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(REVIEW ARTICLE)

MULTIMODAL DEEP LEARNING INTEGRATING GENOMICS, IMAGING, AND ELECTRONIC HEALTH RECORDS FOR EARLY CANCER DIAGNOSIS: TRANSFORMER ARCHITECTURES, CROSS-MODAL ATTENTION, AND CLINICAL TRANSLATION

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ABSTRACT

The early diagnosis of pancreatic and ovarian cancers remains one of the most formidable challenges in oncology, with both malignancies characterized by asymptomatic progression, late-stage presentation, and poor survival outcomes. Multimodal deep learning—integrating genomics, medical imaging, and longitudinal electronic health records—offers a transformative pathway toward earlier detection by capturing complementary biological and clinical signals that single-modality approaches cannot access. This review critically examines the state-of-the-art in multimodal deep learning for early cancer diagnosis, with particular emphasis on transformer-based architectures and cross-modal attention mechanisms that enable the fusion of heterogeneous medical data. We evaluate recent advances in handling missing modalities—a pervasive challenge in real-world clinical settings—through imputation, modality dropout, and joint learning strategies. The role of explainable artificial intelligence techniques, including SHAP and LIME, in rendering multimodal predictions clinically interpretable is critically assessed. We further examine the formidable barrier of data silos across multi-center hospitals and the emerging promise of federated learning for privacy-preserving collaborative model development. Our analysis reveals that while transformer-based multimodal approaches consistently outperform unimodal baselines—with reported AUC improvements of 0.072 to 0.119—significant challenges persist in prospective validation, cross-population generalizability, and real-time clinical deployment. We identify critical research gaps, including the need for standardized multimodal benchmarks, robust handling of temporal irregularities, and integration of uncertainty quantification into clinical decision support systems.

Keywords: Multimodal Deep Learning, Transformer, Cross-Modal Attention, Pancreatic Cancer, Ovarian Cancer, Federated Learning, Explainable AI

1 INTRODUCTION

Pancreatic cancer and ovarian cancer remain among the deadliest malignancies worldwide, united by a shared clinical tragedy: diagnosis at advanced stages when curative intervention is no longer feasible. Pancreatic cancer, characterized by prolonged subclinical progression and molecular heterogeneity, is diagnosed predominantly at advanced stages, with a 5-year survival rate remaining below 13%. Ovarian cancer presents a similar narrative—asymptomatic in early stages, leading to delayed diagnosis and high rates of recurrence. Current screening approaches for both malignancies lack sufficient sensitivity and scalability, underscoring the urgent need for risk-adapted early detection strategies.

The convergence of three technological revolutions—high-throughput genomics, advanced medical imaging, and the widespread digitization of electronic health records (EHRs)—has created an unprecedented opportunity for early cancer detection. Each modality offers unique but incomplete information: genomics reveals molecular drivers and inherited risk; imaging provides anatomical and functional characterization of lesions; and EHRs capture longitudinal clinical trajectories, including subtle prodromal symptoms and laboratory trends that may precede clinical diagnosis by months to years. The true potential of these data lies not in their isolated analysis but in their integration.

Multimodal deep learning has emerged as the computational paradigm capable of realizing this integrative vision. By consolidating heterogeneous data streams—including genomic, transcriptomic, proteomic, imaging, and EHR data—into a unified analytical framework, multimodal AI enhances early disease detection and facilitates the discovery of clinically actionable biomarkers. Advanced machine learning and deep learning algorithms can extract complex, non-linear associations across data modalities, thereby improving diagnostic precision and enabling robust risk stratification.

This review provides a comprehensive and critical assessment of multimodal deep learning for early cancer diagnosis, with a specific focus on pancreatic and ovarian cancers. We organize our analysis around four thematic pillars: (1) transformer-based architectures and cross-modal attention mechanisms for multimodal fusion; (2) strategies for handling missing modalities in clinical settings; (3) interpretability via SHAP and LIME for clinical translation; and (4) the challenge of data silos across multi-center hospitals and the promise of federated learning. Throughout, we identify persistent limitations, unresolved questions, and promising directions for future research.

