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Clinical Digital Twins in Oncology: From Concept to Clinical Translation

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ABSTRACT:

Clinical digital twins have emerged as one of the most promising innovations in precision oncology, offering a transformative approach to individualized cancer diagnosis, treatment planning, disease monitoring, and survivorship care. A clinical digital twin is a continuously evolving virtual representation of an individual patient that integrates multimodal biomedical information—including clinical records, radiological imaging, digital pathology, genomic sequencing, molecular profiling, laboratory biomarkers, physiological monitoring, and longitudinal health data—to simulate disease progression and therapeutic response. Unlike conventional predictive models that analyze isolated datasets, digital twins continuously update patient-specific computational models as new clinical information becomes available, enabling adaptive and personalized clinical decision-making. Recent advances in artificial intelligence (AI), machine learning, deep learning, multimodal learning, graph neural networks, transformer architectures, foundation models, and generative AI have significantly accelerated the development of clinically applicable oncology digital twins. These intelligent systems demonstrate considerable potential in cancer diagnosis, radiogenomics, computational pathology, immunotherapy prediction, adaptive radiation therapy, surgical planning, drug discovery, clinical trial optimization, and real-time clinical decision support. Furthermore, integration with cloud computing, wearable technologies, federated learning, and electronic health records enables continuously learning healthcare ecosystems capable of supporting precision medicine throughout the cancer care continuum. Despite substantial progress, important challenges remain regarding data interoperability, computational complexity, explainability, cybersecurity, regulatory approval, ethical governance, and large-scale clinical implementation. This review discusses the evolution of clinical digital twins in oncology, emphasizing their computational architecture, current clinical applications, translational opportunities, and future role in personalized cancer care.[1]

Keywords: Clinical digital twins, Precision oncology, Artificial intelligence, Personalized medicine, Computational oncology, Machine learning, Clinical decision support, Digital pathology, Radiogenomics, Cancer informatics.

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Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide despite remarkable advances in molecular diagnostics, targeted therapies, immunotherapy, and precision medicine. The extraordinary biological heterogeneity observed among tumors arises from complex interactions involving genetic mutations, epigenetic regulation, immune responses, metabolic remodeling, and the tumor microenvironment. Consequently, patients with apparently similar pathological diagnoses frequently experience markedly different therapeutic responses, recurrence patterns, and survival outcomes, illustrating the limitations of conventional population-based treatment strategies.[2]

Modern oncology increasingly depends upon diverse biomedical information generated through medical imaging, digital pathology, genomic sequencing, transcriptomics, proteomics, laboratory investigations, wearable health technologies, and electronic health records. While these datasets collectively provide a comprehensive understanding of tumor biology, their complexity often exceeds the analytical capacity of conventional statistical approaches and routine clinical workflows, creating challenges for individualized clinical decision-making.[3]

Artificial intelligence has emerged as a transformative technology capable of integrating heterogeneous biomedical data into clinically actionable knowledge. More recently, computational medicine has advanced beyond isolated predictive algorithms toward continuously evolving virtual patient models known as clinical digital twins. These systems combine multidimensional patient information to simulate disease progression, predict therapeutic response, estimate toxicity, and support personalized treatment planning throughout the cancer care continuum.[4]

Clinical digital twins represent a paradigm shift in precision oncology by allowing physicians to evaluate multiple therapeutic strategies within a virtual environment before implementing treatment. Their ability to continuously incorporate newly acquired patient information creates adaptive computational models that evolve alongside the biological patient, providing unprecedented opportunities for truly individualized cancer care.[5]

2. Evolution of Clinical Digital Twins

The concept of digital twins originated in engineering and manufacturing industries, where virtual replicas of complex systems were developed to monitor operational performance, predict equipment failure, and optimize maintenance. Aerospace engineering was among the earliest adopters, followed by widespread implementation across automotive manufacturing, robotics, smart infrastructure, and industrial automation.[6]

