OncoIntelligence Journal. 2026, 1(1): 3-36
https://doi.org/10.59786/OIJ260102

Review Article

Hallmarks of Cancer in the Age of Artificial Intelligence

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Article Info

Received: Mar 04, 2026
Revised: May 04, 2026
Accepted: May 11, 2026
Published: May 30, 2026

Abstract

Artificial intelligence (AI) is redefining cancer research by enabling the integration of molecular, spatial, imaging, and clinical data at unprecedented scale. In parallel, the Hallmarks of Cancer framework has evolved from a descriptive model of malignant traits into a dynamic, systems-level view of tumor biology. This Review examines how AI can operationalize both classical and emerging hallmarks of cancer, spanning proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenesis, invasion and metastasis, metabolic rewiring, and immune evasion, together with newer dimensions including tumor microenvironment complexity, phenotypic plasticity, epigenetic reprogramming, and microbiome–tumor interactions. AI-driven advances in multi-omics integration, diagnostic and prognostic modeling, treatment selection, and drug discovery are also highlighted. Major barriers to clinical translation, including bias, interpretability, validation, and ethics, are considered, alongside future directions such as digital twins and adaptive oncology. AI is positioned not merely as an analytical tool, but as a unifying framework for translating cancer complexity into next-generation precision oncology.

Keywords: Hallmarks of Cancer, Artificial Intelligence, Precision Oncology, Multi-Omics Integration, Tumor Microenvironment.

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INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide, imposing a substantial and growing global health burden[1]. Despite significant advances in prevention, early detection, and therapeutic strategies, cancer incidence continues to rise due to population aging, environmental exposures, and lifestyle factors[2]. Conventional treatment paradigms, largely based on histopathological classification and limited molecular markers, often fail to capture the profound heterogeneity that characterizes tumor biology[3]. This heterogeneity underlies variable treatment responses and clinical outcomes, highlighting the urgent need for precision oncology approaches that integrate molecular, cellular, and clinical data to guide individualized patient management[4]. In this context, AI has emerged as a transformative tool in biomedical research and clinical oncology[5]. Advances in machine learning, deep learning, and data science have enabled the analysis of complex, high-dimensional datasets, including genomics, transcriptomics, proteomics, imaging, and electronic health records. AI-driven models can uncover hidden patterns, predict disease trajectories, and optimize therapeutic decision-making with unprecedented accuracy[6]. These capabilities position AI at the forefront of efforts to address the complexity of cancer as a dynamic and multifactorial disease.

A conceptual framework that has

profoundly shaped our understanding of tumor biology is the Hallmarks of Cancer[7], originally proposed by Hanahan and Weinberg and subsequently expanded to reflect emerging insights into cancer complexity. This framework defines a set of core biological capabilities acquired during tumor development, including sustained proliferative signaling, resistance to cell death, angiogenesis, invasion and metastasis, metabolic reprogramming, and immune evasion, along with enabling characteristics such as genomic instability and tumor-promoting inflammation[8]. More recent refinements have introduced additional dimensions, including cellular plasticity, epigenetic reprogramming, and the influence of the tumor microenvironment and microbiome, emphasizing cancer as a highly adaptive and evolving system[9,10].

Despite these conceptual advances, translating the hallmarks framework into actionable clinical strategies remains challenging due to the intricate, interconnected nature of these processes. Here, AI offers a powerful integrative platform capable of mapping multidimensional biological data onto hallmark-driven models of cancer. By bridging molecular mechanisms with clinical phenotypes, AI has the potential to transform the hallmarks from a descriptive paradigm into a predictive and actionable framework. Accordingly, this review aims to explore the intersection between AI and the evolving hallmarks of cancer, highlighting how AI-driven approaches can redefine our understanding of tumor biology and accelerate the development of next-generation precision oncology.

EVOLUTION of the HALLMARKS of CANCER FRAMEWORK

The Hallmarks of Cancer framework represents one of the most influential conceptual advances in oncology, providing a unifying schema that links diverse genetic and epigenetic alterations to a finite set of functional capabilities required for malignant transformation. Since its initial formulation, the framework has undergone iterative refinement in response to rapid progress in molecular biology, systems oncology, and tumor ecology. This evolution reflects a shift from a predominantly tumor cell–centric model toward a multidimensional and dynamic understanding of cancer as a complex, adaptive biological system.

The Original Hallmarks (2000)

In their landmark 2000 synthesis, Hanahan and Weinberg[7] proposed that the vast heterogeneity of cancer could be distilled into six essential biological capabilities acquired during multistep tumorigenesis. These included sustained proliferative signaling, whereby cancer cells achieve autonomy from exogenous growth cues through constitutive activation of oncogenic pathways such as RAS–MAPK and PI3K–AKT. Complementing this, tumor cells exhibit evasion of growth suppressors, disabling critical checkpoint regulators including *TP53* and *RB*, thereby uncoupling proliferation from normal tissue constraints. A third hallmark, resistance to apoptosis, reflects the capacity of cancer cells to circumvent programmed cell death through dysregulation of intrinsic and extrinsic apoptotic pathways, often via modulation of *BCL-2* family proteins and caspases. In parallel, tumors acquire replicative immortality, typically through activation of telomerase or alternative lengthening of telomeres (ALT), enabling indefinite proliferative potential.

The induction of angiogenesis constitutes another critical adaptation,

allowing tumors to secure a sustained supply of oxygen and nutrients through pro-angiogenic factors such as vascular endothelial growth factor (*VEGF*). Finally, activation of invasion and metastasis enables dissemination beyond the primary tumor site, involving complex processes such as epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and cytoskeletal reorganization. Collectively, these six hallmarks established a robust framework linking molecular aberrations to phenotypic traits that define malignancy.

The Next Generation (2011)

A decade of subsequent research necessitated expansion of the framework to incorporate emerging insights into cancer metabolism, immune surveillance, and genomic instability. Two additional hallmarks were introduced[8]. The first, reprogramming of energy metabolism, recognizes the metabolic plasticity of cancer cells, exemplified by the Warburg effect, wherein glycolysis is favored even under normoxic conditions. Beyond glycolysis, tumors exhibit adaptive rewiring of lipid, amino acid, and mitochondrial metabolism to sustain biosynthetic and bioenergetic demands.

