

Cross-Modal Foundation Models for Precision Oncology: Unifying Imaging, Histopathology, Multi-Omics, and Clinical Data

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ABSTRACT:

Precision oncology has undergone a profound transformation with the emergence of artificial intelligence (AI) capable of integrating heterogeneous biomedical information into unified computational frameworks for individualized cancer care. Traditional machine learning approaches typically analyze single-modality datasets, limiting their ability to capture the complex biological interactions underlying tumor evolution, therapeutic response, and clinical outcomes. Recent advances in cross-modal foundation AI models have fundamentally redefined computational oncology by enabling generalized representation learning across radiological imaging, digital histopathology, genomics, transcriptomics, proteomics, metabolomics, epigenomics, spatial biology, laboratory biomarkers, electronic health records, wearable technologies, and longitudinal clinical outcomes. Built upon transformer architectures, self-supervised learning, graph neural networks, multimodal fusion, and generative AI, these models learn transferable biomedical representations that support diagnosis, biomarker discovery, prognostic prediction, therapeutic optimization, immunotherapy selection, adaptive disease monitoring, digital twins, and intelligent clinical decision support. Emerging technologies including large language models, retrieval-augmented generation, federated learning, reinforcement learning, explainable artificial intelligence, and agentic AI further expand the capabilities of cross-modal computational oncology while accelerating clinical translation. Despite remarkable progress, substantial challenges remain regarding multimodal data harmonization, computational scalability, interpretability, interoperability, regulatory validation, ethical governance, and equitable implementation. This review provides a comprehensive overview of cross-modal foundation models for precision oncology, highlighting computational principles, multimodal integration strategies, clinical applications, implementation challenges, and future perspectives for unifying imaging, histopathology, multi-omics, and clinical data through artificial intelligence.[1]

Keyword: Cross-modal learning, Foundation models, Artificial intelligence, Precision oncology, Multi-omics, Digital pathology, Radiomics, Multimodal learning, Clinical decision support, Computational oncology.

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1.Introduction

Cancer is a highly heterogeneous disease characterized by dynamic interactions among molecular alterations, cellular organization, tissue

architecture, anatomical structures, immune responses, environmental influences, and longitudinal clinical factors. Comprehensive understanding of these complex biological processes requires integration of information

spanning multiple diagnostic modalities rather than isolated analysis of individual datasets.[2]

Modern oncology routinely generates enormous quantities of heterogeneous biomedical information through radiological imaging, digital histopathology, genomic sequencing, transcriptomics, proteomics, metabolomics, spatial biology, laboratory investigations, wearable technologies, and electronic health records. Although each modality contributes unique biological insight, traditional computational methods frequently analyze these datasets independently, limiting comprehensive understanding of tumor biology and therapeutic response.[3]

Cross-modal foundation AI models have emerged as transformative computational frameworks capable of integrating multimodal biomedical information into unified patient-specific representations. Through self-supervised learning and large-scale multimodal pretraining, these models acquire generalized biomedical knowledge transferable across numerous precision oncology applications, thereby advancing personalized cancer care.[4]

The convergence of cross-modal artificial intelligence, foundation models, systems oncology, and precision medicine is therefore redefining computational oncology by enabling holistic understanding of cancer biology across multiple biological and clinical scales.[5]

2.Evolution of Cross-Modal Artificial Intelligence

Early artificial intelligence applications in oncology relied primarily on modality-specific algorithms developed independently for radiological imaging, computational pathology, genomic analysis, or clinical prediction. Although these models demonstrated considerable success, limited interaction among diverse biomedical modalities frequently constrained predictive performance and biological interpretation.[6]

Advances in multimodal deep learning introduced computational frameworks capable of combining imaging with molecular diagnostics and clinical variables. Subsequently, transformer architectures enabled increasingly sophisticated cross-modal attention mechanisms capable of aligning heterogeneous biomedical representations within shared embedding spaces.

The emergence of foundation AI models has further expanded multimodal learning through generalized self-supervised pretraining across diverse biomedical datasets, enabling transfer learning, few-shot learning, zero-shot learning, and improved generalizability across numerous oncology applications.