Healthcare researchers recognized that the same computational principles could be applied to biological systems. Instead of simulating mechanical components, healthcare digital twins model physiological processes, disease progression, therapeutic interventions, and clinical outcomes. Early medical applications focused primarily on cardiovascular medicine, diabetes management, orthopedic biomechanics, and intensive care monitoring, where continuous physiological measurements supported predictive computational modeling.[7]

Rapid advances in biomedical technologies—including next-generation sequencing, advanced imaging, molecular diagnostics, wearable biosensors, and cloud-based electronic health records—substantially accelerated healthcare digital twin development. Artificial intelligence became indispensable for integrating these massive heterogeneous datasets into clinically meaningful predictive systems capable of supporting precision medicine.[8]

Cancer care emerged as one of the most promising applications because oncology requires continuous integration of imaging, pathology, molecular biology, laboratory investigations, treatment history, and longitudinal clinical information. Every patient's tumor evolves uniquely throughout therapy, making digital twins ideally suited for adaptive, individualized oncology.[9]

Today, clinical oncology digital twins extend beyond traditional predictive algorithms by integrating systems biology, mathematical modeling, multimodal artificial intelligence, graph-based learning, mechanistic simulations, and probabilistic inference into comprehensive computational ecosystems capable of representing the entire cancer journey from diagnosis through survivorship.[10]

3. Computational Architecture of Clinical Digital Twins

A clinical digital twin consists of multiple computational layers that continuously exchange information to create and maintain an accurate virtual representation of an individual patient. Rather than functioning as a single artificial intelligence model, digital twins integrate several complementary computational systems operating simultaneously across different biological and clinical domains.[11]

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The first computational layer involves acquisition of patient-specific information from radiological imaging, digital pathology, genomic sequencing, transcriptomics, proteomics, laboratory biomarkers, physiological monitoring, treatment records, medication history, and electronic health documentation. Each source contributes unique biological and clinical information regarding tumor characteristics and patient health status.[12]

The second layer performs multimodal data harmonization. Since biomedical information originates from diverse technologies and formats, sophisticated preprocessing pipelines normalize molecular profiles, standardize imaging data, extract quantitative biomarkers, encode clinical narratives using natural language processing, and align heterogeneous datasets into unified computational representations.[13]

Artificial intelligence forms the third computational layer, where deep learning, transformer architectures, graph neural networks, probabilistic learning algorithms, and multimodal foundation models analyze integrated patient information to estimate disease progression, treatment response, recurrence risk, toxicity, and survival outcomes. These computational methods generate personalized biological representations that support downstream clinical decision-making.[14]

Simulation engines represent another essential component by modeling tumor growth, metastatic dissemination, immune interactions, therapeutic interventions, pharmacological response, and resistance mechanisms. By continuously incorporating new patient information, these mathematical models dynamically update disease trajectories, enabling clinicians to compare multiple therapeutic strategies before implementation.[15]

The final layer involves visualization and clinical decision support. Interactive dashboards present individualized predictions regarding disease progression, therapeutic response, toxicity risk, recurrence probability, and survival outcomes in clinically interpretable formats that facilitate multidisciplinary collaboration while maintaining physician oversight.[16]

4. Artificial Intelligence Technologies Driving Clinical Digital Twins

Artificial intelligence provides the computational foundation that enables construction and continuous refinement of oncology digital twins. Multiple complementary AI methodologies work together to transform complex biomedical information into clinically actionable insights.[17]

Machine learning algorithms initially established the foundation for predictive modeling by identifying statistical relationships between clinical variables and patient outcomes. Decision trees, random forests, support vector machines, and gradient boosting algorithms demonstrated considerable success in predicting recurrence, survival, treatment response, and toxicity across multiple malignancies.[18]

Deep learning significantly expanded predictive capabilities by automatically extracting hierarchical features from medical imaging, digital pathology, and molecular datasets. Convolutional neural networks transformed radiological interpretation, while recurrent neural networks improved temporal analysis of longitudinal patient information.