The second addition, evasion of immune destruction, reflects the ability of tumor cells to avoid recognition and elimination by the host immune system. Mechanisms include downregulation of antigen presentation machinery, secretion of immunosuppressive cytokines, and exploitation of immune checkpoint pathways such as *PD-1*/*PD-L1* and *CTLA-4*. Importantly, the 2011 update also introduced two enabling characteristics that facilitate the acquisition of hallmark capabilities. Genome instability and mutation generate the genetic diversity necessary for clonal selection and tumor evolution, while tumor-promoting inflammation provides a supportive microenvironment enriched in growth factors, survival signals, and pro-angiogenic mediators. This expanded framework underscored the interplay between intrinsic genetic alterations and extrinsic microenvironmental influences in driving tumor progression.

New Dimensions (2022)

Recent conceptual advances have further refined the hallmarks paradigm by incorporating insights from epigenetics, tumor ecology, and cellular dynamics[9]. A central addition is epigenetic reprogramming, which enables heritable yet reversible modulation of gene expression through mechanisms such as DNA methylation, histone modification, and chromatin remodeling. These processes contribute to tumor heterogeneity, lineage plasticity, and therapeutic resistance without requiring changes in DNA sequence. Another critical dimension is the Tumor Microenvironment (TME), now recognized as an active participant in cancer progression rather than a passive scaffold. The TME comprises a heterogeneous assembly of stromal cells, immune infiltrates, endothelial cells, and extracellular matrix components, all of which engage in bidirectional signaling with tumor cells. This crosstalk shapes key processes including angiogenesis, immune evasion, and metastatic dissemination.

The concept of cellular plasticity has also emerged as a defining feature of malignancy. Cancer cells can dynamically transition between differentiated and stem-like states, as well as between epithelial and mesenchymal phenotypes, enabling adaptation to environmental stress and therapeutic pressure. In parallel, the microbiome has been implicated as a modulator of tumorigenesis, influencing

inflammation, immune responses, metabolism, and even the efficacy of anticancer therapies. These additions collectively expand the hallmarks framework into a more integrative model encompassing both genetic and non genetic determinants of cancer behavior.

Emerging Concepts (2025–2026)

The most recent conceptual developments move beyond discrete hallmark categories toward a systems-level paradigm that conceptualizes cancer as a dynamic, evolving ecosystem[10]. Within this framework, tumors are understood as complex multicellular communities, characterized by spatial and temporal heterogeneity and governed by intricate networks of intercellular communication. These include paracrine signaling, metabolic coupling, extracellular vesicle exchange, and immune modulation. A key feature of this emerging perspective is the recognition of intercellular interactions as fundamental drivers of tumor behavior. Cooperative and competitive dynamics among cancer subclones, stromal elements, and immune populations contribute to adaptive evolution, therapeutic resistance, and metastatic potential. Moreover, cancer is increasingly viewed as a systemic disease, influenced by host physiology, including endocrine, metabolic, and immune systems, as well as environmental and lifestyle factors.

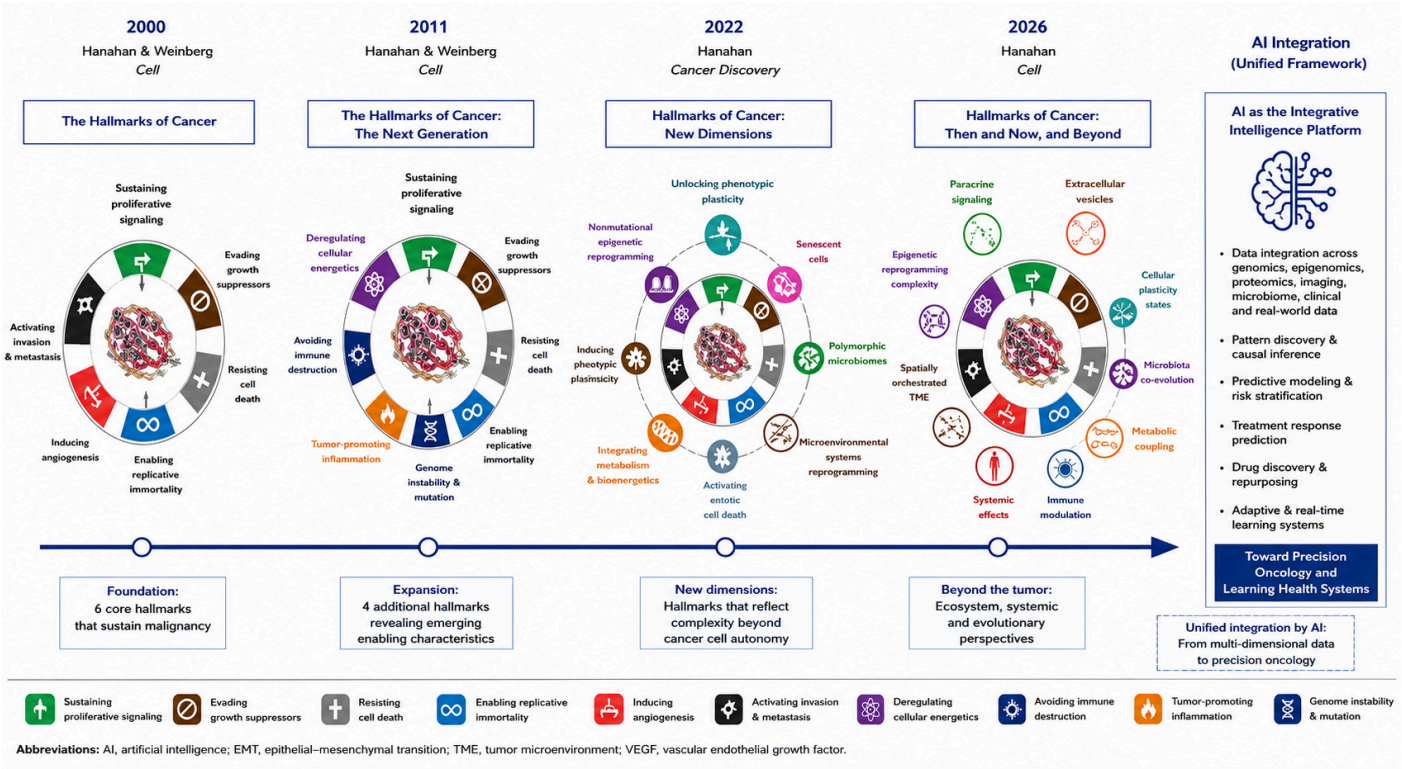


Figure 1. Evolution of the Hallmarks of Cancer and AI as a Unified Integration Framework. Shows the evolution of cancer hallmarks from the six original hallmarks (2000) through the expanded 2011 and 2022 frameworks to a systems-level cancer ecosystem perspective in 2026, with AI connecting multimodal data to biomarker discovery, biological interpretation, prediction, and precision oncology. AI, Artificial Intelligence; VEGF, Vascular Endothelial Growth Factor; EMT, Epithelial–Mesenchymal Transition.