Today, cross-modal foundation models represent one of the most advanced paradigms for computational precision oncology and translational cancer research.[7]

3.Principles of Cross-Modal Foundation Models

Cross-modal foundation models differ fundamentally from conventional machine learning systems because they learn generalized biomedical representations simultaneously across multiple diagnostic modalities rather than focusing on isolated prediction tasks. Artificial intelligence aligns heterogeneous biomedical information within unified computational embedding spaces while preserving modality-specific biological characteristics.[8]

Self-supervised learning enables discovery of latent relationships among radiological imaging, digital pathology, genomics, transcriptomics, proteomics, metabolomics, laboratory biomarkers, physician documentation, and electronic health records without requiring extensive manual annotation.

Transformer architectures facilitate cross-modal attention between complementary biomedical modalities, whereas graph neural networks model interactions among genes, proteins, signaling pathways, immune populations, imaging phenotypes, tissue architecture, therapeutic targets, and clinical outcomes, enabling systems-level computational reasoning.[9]

4.Computational Architecture

Modern cross-modal foundation models consist of interconnected computational layers responsible for multimodal data acquisition, preprocessing, representation learning, cross-modal alignment, predictive analytics, adaptive learning, and intelligent clinical decision support.[10]

The acquisition layer continuously integrates radiological imaging, digital pathology, genomic sequencing, transcriptomics, proteomics, metabolomics, epigenomics, spatial biology,

laboratory investigations, wearable physiological monitoring, medication history, and longitudinal electronic health records. Advanced preprocessing pipelines normalize imaging studies, harmonize molecular datasets, encode clinical narratives using natural language processing, and synchronize temporal patient information.

Foundation AI models subsequently generate generalized multimodal embeddings representing molecular biology, tissue architecture, anatomical imaging, physiological status, and clinical trajectories. Cross-modal fusion mechanisms integrate these embeddings into comprehensive patient-centered computational representations supporting precision oncology.[11]

5.Artificial Intelligence for Imaging-Histopathology Integration

Radiological imaging and digital histopathology provide complementary biological information across macroscopic and microscopic scales. Medical imaging characterizes tumor morphology, vascularity, metabolism, organ involvement, and metastatic dissemination, whereas digital pathology reveals cellular morphology, tissue architecture, immune infiltration, stromal remodeling, angiogenesis, and extracellular matrix organization.[12]

Cross-modal foundation AI models integrate these complementary diagnostic modalities through transformer architectures and graph neural networks capable of identifying latent relationships between imaging phenotypes and microscopic tissue characteristics.

These unified computational representations improve diagnostic accuracy, tumor classification, biomarker prediction, prognostic assessment, therapeutic planning, and systems-level understanding of cancer biology while strengthening computational precision medicine.[13]

6.Multi-Omics Representation Learning

Comprehensive precision oncology increasingly depends upon integration of genomics, transcriptomics, proteomics, metabolomics, epigenomics, lipidomics, immunomics, microbiomics, and spatial biology into unified molecular representations of tumor biology.[14]

Cross-modal foundation models utilize multimodal transformers, biological knowledge

graphs, graph neural networks, and self-supervised learning to identify latent biological relationships among genes, proteins, metabolites, signaling pathways, immune responses, imaging phenotypes, and therapeutic targets that remain difficult to detect using isolated analytical approaches.

These integrated molecular representations substantially improve biomarker discovery, molecular subtype classification, therapeutic response prediction, systems biology research, and individualized treatment planning while strengthening computational oncology.[15]

7.Clinical Data Integration

Electronic health records, laboratory investigations, medication history, physician documentation, patient-reported outcomes, wearable technologies, and longitudinal clinical trajectories provide essential patient-level information complementing imaging and molecular diagnostics. Cross-modal foundation AI models integrate structured and unstructured clinical information using natural language processing, temporal transformers, and sequential learning architectures.[16]

Artificial intelligence continuously incorporates evolving clinical information into patient-specific computational representations while modeling temporal relationships among diagnosis, treatment, toxicity, recurrence, hospitalization, disease progression, and survival.

These adaptive clinical representations substantially improve prognostic prediction, therapeutic optimization, disease monitoring, and personalized clinical decision-making across the entire cancer care continuum.[17]

8.Biomarker Discovery and Predictive Oncology

Cross-modal foundation models enable comprehensive biomarker discovery by simultaneously analyzing radiological imaging, digital pathology, molecular biology, laboratory biomarkers, and longitudinal clinical outcomes. Unlike conventional biomarker discovery based on isolated datasets, multimodal artificial intelligence identifies complex biological interactions spanning multiple organizational levels.[18]

These computational frameworks discover diagnostic, prognostic, predictive, pharmacodynamic, and therapeutic biomarkers associated with treatment sensitivity, resistance, immune activation, recurrence, metastatic dissemination, and survival. Integration of heterogeneous biomedical information substantially improves predictive accuracy while accelerating translation of computational discoveries into clinical precision oncology.