More recently, transformer architectures have become central to clinical digital twin development because they efficiently process multimodal biomedical information while preserving long-range contextual relationships. Simultaneous analysis of imaging, pathology, genomics, laboratory investigations, and clinical documentation enables generation of highly individualized patient representations that support precision oncology.[19]

Foundation models further enhance scalability by learning generalized biomedical representations from enormous collections of unlabeled healthcare data. Following pretraining, these models can be adapted to multiple oncology applications through transfer learning, improving robustness across different cancer types while reducing dependence on manually annotated datasets.[20]

5. Multimodal Data Integration

The success of clinical digital twins depends upon effective integration of heterogeneous biomedical information into unified computational frameworks. Cancer is a multifactorial disease influenced by genetic alterations, epigenetic regulation, immune responses, metabolism, anatomical characteristics, treatment history, and numerous patient-specific clinical variables. Consequently, no individual dataset sufficiently captures the biological complexity of cancer.[21]

Medical imaging contributes anatomical and functional information regarding tumor morphology, vascularity, metabolic activity, and disease progression. Digital pathology provides microscopic assessment of tumor architecture, immune infiltration, stromal remodeling, and cellular differentiation. Molecular profiling identifies genomic alterations, transcriptomic signatures, proteomic pathways, and epigenetic modifications associated with prognosis and therapeutic response. Clinical information—including laboratory investigations, medication history, comorbidities, treatment records, and longitudinal follow-up—adds essential context for individualized predictive modeling.[22]

Artificial intelligence harmonizes these heterogeneous datasets through multimodal representation learning. Advanced computational models identify biological relationships linking imaging biomarkers, molecular signatures, pathology, and clinical variables, enabling increasingly accurate personalized predictions while continuously adapting as new patient information becomes available.[23]

6. Clinical Applications in Cancer Diagnosis

Clinical digital twins are increasingly supporting diagnostic oncology through integration of radiological imaging, computational pathology, molecular diagnostics, and laboratory investigations into comprehensive virtual patient models. Medical imaging—including computed tomography, magnetic resonance imaging, positron emission tomography, mammography, and ultrasound—provides continuous non-invasive assessment of tumor characteristics throughout disease progression.[24]

Artificial intelligence automatically detects malignant lesions, segments anatomical structures, measures tumor burden, and characterizes imaging phenotypes associated with disease aggressiveness. Radiomics further enhances diagnostic precision by extracting quantitative imaging biomarkers describing tumor morphology, vascularity, heterogeneity, texture, and spatial organization. These imaging-derived characteristics are continuously incorporated into the digital twin, enabling adaptive virtual patient models that evolve alongside the biological patient.[25]

7. Computational Pathology and Radiogenomics

Digital pathology has become another fundamental component of clinical digital twins through whole-slide imaging and AI-assisted computational analysis. Deep learning models identify subtle histopathological features associated with tumor subtype, metastatic potential, stromal remodeling, angiogenesis, immune infiltration, and therapeutic response.[26]

Artificial intelligence can also infer clinically relevant molecular alterations—including EGFR mutations, KRAS mutations, HER2 amplification, microsatellite instability, and PD-L1 expression—directly from routine histopathological images, potentially reducing dependence on expensive molecular testing while accelerating precision oncology workflows.[27]

Radiogenomics further enhances clinical digital twins by integrating quantitative imaging biomarkers with genomic sequencing and molecular profiling. These computational approaches enable non-invasive prediction of molecular tumor characteristics using routine clinical imaging while facilitating repeated assessment of tumor evolution without multiple invasive biopsies.[28]

The integration of computational pathology, radiogenomics, and multimodal artificial intelligence substantially improves diagnostic accuracy, prognostic prediction, and personalized treatment planning, moving clinical digital twins closer to routine implementation in precision oncology.[29]

8. Clinical Digital Twins in Immuno-Oncology

Immunotherapy has revolutionized modern cancer treatment, yet predicting which patients will achieve durable clinical benefit remains a major challenge. Clinical digital twins address this limitation by integrating genomic alterations, immune-cell composition, cytokine signaling pathways, digital pathology, radiological imaging, laboratory biomarkers, and clinical characteristics into comprehensive computational models capable of simulating patient-specific immune responses.[1]