This paradigm emphasizes the dynamic and non-linear nature of tumor progression, where feedback loops, stochastic events, and ecological pressures shape disease trajectories. Such complexity challenges traditional reductionist approaches and necessitates integrative analytical frameworks capable of capturing multi-scale biological interactions. The progressive evolution of the hallmarks framework, from a set of static cellular capabilities to a dynamic, systems-level model, provides a critical foundation for

integrating AI. AI-driven approaches offer unprecedented capacity to decode high-dimensional data, model complex biological networks, and translate hallmark-based concepts into predictive and actionable insights, thereby enabling the realization of next-generation precision oncology.

ARTIFICIAL INTELLIGENCE in ONCOLOGY: an OVERVIEW

Artificial intelligence has rapidly emerged as a transformative force in oncology, offering computational approaches that extract clinically meaningful knowledge from the growing volume and complexity of cancer-related data[11]. As cancer is increasingly recognised as a heterogeneous, dynamic, and multi-scale disease, conventional analytical methods often prove insufficient to capture the intricate biological relationships underlying tumour initiation, progression, therapeutic response, and resistance. AI addresses this challenge by enabling the analysis of high-dimensional datasets, uncovering latent patterns, generating predictive models, and supporting integrative interpretations across molecular, pathological, radiological, and clinical domains[12]. In oncology, AI is no longer limited to technical assistance; it is increasingly shaping biomarker discovery, molecular classification, diagnostic stratification, prognosis estimation, treatment optimization, and drug development[13].

Types of Artificial Intelligence Relevant to Oncology

The broad field of AI encompasses several computational paradigms, among which machine learning (ML), deep learning (DL), and generative AI have become particularly relevant in cancer research and practice[14]. Machine learning refers to a class of algorithms that learn patterns from data and improve performance without explicit rule-based programming. In oncology, supervised, unsupervised, and reinforcement learning approaches have been applied to tasks such as tumor classification, survival prediction, biomarker identification, and treatment response modeling[15]. Traditional ML methods, including random forests, support vector machines, gradient boosting, and clustering algorithms, have proven useful for structured biomedical datasets, especially when interpretable outputs are needed[16].

Deep learning, a specialized subset of machine learning, relies on multilayered artificial neural networks capable of automatically learning hierarchical feature representations from complex and unstructured data. Deep learning has shown particular strength in oncology applications involving digital pathology, radiology, histomorphology, and multimodal biomarker analysis[17]. Convolutional neural networks, recurrent neural networks, graph neural networks, and transformer-based architectures are increasingly used to analyze images, genomic sequences, longitudinal patient trajectories, and network-level biological interactions[18].

More recently, generative AI has introduced a new dimension to oncology research. These models, including generative adversarial networks, variational autoencoders, and large language models, are capable of generating synthetic data, simulating biological scenarios, assisting hypothesis generation, supporting drug design, and enhancing clinical decision support[19]. In cancer research, generative AI holds promise for augmenting limited datasets, modeling tumor evolution, designing novel molecules, and facilitating literature synthesis, although its reliability, interpretability, and ethical implications remain

under active evaluation[20].

Major Data Sources for Artificial Intelligence in Oncology

The utility of AI in oncology is fundamentally dependent on the diversity, scale, and quality of the data on which it operates. Modern cancer research generates a wide spectrum of data types, each reflecting different layers of tumor biology and patient status[20]. At the molecular level, genomic data provide information on somatic mutations, copy number alterations, structural rearrangements, and mutational signatures, offering insight into the genetic drivers of tumorigenesis[21]. Transcriptomic data add a dynamic layer by capturing gene expression patterns, alternative splicing events, and regulatory activity, thereby revealing cellular states and pathway activation[22]. Proteomic data further extend this framework by characterizing protein abundance, post-translational modifications, and signaling dynamics, which are often more proximal to phenotype than genomic alterations alone[23].

Beyond molecular profiling, imaging data represent one of the most powerful domains for AI application in oncology. Radiological imaging, histopathological slides, immunohistochemical staining, and advanced digital pathology platforms generate rich spatial and structural information that can be mined for tumor classification, grading, microenvironment characterization, and treatment response prediction. Increasingly, radiomics and pathomics approaches are being integrated with molecular data to create multidimensional predictive models[24]. Equally important are clinical data, including demographic characteristics, disease stage, laboratory parameters, treatment regimens, comorbidities, longitudinal outcomes, and electronic health records. These data provide the real-world clinical context necessary for translating AI-derived patterns into patient-centered applications. When integrated across modalities, such datasets enable a more complete and biologically meaningful representation of cancer than any single data source alone[25].

Functional Roles of AI in Cancer Research

The primary value of AI in oncology lies in its ability to transform heterogeneous datasets into actionable knowledge. One of its most fundamental roles is pattern recognition, whereby AI can detect subtle, multidimensional relationships that may be inaccessible to traditional statistical approaches. This includes identifying molecular subtypes, recognizing histopathological features, detecting radiological signatures, and uncovering latent associations among biomarkers, pathways, and outcomes[11]. A second major role is prediction modeling. AI-driven models are increasingly used to estimate diagnosis, prognosis, recurrence risk, metastatic potential, drug sensitivity, and treatment toxicity. These predictive functions are particularly relevant to precision oncology, where individualized therapeutic decisions require accurate, data-informed risk stratification and response forecasting.A third and increasingly important role is systems biology integration[14].

AI provides a framework for integrating these multi-level data into coherent biological models, enabling the study of tumor ecosystems, intercellular communication, metabolic rewiring, immune interactions, and dynamic disease evolution. In this sense, AI is not merely a computational tool but a conceptual bridge between biological complexity and clinical application[26]. Taken together, AI has become indispensable to

contemporary oncology by enabling a transition from fragmented data interpretation to integrated, predictive, and biologically informed cancer analysis. Its growing relevance is especially evident when viewed through the lens of the Hallmarks of Cancer, where the challenge is not simply to describe tumor capabilities, but to decode how these capabilities emerge, interact, and evolve across diverse datasets and clinical contexts[5].