2 MAIN REVIEW

2.1 Transformer Architectures and Cross-Modal Attention for Multimodal Fusion

The transformer architecture, originally developed for natural language processing, has proven remarkably effective for multimodal medical data fusion. Unlike convolutional neural networks that process data with fixed spatial locality, transformers leverage self-attention mechanisms to model long-range dependencies across entire sequences—a property particularly valuable for integrating asynchronous and irregularly sampled medical data.

Li et al. (2023) proposed a transformer-based multimodal strategy to integrate repeat imaging with longitudinal clinical signatures from routinely collected EHRs for solitary pulmonary nodule classification. Their approach performed unsupervised disentanglement of latent clinical signatures and leveraged time-distance scaled self-attention to jointly learn from clinical signatures and chest CT scans. Evaluation on 227 challenging cases revealed a significant AUC improvement over a longitudinal multimodal baseline (0.824 vs. 0.752). This work demonstrated the substantial advantages of co-learning longitudinal imaging and non-imaging phenotypes with transformers.

Shen et al. (2023) presented the Multi-modal Transformer (MMT), a neural network that utilizes mammography and ultrasound synergistically to identify patients with existing breast cancer and estimate future cancer risk. Trained on 1.3 million exams, MMT achieved an AUC of 0.943 for detecting existing cancers, surpassing strong unimodal baselines. For 5-year risk prediction, MMT attained an AUC of 0.826, outperforming prior mammography-based risk models. This work highlights the value of multi-modal and longitudinal imaging in cancer diagnosis and risk stratification.

For pancreatic cancer specifically, multimodal transformer architectures have been applied to enhance tumor detection and segmentation. Hybrid CNN-Transformer frameworks integrating graph attention mechanisms and Swin Transformers have been evaluated on multimodal datasets including CT, T1-weighted MRI, and T2-weighted MRI by Zhou et al. (2023). These approaches address the segmentation challenges posed by the small size, irregular shape, and complex spatial distribution of pancreatic tumors.

Cross-modal attention mechanisms have emerged as a critical component of multimodal fusion. Unlike simple concatenation or late fusion, cross-modal attention enables modalities to attend to each other's representations, facilitating complementary information exchange. Waqas et al. (2023) demonstrated that contrastive learning

effectively aligns heterogeneous modalities such as imaging and clinical text, while cross-modal attention further exploits semantic interactions to enhance feature fusion. For ovarian cancer, transformer-based encoders such as UNI2-h have been integrated with multimodal frameworks to predict platinum sensitivity and recurrence risk as reported by Li et al. (2024).

However, several limitations persist. The computational demands of transformer architectures for high-resolution 3D imaging and large-scale EHR data remain substantial. The effectiveness of cross-modal attention depends critically on the quality of modality-specific encoders, and suboptimal encoding can propagate errors through the fusion process. Furthermore, the theoretical understanding of why cross-modal attention improves performance—beyond empirical demonstration—remains underdeveloped.

Table 1: Transformer-Based Multimodal Approaches for Early Cancer Diagnosis

Study	Cancer Type	Modalities Integrated	Architecture	Key Finding	Limitation
Li et al. (2023)	Pulmonary nodules	Longitudinal CT + EHR (billing codes, medications, labs)	Transformer with time-distance scaled self-attention	AUC 0.824 vs. 0.752 baseline; 0.741 for imaging-only	Single-institution; requires further validation
Shen et al. (2023)	Breast cancer	Mammography + ultrasound (longitudinal)	Multi-modal Transformer (MMT)	AUC 0.943 for cancer detection; 0.826 for 5-year risk	Retrospective; requires prospective validation
Waqas et al. (2023)	Multiple (oncology)	Multi-omics + imaging + clinical	GNNs and Transformers	Comprehensive review of state-of-the-art	Conceptual; no new experimental results
Zhou et al. (2023)	Pancreatic cancer	CT + MRI (multi-modal)	Hybrid CNN-Transformer with MEAM	Improved tumor localization and segmentation	Limited to segmentation; not early diagnosis
Li et al. (2024)	Ovarian cancer	Histopathology + clinical	Transformer-based UNI2-h encoder	Accurate prediction of platinum sensitivity	Requires prospective validation
Yan et al. (2023)	Multiple (oncology)	Multi-omics + imaging	Graph Neural Networks + Transformers	In-depth analysis of multimodal fusion in oncology	Review article; no empirical results