Artificial intelligence quantifies tumor-infiltrating lymphocytes, immune checkpoint expression, stromal barriers, inflammatory signaling pathways, and spatial organization of immune cells within the tumor microenvironment. These integrated models estimate the probability of response to immune checkpoint inhibitors, CAR-T cell therapy, cancer vaccines, bispecific antibodies, and combination immunotherapies while supporting individualized treatment selection and minimizing unnecessary toxicity.[2]

9. Personalized Treatment Planning

One of the greatest clinical advantages of digital twins lies in individualized treatment optimization. Rather than relying solely on standardized treatment protocols, physicians can evaluate multiple therapeutic strategies within a patient's virtual model before initiating therapy.[3]

Simulation engines estimate tumor response, recurrence probability, progression-free survival, overall survival, and treatment-related toxicity under different combinations of chemotherapy, targeted therapy,

immunotherapy, surgery, and radiation therapy. These computational simulations enable clinicians to compare therapeutic alternatives while reducing unnecessary patient risk and improving evidence-based precision medicine.[4]
Because digital twins continuously incorporate updated imaging, laboratory findings, genomic information, and treatment outcomes, therapeutic recommendations evolve throughout the patient's disease course, reflecting the dynamic biology of cancer.

10. Adaptive Radiation Oncology

Radiation therapy remains an essential component of cancer management; however, anatomical changes occurring during treatment often reduce the effectiveness of conventional static radiation plans. Clinical digital twins overcome these limitations by integrating sequential imaging throughout radiation therapy and continuously updating patient-specific computational models.[5]
Artificial intelligence automatically refines tumor contours, predicts anatomical changes, estimates radiation sensitivity, and recommends adaptive treatment modifications according to the patient's evolving anatomy and biological response. These capabilities improve tumor control while minimizing radiation exposure to surrounding healthy tissues and reducing treatment-related complications.[6]

11. Surgical Planning and Intraoperative Decision Support

Digital twins are increasingly being explored in surgical oncology through three-dimensional patient-specific anatomical models generated from multimodal imaging. These virtual models provide detailed visualization of tumor location, vascular anatomy, adjacent organs, and critical neurovascular structures before surgery.[7]
Artificial intelligence further enhances surgical planning by predicting resection margins, estimating operative complexity, modeling postoperative functional outcomes, and assessing complication risk. Future integration with robotic surgery, intraoperative imaging, and physiological monitoring may allow digital twins to update continuously during surgical procedures, providing dynamic intraoperative guidance and improving surgical precision.[8]

12. Drug Discovery and Clinical Trial Optimization

Clinical digital twins offer important opportunities for accelerating oncology drug development through computational simulation of therapeutic response before laboratory or clinical evaluation. Artificial intelligence integrates molecular biology, pharmacogenomics, systems pharmacology, and patient-specific disease models to predict drug efficacy, toxicity, resistance mechanisms, and optimal dosing strategies.[9]
Digital twins may also improve clinical trial design by identifying patients most likely to benefit from investigational therapies, reducing trial variability, improving patient stratification, and enabling development of validated virtual control groups. These approaches have the potential to accelerate evaluation of innovative cancer therapies while reducing development costs and timelines.[10]

13. Intelligent Clinical Decision Support

Modern oncology requires interpretation of enormous quantities of biomedical information generated throughout diagnosis, treatment, and follow-up. Clinical digital twins function as intelligent clinical decision-support systems by continuously integrating laboratory investigations, imaging studies, pathology findings, genomic reports, medication histories, and treatment outcomes into unified computational platforms.[11]
Interactive clinical dashboards present individualized predictions regarding disease progression, therapeutic response, toxicity risk, recurrence probability, and long-term survival. Rather than replacing physician expertise, these systems provide evidence-based recommendations that strengthen multidisciplinary collaboration and improve consistency in personalized cancer care.[12]

14. Explainable Artificial Intelligence and Trustworthy Clinical Digital Twins

For digital twins to become widely accepted in clinical practice, clinicians must understand how artificial intelligence generates its predictions. Explainable artificial intelligence (XAI) improves transparency by identifying the clinical and biological variables contributing to computational recommendations.[13]
Methods including saliency maps, attention visualization, SHAP (Shapley Additive Explanations), feature attribution analysis, and counterfactual explanations enable clinicians to interpret AI outputs while increasing confidence in clinical decision-making. Explainability also facilitates communication among oncologists, radiologists, pathologists, surgeons, and molecular scientists while supporting regulatory evaluation of digital twin technologies.[14]