ARTIFICIAL INTELLIGENCE MAPPING ACROSS the HALLMARKS of CANCER

The integration of AI into oncology has enabled a paradigm shift from descriptive characterization of tumor biology to predictive, systems-level modeling of cancer hallmarks. By leveraging high-dimensional datasets, including genomics, transcriptomics, proteomics, radiomics, and clinical variables, AI approaches facilitate the identification of latent patterns and mechanistic relationships that underlie hallmark acquisition and tumor evolution[27]. This section synthesizes current advances in mapping AI methodologies across the canonical and emerging hallmarks of cancer, highlighting their transformative potential in precision oncology. Table 1 presents a comprehensive summary of AI applications across the hallmarks of cancer.

Table 1. Artificial intelligence applications across the hallmarks of cancer

Hallmark	Biological Process	AI Approach	Data Type	Clinical Application	Ref.
Sustained proliferative signaling	Constitutive activation of oncogenic pathways (EGFR, MYC, PI3K–AKT)	Deep learning, pathway inference models, network analysis	Genomics, transcriptomics, proteomics	Identification of driver mutations; prediction of response to targeted therapies (e.g., EGFR inhibitors)	8,28, 29
Evading growth suppressors	Loss of tumor suppressor function (TP53, RB1, PTEN)	Machine learning classifiers, integrative genomics models	Genomics, methylation, transcriptomics	Functional prediction of tumor suppressor loss; patient stratification	30
Resisting cell death	Dysregulation of apoptosis pathways (BCL-2, caspases)	Predictive modeling, drug response ML models	Transcriptomics, proteomics, pharmacogenomics	Prediction of chemotherapy and targeted drug sensitivity	31
Replicative immortality	Telomerase activation, telomere maintenance, genomic instability	AI-based genomic instability scoring, survival modeling	Genomics, WGS, epigenomics	Prognostic biomarkers; survival prediction	32,33
Inducing angiogenesis	VEGF signaling, hypoxia-driven vascularization	Radiomics, deep learning imaging analysis, pathway modeling	Imaging (CT/MRI), transcriptomics	Prediction of anti-angiogenic therapy response; tumor vascular assessment	34
Activating invasion & metastasis	EMT, extracellular matrix remodeling, cell motility	Machine learning prediction models, image-based AI	Histopathology, genomics, imaging	Metastasis risk prediction; early detection of invasive phenotypes	35
Reprogram ming cellular metabolism	Warburg effect, metabolic pathway rewiring	Metabolic network modeling, AI-based flux analysis	Metabolomics, transcriptomics	Identification of metabolic vulnerabilities; targeted therapy development	36
Avoiding immune destruction	Immune checkpoint activation (PD-1/PD-L1), immune evasion	AI-based immunotherapy prediction models, single-cell analysis	Genomics, transcriptomics, scRNA-seq	Prediction of immunotherapy response; immune profiling	37,38

Sustained Proliferative Signaling

Sustained proliferative signaling is a defining feature of malignancy, driven by constitutive activation of oncogenic pathways

such as *EGFR*, *RAS*, *MYC*, and *PI3K–AKT*. AI-based frameworks, particularly deep learning and network-based machine learning models, have demonstrated remarkable capacity to identify aberrant signaling cascades from multi-omics data. Integrative approaches combining genomic mutations, transcriptomic profiles, and proteomic signatures enable the reconstruction of oncogenic networks with high resolution [3].

Predictive AI models have been employed to infer cell cycle dysregulation, including alterations in cyclins, cyclin-dependent kinases (CDKs), and checkpoint regulators. These models can stratify tumors based on proliferative indices and predict responsiveness to targeted therapies such as CDK inhibitors. Furthermore, AI-driven pathway inference algorithms uncover nonlinear interactions within proliferative signaling networks, providing insights into tumor heterogeneity and clonal evolution[39].

Evading Growth Suppressors

The inactivation of tumor suppressor pathways, particularly those governed by *TP53*, *RB1*, and *PTEN*, represents a critical step in tumorigenesis. AI methodologies have significantly enhanced the detection and functional interpretation of tumor suppressor gene alterations, including point mutations, copy number variations, and epigenetic silencing[40].

Machine learning classifiers trained on large-scale cancer datasets can accurately predict *TP53* functional status and downstream pathway disruption, even in the absence of overt genomic alterations. Additionally, AI-driven integrative analyses can identify compensatory pathways that emerge following tumor suppressor loss, offering opportunities for synthetic lethality-based therapeutic strategies. These approaches enable a more nuanced understanding of how tumor cells circumvent growth inhibitory signals[41].

Resisting Cell Death (Apoptosis)

Resistance to programmed cell death is mediated through complex alterations in apoptotic signaling networks, including dysregulation of *BCL*-2 family proteins, caspases, and mitochondrial pathways. AI-based models have been instrumental in reconstructing these pathways and identifying critical nodes that confer survival advantage [42].

Deep learning approaches applied to transcriptomic and proteomic data enable apoptosis pathway modeling, revealing context-specific dependencies across cancer types. Moreover, AI-driven drug response prediction platforms integrate molecular profiles with pharmacogenomic datasets to forecast sensitivity or resistance to pro-apoptotic agents, including BH3 mimetics and chemotherapy. These predictive frameworks are increasingly being incorporated into precision oncology pipelines to optimize therapeutic selection [43].

Replicative Immortality

Replicative immortality, primarily mediated by telomerase activation (*TERT*) and alternative telomere maintenance mechanisms, is essential for sustained tumor growth. AI approaches have been utilized to analyze telomere length dynamics, *TERT* promoter mutations, and associated epigenetic modifications across diverse malignancies[44].

Machine learning models integrating genomic instability metrics, such as mutational burden and chromosomal aberrations, provide insights into the relationship between telomere maintenance and genomic evolution. AI-driven analyses

also enable the identification of biomarkers associated with replicative potential and prognosis, offering potential avenues for targeting telomere biology in cancer therapy[45].

Inducing Angiogenesis

Tumor angiogenesis is orchestrated by a network of pro-angiogenic factors, most notably vascular endothelial growth factor (*VEGF*), and is critical for tumor expansion and metastasis. AI methodologies have been widely applied to model angiogenic signaling pathways and to quantify vascular characteristics within tumors[46].

In silico modeling approaches leverage multi-omics data to predict *VEGF* pathway activation and identify regulatory interactions with hypoxia-inducible factors (HIFs). Concurrently, deep learning applied to medical imaging, particularly radiomics and histopathology, enables non-invasive assessment of tumor vascularization, microvessel density, and perfusion patterns. These imaging-based AI tools have demonstrated utility in predicting response to anti-angiogenic therapies and monitoring treatment efficacy[47].