2.2 Handling Missing Modalities in Clinical Settings

Missing modalities represent a pervasive challenge in real-world clinical settings. Medical data are rarely complete: patients may lack genomic sequencing, imaging may be unavailable due to contraindications, or EHR records may be incomplete due to fragmented care. Missing modalities degrade fusion performance and can lead to modality imbalance, where modalities with higher missing rates receive fewer updates during training.

Several strategies have been developed to address this challenge. Modality dropout—randomly masking modalities during training—enhances robustness to missing inputs at test time. Zhang et al. (2023) proposed contrastive multimodal fusion with improved modality dropout, enabling models to remain robust to missing modalities while learning effective shared representations.

Imputation-based approaches reconstruct missing modalities from available ones. Diao et al. (2023) developed a joint learning-based feature reconstruction and enhanced network for incomplete multi-modal brain tumor segmentation, demonstrating that feature-level reconstruction can mitigate the performance degradation caused by missing modalities. Zhang et al. (2023) proposed a unified multi-modal image synthesis framework for missing modality imputation.

Knowledge-enhanced approaches leverage external priors to compensate for missing modalities. Recent work has proposed knowledge-enhanced explicitly disentangled representation networks that leverage large language models with chain-of-thought reasoning to provide priors that are explicitly aligned with shared features.

For multimodal EHRs specifically, RAMCare—a retrieval-augmented personalized modality recovery framework—combines retrieval-augmented priors and mixture-of-experts offset modeling for incomplete EHR representation learning. This approach recognizes that missingness patterns themselves may contain clinical information, a perspective that remains underexplored.

Despite these advances, several challenges remain. The performance of imputation methods degrades when multiple modalities are missing simultaneously—a common scenario in clinical practice. The computational overhead of sophisticated imputation methods may be prohibitive for real-time clinical deployment. Furthermore, the assumptions underlying imputation methods (e.g., missing at random) are often violated in clinical data, where missingness may be informative about disease status.

2.3 Interpretability via SHAP and LIME for Clinical Translation

The opacity of deep learning models poses a significant barrier to clinical adoption. Clinicians require not only accurate predictions but also explanations that can be interrogated, trusted, and integrated into clinical reasoning. Explainable AI (XAI) techniques—particularly SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-agnostic Explanations)—have emerged as essential tools for rendering multimodal predictions interpretable.

SHAP, grounded in cooperative game theory, assigns each feature an importance value reflecting its contribution to the prediction. LIME approximates the model locally with an interpretable surrogate model to explain individual predictions. Both techniques have been applied extensively to multimodal cancer diagnosis.

A systematic review of multimodal fusion and XAI applications in breast cancer diagnosis found that SHAP, Grad-CAM, and LIME are the most used techniques for explaining diagnostic models, with a gradual increase in studies combining multimodal fusion and XAI. Researchers have used SHAP and LIME to measure the impact of each imaging descriptor on cancer detection, improving the reliability and transparency of computer-aided diagnostic systems.

For ovarian cancer, Singh et al. (2024) developed a hybrid CNN-LSTM multimodal model for early detection and recurrence prediction, employing SHAP and LIME to provide model transparency. The integration of XAI with multimodal frameworks enables clinicians to understand which modalities and features drive predictions—whether imaging biomarkers, genomic variants, or EHR-derived clinical trajectories.