15. Federated Learning, Cybersecurity, and Privacy

Large-scale implementation of clinical digital twins requires access to diverse patient datasets collected across multiple healthcare institutions. Federated learning provides a privacy-preserving solution by allowing institutions to collaboratively train artificial intelligence models without transferring raw patient information.[15]

Additional privacy-enhancing technologies—including differential privacy, homomorphic encryption, secure multi-party computation, and blockchain-based auditing—further strengthen cybersecurity while maintaining regulatory compliance. Robust authentication systems, encrypted communication, and continuous threat monitoring remain essential because digital twins exchange information across imaging systems, pathology laboratories, genomic sequencing platforms, wearable devices, and hospital information systems.[16]

16. Digital Biomarkers and Continuous Patient Monitoring

Wearable technologies and remote monitoring systems have expanded the capabilities of clinical digital twins by enabling continuous collection of physiological information throughout treatment and survivorship. Heart rate, respiratory function, physical activity, sleep quality, temperature, and oxygen saturation serve as digital biomarkers reflecting patient health status and treatment tolerance.[17]

Artificial intelligence integrates these longitudinal physiological data with laboratory biomarkers, imaging findings, treatment history, and patient-reported outcomes to identify early signs of toxicity, disease progression, or functional decline. Such continuous monitoring supports timely clinical intervention, personalized follow-up strategies, and improved survivorship care.[18]

17. Future Perspectives

The future of clinical digital twins will be driven by advances in multimodal artificial intelligence, foundation models, generative AI, spatial biology, liquid biopsy, wearable technologies, quantum computing, and cloud-based healthcare infrastructure.[19]

Future oncology ecosystems are expected to integrate radiology, pathology, genomics, pharmacy systems, robotic surgery, adaptive radiation therapy, and electronic health records into continuously learning computational platforms. These intelligent systems will support predictive disease monitoring, adaptive therapeutic optimization, automated risk assessment, and highly personalized cancer care throughout the patient's clinical journey.[30]

18. Discussion

Clinical digital twins represent one of the most important advances in precision oncology because they enable dynamic, patient-specific computational modeling throughout the cancer care continuum. Unlike conventional predictive algorithms that analyze isolated datasets, digital twins continuously integrate multimodal biomedical information to simulate disease progression, optimize treatment selection, predict toxicity, and support survivorship planning.[21]

Applications across diagnostic imaging, computational pathology, radiogenomics, immunotherapy, adaptive radiation therapy, surgical planning, drug discovery, and clinical decision support demonstrate the broad translational potential of this technology. However, successful implementation depends upon overcoming challenges related to interoperability, computational resources, algorithmic bias, cybersecurity, regulatory validation, and clinician acceptance through rigorous prospective evaluation and multidisciplinary collaboration.[22]

19. Conclusion

Clinical digital twins are redefining personalized oncology by creating continuously evolving virtual representations of individual patients that integrate radiology, pathology, genomics, molecular biology, laboratory medicine, wearable technologies, and longitudinal clinical information into unified computational models.[23]

Artificial intelligence enables these virtual patients to simulate disease progression, predict therapeutic response, optimize treatment planning, estimate toxicity, and support long-term survivorship management. Continued advances in multimodal learning, explainable AI, foundation models, federated learning, and computational infrastructure are expected to improve the scalability, accuracy, interpretability, and clinical utility of digital twins.[24]

Although important scientific, technical, ethical, and regulatory challenges remain, ongoing interdisciplinary research is steadily advancing clinical digital twins toward routine implementation in oncology practice. By enabling individualized simulation of disease evolution and therapeutic response, these technologies have the potential to transform cancer care from a predominantly reactive discipline into a predictive, adaptive, and highly personalized model of precision medicine, ultimately improving patient outcomes and quality of life worldwide.[25]

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