Activating Invasion and Metastasis

Metastasis remains the principal cause of cancer-related mortality and involves complex processes such as epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and cellular motility. AI-driven predictive models have been developed to assess metastatic potential by integrating genomic, transcriptomic, and clinical data[48].

Machine learning algorithms can identify molecular signatures associated with metastatic dissemination and stratify patients based on risk of recurrence or distant spread. Additionally, AI-based modeling of EMT dynamics captures the continuum of epithelial and mesenchymal states, providing insights into tumor plasticity and therapeutic resistance. Advanced image analysis techniques further enable the detection of invasive phenotypes at the histological level, enhancing early identification of aggressive disease[49].

Reprogramming Cellular Metabolism

Metabolic reprogramming, including the Warburg effect, is a hallmark of cancer that supports rapid proliferation and adaptation to environmental stress. AI-based systems biology approaches have been pivotal in reconstructing metabolic networks and identifying key regulatory nodes within cancer metabolism[50].

By integrating metabolomic, transcriptomic, and fluxomic data, AI models can characterize tumor-specific metabolic phenotypes and predict metabolic vulnerabilities. These approaches facilitate the identification of therapeutic targets within glycolysis, glutaminolysis, and lipid metabolism pathways. Moreover, AI-driven modeling of metabolic plasticity provides insights into how tumors adapt to nutrient deprivation and therapeutic pressure[51].

Avoiding Immune Destruction

The ability of tumors to evade immune surveillance is central to cancer progression and has become a major focus of therapeutic intervention. AI has significantly advanced the understanding of tumor–immune interactions and the prediction of immunotherapy responses [52].

Machine learning models integrating genomic features such as tumor mutational burden, neoantigen load, and immune gene signatures enable accurate prediction of response to immune checkpoint inhibitors. AI-driven analysis of single-cell sequencing data further elucidates the heterogeneity of immune cell populations within the tumor

microenvironment. Additionally, deep learning applied to histopathological images can quantify immune infiltration and spatial organization, providing clinically relevant biomarkers for immunotherapy stratification [53].

Collectively, these advances demonstrate that AI serves as a powerful integrative platform for decoding the biological complexity underlying the hallmarks of cancer. By linking molecular alterations to functional phenotypes and clinical outcomes, AI not only enhances mechanistic understanding but also enables the translation of hallmark-based concepts into predictive, actionable strategies for next-generation precision oncology.

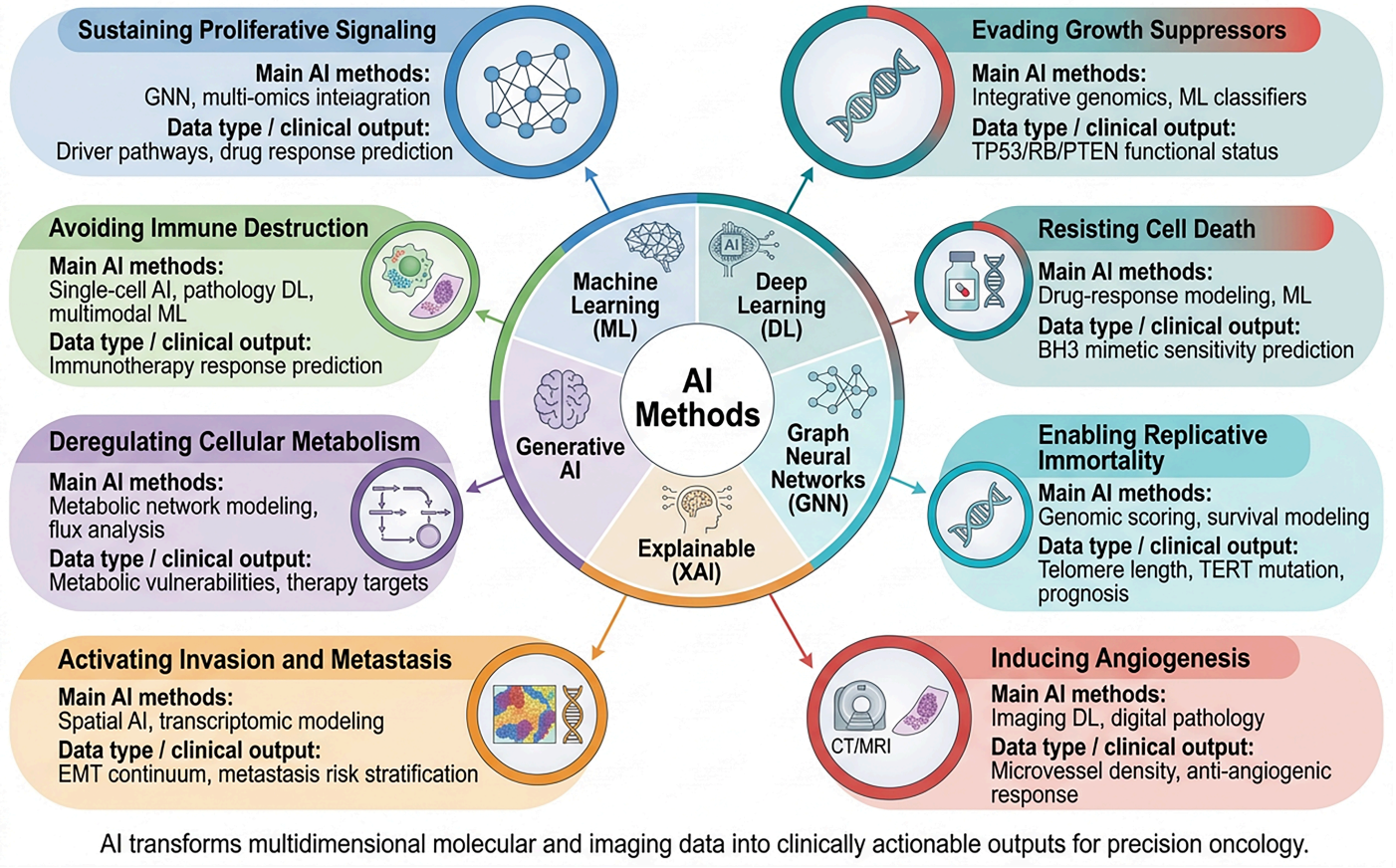


Figure 2. AI Methods Applied to the Hallmarks of Cancer for Precision Oncology. Maps major AI approaches, machine learning, deep learning, graph neural networks, generative AI, and explainable AI, to individual cancer hallmarks and shows their applications in multi-omics integration, imaging/pathology analysis, prognosis, drug-response prediction, metastasis assessment, and biomarker discovery. AI, artificial intelligence; ML, machine learning; DL, deep learning; GNN, graph neural networks; XAI, explainable AI; CT, computed tomography; MRI, magnetic resonance imaging; TP53, tumor protein p53; RB, retinoblastoma; PTEN, phosphatase and tensin homolog; BH3, Bcl-2 homology 3; TERT, telomerase reverse transcriptase.

