategies. Recent advances in

genome-wide and single-cell sequencing technologies have shed light on tumor heterogeneity and molecular mechanisms underlying disease progression. Characterizing mutations, epigenetic features, and gene expression patterns can inform targeted therapy selection for individual patients.[6,7]

To leverage the strengths of both data types, recent efforts have focused on integrating histopathological images and omics data using machine learning frameworks. However, the heterogeneous nature of imaging and genomic data poses technical challenges for integration. Preprocessing steps—such as splitting WSIs into manageable image patches, normalizing stain variability, and selecting informative genomic features—are essential to ensure data compatibility within a multimodal deep learning pipeline.[8,9]

MATERIALS AND METHODS

1. Data Collection

Whole-slide images (WSIs) of hematoxylin and eosin (H&E)-stained tissue samples and genomic data (RNA-seq and mutation profiles) were obtained from The Cancer Genome Atlas (TCGA) for three cancer types: breast, lung, and colon. A total of 500 patients were included (approximately 165 from each cancer type). Each patient had both digital pathology images and matched genomic data. Clinical records included progression-free survival (PFS), which was used to classify patients into progression vs. non-progression groups.

2. Image and Genomic Preprocessing

WSIs were divided into non-overlapping patches (224×224 pixels), and standard stain normalization was applied. Features were extracted using a ResNet-50 convolutional neural network pretrained on ImageNet. Genomic data were filtered to include the top 300 most variable genes, normalized, and converted into numerical feature vectors. Principal Component Analysis (PCA) was used to reduce the dimensionality of both image and gene expression data before fusion.

3. Model Development and Evaluation

A multimodal machine learning model was designed with two separate input branches: one for histopathological image features and one for genomic features. These were combined in a fusion layer before classification. The dataset was randomly split into 70% training (350 patients), 15% validation (75 patients), and 15% testing (75 patients). Performance was evaluated using accuracy, AUC (Area Under the Curve), and F1-score. Results were compared across unimodal (image-only and genomics-only) and multimodal approaches.

RESULTS

Table 1: Model Performance Metrics (n=75 Test Patients)

Model Type	Accuracy (%)	AUC	F1-Score
Image only	71.5	0.75	0.68
Genomics only	73.5	0.78	0.71
Multimodal	82.0	0.88	0.80

On the test set comprising 75 patients, the image-only model achieved an accuracy of 71.5%, an AUC of 0.75, and an F1-score of 0.68. The genomics-only model performed slightly better, with an accuracy of 73.5%, an AUC of 0.78, and an F1-score of 0.71. The multimodal fusion model, which combined both image and genomic features, outperformed both unimodal models, achieving an accuracy of 82.0%, an AUC of 0.88, and an F1-score of 0.80.

Table 2: Cancer Type-Wise AUC Scores (M

Cancer Type	AUC	95% CI
Breast	0.89	0.85–0.93
Lung	0.86	0.82–0.90
Colon	0.87	0.83–0.91

When evaluated separately by cancer type using the multimodal model, the AUC for breast cancer was 0.89, with a 95% confidence interval (CI) of 0.85 to 0.93. For lung cancer, the model achieved an AUC of 0.86 (95% CI: 0.82 to 0.90), while for colon cancer, the AUC was 0.87, with a 95% CI ranging from 0.83 to 0.91.

DISCUSSION

Predicting cancer progression risk is a critical component of personalized oncology, guiding treatment decisions and improving patient outcomes. With the growing availability of digital pathology and high-throughput genomic data, machine learning offers powerful tools to extract meaningful patterns from these complex and complementary sources. Histopathological images provide insights into tissue architecture and cellular morphology, while genomic profiles reveal underlying molecular alterations driving tumor behavior. Integrating these modalities through advanced machine learning models enables more accurate and robust prediction of cancer progression risk. This multimodal approach holds great promise for enhancing diagnostic precision, uncovering novel prognostic biomarkers, and advancing the capabilities of precision medicine. [10]

In our study, the multimodal machine learning model that integrated digital pathology and genomic data outperformed unimodal approaches in predicting cancer progression risk. On a test set of 75 patients, the image-only model achieved an accuracy of 71.5% (AUC: 0.75, F1-score: 0.68), while the genomics-only model showed slightly better performance with 73.5% accuracy (AUC: 0.78, F1-score: 0.71). The multimodal fusion model demonstrated the highest performance, achieving an accuracy of 82.0%, an AUC of 0.88, and an F1-score of 0.80. When analyzed by cancer type, the fusion model yielded strong AUC scores across all three types: 0.89 for breast cancer, 0.86 for lung cancer, and 0.87 for colon cancer, with corresponding 95% confidence intervals indicating consistent robustness.

A systematic review by Schneider L et al. examined various multimodal fusion strategies that combine convolutional neural network (CNN)-based image analysis with omics data to enhance cancer classification performance. The review included 11 peer-reviewed studies published between January 2015 and June 2021, all of which used CNNs to analyze H&E-stained pathology images alongside integrated genomic or transcriptomic data. Of these, seven studies focused on survival prediction, while four aimed to classify cancer subtypes, malignancy, or microsatellite instability using spatial information. The findings consistently showed that combining image and omics data improved predictive performance across all studies. However, the authors noted that most studies are still in early stages and lack external validation, highlighting the need for larger, more comprehensive research to confirm clinical utility and generalizability.[11]

Davri A et al. in their study, emphasized that when addressing human diseases—particularly cancer—it is crucial to utilize all available tools, with artificial intelligence (AI) emerging as a highly promising resource for diagnostic support. Their research highlights the rapidly growing body of literature applying AI in tissue-based cancer diagnosis, particularly in colorectal cancer (CRC), as well as in breast and lung cancers. While initial results are encouraging, the study notes that larger datasets, precise image annotations, and validation on external cohorts are necessary to establish the clinical reliability of deep learning (DL) models. Based on the data collected, they also suggested that part of the current systematic review could be expanded into a meta-analysis, especially using retrospective studies and survival analysis, to provide a more comprehensive evaluation of DL's contribution to CRC diagnosis.[12]

The integration of multimodal machine learning models that combine digital pathology and genomic data represents a significant advancement in personalized oncology, offering more precise predictions of cancer progression risk than traditional unimodal approaches. While promising results have been demonstrated across multiple cancer types, broader clinical adoption will require larger, well-annotated datasets and rigorous external validation to ensure robustness and generalizability. Continued interdisciplinary collaboration and comprehensive research efforts are essential to fully realize the potential of AI-driven diagnostics, ultimately improving patient outcomes through more tailored treatment strategies.

CONCLUSION

Multimodal AI models hold transformative potential to enhance cancer diagnosis and prognostication, paving the way for more precise and personalized cancer care; however, more large-scale, well-validated studies are required to generate definitive clinical evidence and support widespread implementation.

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