High-dimensional multimodal biomarker discovery therefore represents one of the most transformative applications of cross-modal foundation AI models in cancer medicine.[19]

9.Cross-Modal Prediction of Therapeutic Response

One of the most important clinical applications of cross-modal foundation models is prediction of therapeutic response through simultaneous integration of radiological imaging, digital histopathology, multi-omics, laboratory biomarkers, medication history, and longitudinal clinical outcomes into unified patient-specific computational representations.[20]

10.Digital Twins and Virtual Precision Oncology

Digital twin technology represents one of the most advanced applications of cross-modal foundation models by creating continuously evolving virtual representations of individual cancer patients. These computational twins integrate radiological imaging, digital histopathology, genomics, transcriptomics, proteomics, metabolomics, laboratory biomarkers, wearable physiological monitoring, medication history, and longitudinal clinical information into unified patient-specific models capable of simulating disease progression and therapeutic response.[21]

Foundation AI models continuously synchronize these digital twins with newly acquired biomedical information, enabling simulation of tumor evolution, immune dynamics, treatment-related toxicity, recurrence, metastatic dissemination, and survival before clinical intervention. Virtual therapeutic simulations allow clinicians to compare multiple treatment strategies, optimize sequencing of therapies, personalize dosing regimens, and anticipate mechanisms of resistance.

These adaptive computational ecosystems provide an important framework for individualized precision oncology while reducing uncertainty during therapeutic decision-making.

11.Continuous Learning and Adaptive Clinical Intelligence

Cross-modal foundation models are increasingly evolving from static predictive algorithms into continuously learning computational ecosystems capable of incorporating new biomedical knowledge throughout the patient journey. Artificial intelligence continuously integrates serial imaging examinations, digital pathology, liquid biopsy, laboratory biomarkers, wearable physiological monitoring, electronic health records, patient-reported outcomes, and real-world clinical evidence into adaptive predictive models.[22]

Reinforcement learning enables optimization of therapeutic recommendations through iterative evaluation of treatment outcomes, while continual learning strategies update computational knowledge without catastrophic forgetting of previously acquired information. This adaptive intelligence allows predictive models to remain aligned with evolving tumor biology, changing clinical practice, and expanding biomedical evidence.

Continuous learning therefore represents a critical component of next-generation precision oncology, enabling real-time personalization of cancer care.

12.Intelligent Clinical Decision Support

Cross-modal foundation models provide the computational core for intelligent clinical decision-support systems capable of integrating heterogeneous biomedical information into comprehensive patient-centered recommendations. Radiological imaging, computational pathology, molecular diagnostics, laboratory investigations, medication history, wearable technologies, physician documentation, and evidence-based treatment guidelines are harmonized into unified computational environments supporting multidisciplinary oncology care.[23]

Interactive clinical dashboards generate individualized diagnostic summaries, multimodal biomarker analyses, prognostic estimates, therapeutic recommendations, toxicity predictions, recurrence probabilities, and survival

forecasts while facilitating collaboration among oncologists, radiologists, pathologists, surgeons, molecular biologists, pharmacists, and computational scientists.

These intelligent decision-support platforms improve workflow efficiency, reduce fragmentation of biomedical information, strengthen multidisciplinary communication, and promote evidence-based precision medicine throughout routine oncology practice.

13.Federated Learning and Collaborative Oncology Networks

The effectiveness of cross-modal foundation models depends upon access to diverse biomedical datasets representing multiple cancer types, healthcare systems, imaging platforms, and patient populations. Federated learning addresses challenges related to privacy protection and institutional governance by enabling collaborative artificial intelligence without requiring centralized sharing of patient data.[24]

Healthcare institutions independently train local foundation models using their own radiological imaging, pathology, molecular diagnostics, and clinical records while securely exchanging encrypted model parameters for global optimization. This decentralized learning strategy substantially improves model robustness, generalizability, fairness, and representation of diverse patient populations while maintaining compliance with privacy regulations.