ARTIFICIAL INTELLIGENCE and the NEW DIMENSIONS of CANCER BIOLOGY

Recent extensions of the hallmarks framework emphasize cancer as a multiscale, ecosystem-driven, and dynamically evolving disease. AI is uniquely positioned to interrogate these dimensions by integrating heterogeneous data modalities, modeling non-linear interactions, and resolving spatial–temporal complexity. Below, we outline how AI operationalizes these emerging dimensions into quantifiable, clinically actionable insights.

Tumor Microenvironment

The Tumor Microenvironment (TME) comprising malignant cells, cancer-associated fibroblasts (CAFs), endothelial cells, immune infiltrates, and extracellular matrix (ECM) is a central determinant of tumor progression and therapeutic response. AI has enabled high-resolution decoding of TME architecture

through multimodal data integration[53].

Deep learning applied to digital pathology (whole-slide images) and radiomics can quantify immune infiltration (e.g., TIL density), stromal composition, vascular patterns, and spatial organization. Convolutional neural networks (CNNs) and transformer-based models extract features that correlate with immune phenotypes (inflamed vs. "cold" tumors) and predict outcomes to checkpoint blockade[54]. In parallel, single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics analyzed with machine learning (e.g., graph neural networks, variational autoencoders) reconstruct cell–cell communication networks, including ligand–receptor interactions and cytokine signaling axes[55]. Network-based AI models further integrate angiogenic signaling (VEGF/HIF), ECM remodeling, and immune checkpoints, enabling prediction of therapeutic vulnerabilities within the TME. Importantly, spatially aware AI captures heterogeneity across tumor regions, revealing niches of immune exclusion or hypoxia that drive resistance[56].

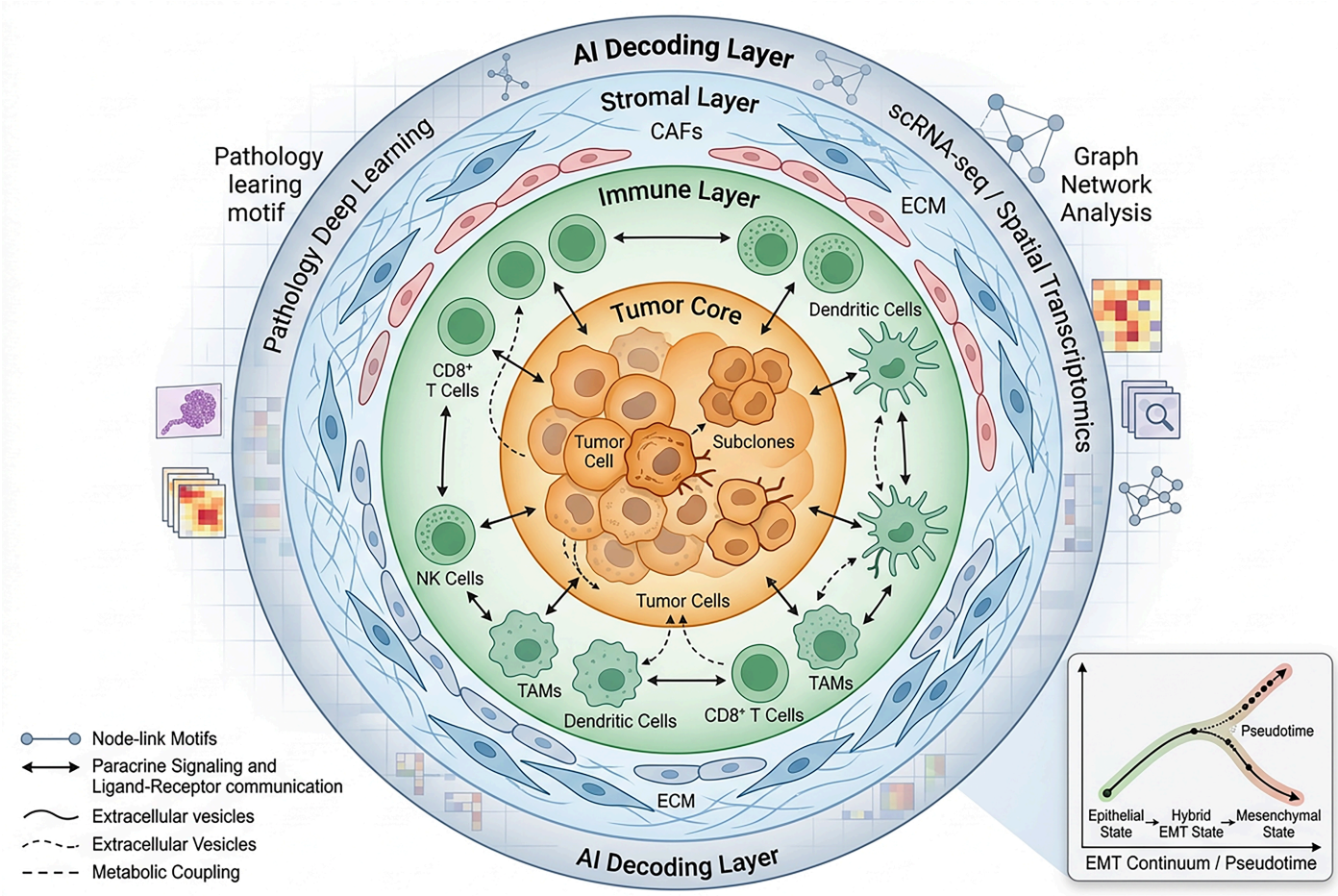


Figure 3. AI Decoding the Tumor Microenvironment and Cellular Interactions. Depicts the tumor microenvironment as an interconnected cellular ecosystem, emphasizing immune cells, stromal components, spatial organization, and cell–cell interactions. It illustrates how AI, single-cell analysis, spatial transcriptomics, and digital pathology can identify ecological niches associated with immune escape and treatment resistance. TME, tumor microenvironment; T cells, T lymphocytes; NK, natural killer cells; TAMs, tumorassociated macrophages; DCs, dendritic cells; CAFs, cancer-associated fibroblasts; ECs, endothelial cells; ECM, extracellular matrix; EVs, extracellular vesicles; EMT, epithelial–mesenchymal transition; scRNA-seq, single-cell RNA sequencing; ST, spatial transcriptomics; DL, deep learning; AI, artificial intelligence; L–R, ligand–receptor; DP, digital pathology; GN, graph networks.