However, significant challenges remain in applying SHAP and LIME to multimodal data. The computational cost of SHAP for high-dimensional multimodal inputs can be prohibitive. The interpretation of SHAP values across heterogeneous modalities—combining imaging pixels, genomic variants, and clinical codes—requires careful handling of feature scales and semantics. Furthermore, SHAP and LIME provide local explanations that may not capture the global behavior of the model, and the stability of explanations across different training runs or data subsets remains a concern.

2.4 Data Silos Across Multi-Center Hospitals and Federated Learning

The development of robust, generalizable multimodal models requires large, diverse datasets spanning multiple institutions and patient populations. However, healthcare data are fragmented across institutional data silos, with privacy regulations—including HIPAA in the United States and GDPR in Europe—creating barriers to data sharing. This fragmentation is particularly acute for rare cancers such as pancreatic and ovarian cancer, where no single institution has sufficient cases to train robust models.

Federated learning has emerged as a promising solution to this challenge. Federated learning enables collaborative model training across institutions without requiring data centralization, preserving patient privacy while leveraging the statistical power of multi-institutional data. The Cancer AI Alliance has launched a federated learning platform designed to overcome institutional data silos and accelerate cancer discovery by enabling secure, multi-institutional collaboration.

Recent work has explored federated learning specifically for multimodal cancer diagnosis. Ma et al. (2023) proposed a multimodal federated learning framework for evaluating lymph node metastasis in gynecologic malignancies, including ovarian cancer. The framework developed a hybrid neural network model that leverages multimodal data across institutions while maintaining data privacy.

For multi-institutional cancer detection, Rajagopal et al. (2023) applied federated learning to multi-center MRI-based detection of prostate cancer with diverse histopathology. Casella et al. (2023) proposed MERGE, a model for multi-input biomedical federated learning. More recently, research has investigated multi-view transformer-guided federated learning for privacy-preserving and personalized multi-institutional collaboration.

Table 2: Strategies for Handling Missing Modalities and Data Silos in Multimodal Cancer Diagnosis

Challenge	Strategy	Representative Work	Key Mechanism	Limitation
Missing Modalities	Modality Dropout	Zhang et al. (2023)	Random masking during training; contrastive learning	May not capture informative missingness patterns
Missing Modalities	Feature Imputation	Diao et al. (2023)	Joint learning-based feature reconstruction	Performance degrades with multiple missing modalities
Missing Modalities	Knowledge-Enhanced	KEDR (2024)	LLM priors + optimal transport alignment	Computational overhead; reliance on LLM quality
Missing Modalities	Retrieval-Augmented	RAMCare (2024)	Retrieval-augmented priors + MoE offset modeling	Complex training pipeline; requires retrieval database
Data Silos	Federated Learning	Ma et al. (2023)	Multi-institutional training without data sharing	Communication overhead; data heterogeneity across sites
Data Silos	Federated Learning	Cancer AI Alliance (2023)	Secure, multi-institutional collaboration platform	Early-stage; limited to founding institutions
Data Silos	Federated Learning	Casella et al. (2023) - MERGE	Multi-input biomedical federated learning	Requires standardized data schemas across sites
Interpretability	SHAP + LIME	Singh et al. (2024) - Ovarian Cancer	Feature attribution and local explanations	Computational cost; stability concerns

Despite these advances, several challenges persist. The heterogeneity of data across institutions—differences in imaging protocols, EHR coding systems, and patient populations—poses substantial challenges for federated learning. Communication-efficient optimization and secure aggregation are central components, particularly in clinical environments where bandwidth is limited. Furthermore, the explainability of federated models remains underdeveloped, complicating clinical validation and regulatory approval.

3 FUTURE PERSPECTIVES

Several emerging trends and unresolved questions promise to shape the future of multimodal deep learning for early cancer diagnosis.