Federated cross-modal learning therefore enables large-scale international collaboration while supporting equitable precision oncology across geographically distributed healthcare systems.

14.Explainability, Validation, and Ethical Governance

Despite remarkable advances in multimodal artificial intelligence, successful clinical implementation requires transparency, interpretability, reproducibility, and rigorous validation. Explainable artificial intelligence (XAI) enables clinicians to understand computational reasoning through attention visualization, saliency maps, SHAP (Shapley Additive Explanations), feature attribution analysis, uncertainty estimation, and counterfactual explanations that identify the imaging, molecular, histopathological, and

clinical variables contributing to AI-generated predictions.[25]

Clinical translation also requires standardized multimodal datasets, interoperable computational infrastructure, prospective multicenter validation, external benchmarking, cybersecurity safeguards, continuous monitoring for algorithmic bias, and compliance with evolving international regulatory frameworks governing AI-enabled healthcare technologies.

Ethical implementation further depends upon protection of patient privacy, informed consent, transparency, accountability, equitable access, responsible governance, and continuous post-deployment surveillance to ensure safe and trustworthy adoption of cross-modal AI systems.

15.Future Perspectives

Future cross-modal foundation models will increasingly integrate multimodal transformers, large language models, agentic artificial intelligence, graph neural networks, federated learning, reinforcement learning, digital twins, spatial multi-omics, liquid biopsy, quantum computing, Internet of Medical Things (IoMT) technologies, and cloud-native healthcare infrastructure into unified computational oncology ecosystems.[26]

These next-generation systems will continuously integrate imaging, pathology, molecular biology, laboratory medicine, wearable physiological monitoring, environmental exposures, electronic health records, and real-world clinical outcomes while autonomously coordinating diagnostic workflows, optimizing therapeutic strategies, generating personalized patient communication, supporting adaptive clinical trials, and continuously synthesizing biomedical evidence.

Such intelligent ecosystems are expected to transform precision oncology from fragmented modality-specific analysis toward fully integrated computational medicine capable of supporting personalized cancer care throughout the entire disease continuum.

16.Discussion

Cross-modal foundation models represent one of the most significant paradigm shifts in computational oncology by unifying imaging, histopathology, multi-omics, and clinical intelligence into comprehensive patient-centered

computational representations. Unlike conventional artificial intelligence systems designed for isolated diagnostic tasks, these models capture dynamic biological relationships across multiple organizational scales while supporting diagnosis, biomarker discovery, prognostic assessment, therapeutic optimization, digital twins, adaptive learning, and intelligent clinical decision support.[27]

Applications spanning radiogenomics, computational pathology, systems oncology, precision immunotherapy, federated learning, digital health, and multimodal biomarker discovery demonstrate the extraordinary potential of cross-modal AI to accelerate personalized cancer medicine. Nevertheless, successful implementation requires continued advances in multimodal data harmonization, explainable artificial intelligence, interoperability, computational infrastructure, cybersecurity, regulatory science, ethical governance, and multidisciplinary collaboration.

As biomedical datasets continue to expand in scale and complexity, cross-modal foundation models are expected to become a central computational framework supporting next-generation precision oncology.

17. Conclusion

Cross-modal foundation models are redefining precision oncology by integrating radiological imaging, digital histopathology, multi-omics, laboratory biomarkers, electronic health records, wearable technologies, and longitudinal clinical intelligence into unified computational frameworks capable of supporting individualized cancer management throughout the entire patient journey.[28]

Advances in transformer architectures, multimodal learning, graph neural networks, self-supervised learning, federated learning, reinforcement learning, digital twins, large language models, agentic AI, and generative artificial intelligence are expected to further strengthen computational oncology by enabling increasingly accurate diagnosis, biomarker discovery, molecular characterization, therapeutic optimization, adaptive disease monitoring, and evidence-based clinical decision-making.[29]

Although important scientific, technical, ethical, regulatory, and implementation challenges

remain, sustained collaboration among oncologists, radiologists, pathologists, molecular biologists, biomedical engineers, computer scientists, healthcare organizations, industry partners, and regulatory agencies will accelerate responsible implementation of cross-modal foundation models. These innovations have the potential to improve patient outcomes, enhance diagnostic precision, reduce healthcare disparities, and establish a new era of intelligent, integrated, and personalized cancer medicine worldwide.[30]

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