Phenotypic Plasticity

Phenotypic plasticity, the capacity of cancer cells to transition between states (e.g., epithelial–mesenchymal transition [EMT], stem-like states, drug-tolerant persisters)

underlies metastasis and therapy resistance. AI enables longitudinal and cross-sectional modeling of these dynamic state transitions[57].

Unsupervised learning (e.g., non-negative matrix factorization, diffusion maps, pseudotime inference) applied to single-cell data reconstructs cellular trajectories and lineage relationships, capturing EMT continua rather than binary states. Deep generative models (e.g., variational autoencoders, GANs) simulate state transitions under perturbations, enabling in silico exploration of plasticity-driven resistance[58]. Clonal evolution is further resolved using AI methods that integrate somatic mutation profiles, copy number alterations, and phylogenetic inference, delineating subclonal architectures and their temporal dynamics. Coupled with longitudinal liquid biopsy data, AI supports real-time tracking of tumor evolution, anticipating resistance before clinical relapse[59].

Epigenetic Reprogramming

Epigenetic reprogramming, including DNA methylation, histone modification, chromatin accessibility, and 3D genome organization, drives tumor heterogeneity independent of DNA sequence changes. AI has transformed epigenomic analysis by enabling high-dimensional pattern recognition and integrative modeling[60].

Machine learning frameworks analyze whole-genome bisulfite sequencing and array-based methylation data to identify cancer-specific methylation signatures for early detection and classification. Deep learning models applied to ATAC-seq and ChIP-seq infer regulatory element activity and transcription factor binding landscapes, linking epigenetic states to gene expression programs[61]. Importantly, AI integrates epigenomic layers with transcriptomics to define regulatory circuits governing plasticity and resistance (e.g., enhancer reprogramming, super-enhancers). Emerging 3D genome models (Hi-C–based) analyzed with graph-based AI capture chromatin topology and long-range interactions, revealing structural determinants of oncogene activation. These approaches enable the identification of epigenetic vulnerabilities and rational targeting with epigenetic therapies[62].

Microbiome–Cancer Interactions

The microbiome has emerged as a critical modulator of tumor biology, influencing inflammation, metabolism, immune tone, and response to therapy. AI facilitates the integration of metagenomic, metabolomic, and host data to decipher microbiome–cancer interactions[63].

Machine learning models applied to 16S rRNA and shotgun metagenomics identify microbial signatures associated with cancer risk, progression, and treatment response (notably to immunotherapy). Network-based approaches map microbe–host–immune interactions, linking microbial metabolites (e.g., short-chain fatty acids, bile acids) to signaling pathways in tumor and immune cells[64]. Multi-view learning frameworks integrate microbiome profiles with host genomics and immune phenotypes, improving prediction of therapeutic outcomes. These models also support causal inference strategies to distinguish correlation from functional impact, guiding microbiome-targeted interventions (e.g., probiotics, fecal microbiota transplantation)[65].

AI-DRIVEN MULTI-OMICS INTEGRATION

The convergence of genomics, transcriptomics, proteomics, metabolomics, and clinical data has given rise to multi-omics oncology, where AI serves as the central integrative engine. By capturing cross-layer interactions, AI enables a systems-level

understanding of cancer that transcends single-modality analyses[27]. The principal AI methods currently applied in cancer research, together with their representative uses, strengths, limitations, and key references, are summarized in Table 2.

Table 2. Key AI methods used in cancer research.

AI technique	Core principle	Typical oncology application	Common data type(s)	Main strengths	Key limitations	Ref.
Supervised machine learning	Learns associations between labeled inputs and outcomes	Risk stratification, biomarker discovery, treatment response prediction, recurrence classification	Clinical variables, genomics, transcriptomics, radiomics	Interpretable with appropriate feature engineering; suitable for structured datasets	Sensitive to feature quality, class imbalance, and overfitting	[28,66]
Deep learning	Learns hierarchical representations directly from raw or minimally processed data	Cancer detection, subtype classification, survival modeling, response prediction	Imaging, pathology slides, genomics, multimodal datasets	High performance on complex, high-dimensional data; reduces manual feature extraction	Lower interpretability; requires large datasets and careful validation	[67,68]
Convolutional neural networks (CNNs)	Specialized deep learning architecture for spatially structured data	Radiology, digital pathology, lesion detection, tumor segmentation	CT, MRI, PET, whole-slide images	Strong pattern recognition for image analysis; scalable to large imaging cohorts	Vulnerable to dataset shift, annotation variability, and hidden confounding	[69]
Vision transformers	Attention-based models that capture long-range spatial dependencies	Whole-slide pathology analysis, imaging classification, multimodal image–omics integration	Histopathology, radiology, multiplex imaging	Effective on large-scale image data; captures global contextual information	Computationally intensive; often less transparent for clinicians	[29]
Natural language processing (NLP)	Extracts information from unstructured text using statistical or neural language models	Clinical note mining, trial matching, pathology/radiology report analysis, outcome phenotyping	Electronic health records, reports, publications	Unlocks large volumes of otherwise inaccessible clinical text	Sensitive to documentation bias, language variability, and privacy issues	[70]
Graph neural networks (GNNs)	Models relational structure among nodes and edges in biological or clinical networks	Pathway analysis, protein interaction modeling, patient similarity mapping, target prioritization	Multi-omics networks, signaling pathways, knowledge graphs	Captures systems biology relationships and context-dependent network effects	Model complexity and limited interpretability; dependent on graph quality	[66]
Multimodal deep learning	Integrates heterogeneous data types into a shared predictive framework	Prognosis, precision treatment selection, integrated tumor profiling	Imaging, genomics, transcriptomics, pathology, clinical data	Improves predictive performance by capturing complementary information across platforms	Missing data, harmonization challenges, and limited external validation	[67]
Autoencoders and variational autoencoders (VAEs)	Learn compressed latent representations of high-dimensional data	Multi-omics integration, subtype discovery, denoising, feature extraction	Genomics, transcriptomics, methylation, proteomics	Useful for dimension reduction and latent structure discovery	Biological interpretation of latent features can be difficult	[67]
Reinforcement learning	Optimizes sequential decisions through reward-based learning	Adaptive therapy design, treatment sequencing, radiotherapy planning	Longitudinal clinical data, treatment history, outcomes	Well suited to dynamic decision-making and personalized treatment pathways	Requires robust prospective data and careful reward definition	[29]
Generative AI	Produces synthetic content or novel	Drug design, synthetic data generation,	Molecular structures, imaging,	Accelerates molecule discovery and may	Hallucination risk, limited regulatory	[71]