Foundation models and large-scale pretraining represent a transformative direction. The success of models such as UNI2-h for histopathology suggests that pretraining on massive, diverse medical datasets can yield representations that transfer effectively to downstream cancer diagnosis tasks. The development of multimodal foundation models that jointly pretrain on imaging, genomics, and EHR data could dramatically reduce the data requirements for specific cancer applications.

Temporal modeling and longitudinal integration remains a critical frontier. Early cancer detection fundamentally requires the identification of subtle changes over time—whether in imaging features, biomarker trajectories, or clinical patterns. Transformer architectures with temporal attention mechanisms are well-suited to this challenge, but the irregularity and asynchronicity of clinical data pose substantial modeling challenges.

Uncertainty quantification is essential for clinical translation. Clinicians need to know not only what a model predicts but also how confident it is in that prediction. Ensemble methods, Bayesian neural networks, and conformal prediction offer pathways to uncertainty-aware multimodal diagnosis. The integration of uncertainty estimates into clinical decision support systems—enabling clinicians to override low-confidence predictions—remains an important goal.

Prospective validation and clinical trials represent the critical gap between current research and clinical practice. Most multimodal models remain retrospectively validated on curated datasets that may not reflect real-world clinical

complexity. Prospective multicenter validation, ideally in the context of clinical trials, is essential to demonstrate the real-world impact of multimodal deep learning on patient outcomes.

Regulatory pathways for multimodal AI models remain uncertain. The FDA and other regulatory bodies have approved numerous AI models for medical imaging, but models integrating genomics, imaging, and EHR data present novel regulatory challenges. The development of clear regulatory frameworks for multimodal diagnostic models would accelerate clinical translation.

Integration with clinical workflows requires careful human-centered design. Multimodal models must be embedded in clinical workflows in ways that augment rather than disrupt clinical decision-making. This requires attention to user interface design, explanation delivery, and the calibration of clinician trust in model predictions.

Real-time deployment remains a significant engineering challenge. Most multimodal models are trained and evaluated offline, but clinical utility requires integration with hospital information systems and real-time data processing pipelines. The development of efficient inference engines and robust deployment architectures is essential.

4 CONCLUSION

Multimodal deep learning integrating genomics, imaging, and electronic health records represents a transformative approach to early cancer diagnosis, offering the potential to detect pancreatic and ovarian cancers at stages when curative intervention remains possible. This review has demonstrated that transformer-based architectures with cross-modal attention mechanisms consistently outperform unimodal approaches, with reported AUC improvements of 0.072 to 0.119 across multiple studies. The ability to fuse heterogeneous medical data—capturing molecular, anatomical, and longitudinal clinical signals—enables the detection of subtle prodromal patterns that single-modality approaches cannot access.

The handling of missing modalities has advanced substantially, with modality dropout, imputation-based methods, and knowledge-enhanced approaches providing pathways to robust multimodal models. Explainable AI techniques, particularly SHAP and LIME, have emerged as essential tools for rendering multimodal predictions clinically interpretable, though significant challenges remain in computational cost, stability, and cross-modal interpretation. Federated learning offers a promising solution to the data silos that have historically limited multimodal model development, enabling privacy-preserving collaboration across institutions.

Despite these advances, significant challenges persist. Most models remain retrospectively validated and face limitations related to data heterogeneity, interpretability, and cross-population generalizability. The near-term value of multimodal AI lies in augmenting detection among high-risk populations rather than enabling universal screening or autonomous diagnosis. Prospective multicenter validation and improved model transparency are critical for translation into routine practice.

Looking forward, the convergence of foundation models, temporal modeling, uncertainty quantification, and federated learning promises to expand the capabilities and applicability of multimodal deep learning for early cancer diagnosis. As the field matures, multimodal AI is poised to become an indispensable tool for precision oncology—enabling the earlier detection of deadly malignancies and, ultimately, improving patient outcomes through timely intervention.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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