AI technique	Core principle	Typical oncology application	Common data type(s)	Main strengths	Key limitations	Ref.
	candidates from learned data distributions	hypothesis generation, molecular optimization	clinical data, multi-omics	support data sharing/privacy-preserving research	maturity, and validation burden	
Explainable AI (XAI)	Provides human-readable explanations for model outputs	Clinical decision support, biomarker prioritization, trust-building in diagnostics	Any model output layered onto imaging, omics, or clinical data	Improves transparency, clinician trust, and regulatory acceptability	Explanations can be approximate and not necessarily mechanistic	[70]

Integrative Multi-omics Fusion

Modern AI architectures (e.g., multi-modal deep learning, autoencoders, transformers) integrate heterogeneous datasets to construct composite molecular profiles. These approaches reconcile differences in scale, noise, and dimensionality, enabling robust patient stratification, subtype discovery, and biomarker identification. Feature attribution methods (e.g., SHAP, integrated gradients) enhance interpretability by identifying key drivers across omics layers[72]. Key strategies and clinical applications of AI-based multi-omics integration across cancer research are summarized in Table 3

Table 3. AI-Based Multi-Omics Integration in Cancer

Integration domain	Biological objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Representative Refs.
Genomics + transcriptomics integration	Link DNA alterations to downstream transcriptional programs	Multimodal deep learning, autoencoders, feature fusion, attention models	Somatic mutations, copy number variation, bulk RNA-seq	Molecular subtypes, driver-pathway signatures, risk groups	Improves tumor classification and treatment stratification beyond single-omics models	[73]
Genomics + epigenomics integration	Resolve regulatory effects of mutation and DNA methylation / chromatin state	Variational autoencoders, matrix factorization, graph-based fusion	Mutation, CNV, DNA methylation, ATAC-seq / ChIP-seq	Epigenetically defined tumor states, regulatory dependencies	Supports biomarker discovery and identification of epigenetic vulnerabilities	[74]
Transcriptomics + proteomics integration	Connect expression programs to signaling activity and pathway output	Neural network fusion, correlation-aware embedding, network propagation	Bulk RNA-seq, proteomics, phosphoproteomics	Activated pathways, therapy-response signatures, targetable networks	Refines pathway interpretation and can improve prediction of drug sensitivity	[75]
Multi-omics + histopathology integration	Bridge tissue morphology with molecular phenotype	Multimodal deep learning, cross-attention models, vision-language fusion	Whole-slide images, genomics, transcriptomics, clinicopathologic variables	Histomolecular subtypes, prognosis models, treatment-response scores	Enables non-invasive or minimally invasive molecular inference and stronger risk prediction	[76,77]
Multi-omics + radiology integration	Link imaging phenotype to underlying molecular architecture	Radiogenomics, multimodal fusion, ensemble learning	CT, MRI, PET, genomics, transcriptomics, clinical data	Radiogenomic biomarkers, response prediction, survival models	Supports precision imaging, baseline risk assessment, and longitudinal monitoring	[78]
Graph-based multi-omics integration	Model interactions among genes, proteins, pathways, and patients	Graph neural networks, knowledge graphs, graph machine learning	Omics layers plus pathway / PPI priors	Driver modules, network states, patient similarity graphs	Strengthens biological interpretability and target prioritization	[79]

Integration domain	Biological objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Representative Refs.
Spatial multi-omics integration	Decode intratumoral heterogeneity and cellular niches in context	Spatial graph neural networks, latent-space aggregation, spatial transformers	Spatial transcriptomics, multiplex imaging, scRNA-seq, pathology	Cell–cell interaction maps, prognostic niches, spatial programs	Helps explain resistance, immune exclusion, and regional therapeutic vulnerability	[80]
Single-cell multi-omics integration	Resolve lineage states, plasticity, and clonal/ecological structure	Variational inference, manifold learning, graph learning	scRNA-seq, scATAC-seq, single-cell proteomics	Cell states, trajectories, lineage relationships, resistant subpopulations	Advances precision oncology by identifying rare but clinically meaningful subclones	[81,82]
Systems oncology integration	Build patient-level predictive models from multi-layer biological data	Multimodal deep learning, survival networks, hybrid mechanistic-AI pipelines	Genomics, transcriptomics, proteomics, imaging, clinical data	Prognosis, recurrence risk, treatment benefit estimates, digital twins	Moves precision oncology from descriptive profiling to predictive decision support	[83,84]
Knowledge-guided target discovery	Identify actionable targets and synthetic lethal interactions	Knowledge graph AI, graph reasoning, supervised integration with priors	Multi-omics plus curated pathways, drug–target databases	Target ranking, pathway vulnerabilities, candidate combinations	Accelerates translational prioritization and hypothesis generation for therapy development	[85,86]

Network-based Cancer Modeling

AI-driven network biology reconstructs gene regulatory networks, protein–protein interactions, and signaling pathways. Graph-based models (e.g., graph neural networks) encode biological relationships and propagate information across networks to identify hub nodes and driver modules. These frameworks capture non-linear dependencies and context-specific rewiring of pathways, facilitating discovery of synthetic lethal interactions and combinatorial targets[87].

Systems Oncology and Predictive Modeling

In systems oncology, AI integrates multi-omics with clinical and imaging data to build predictive models of disease trajectory and treatment response. Digital twin frameworks simulate patient-specific tumor behavior under different therapeutic scenarios, enabling in silico trials and adaptive treatment optimization[88]. Crucially, AI supports end-to-end pipelines from data ingestion to decision support: (i) data harmonization and quality control, (ii) representation learning, (iii) predictive modeling, and (iv) clinical translation. When coupled with prospective validation and rigorous benchmarking, these systems move the field toward actionable precision oncology, where hallmark-driven biology is quantitatively mapped to individualized care[89].

By operationalizing the new dimensions of cancer biology, TME complexity, cellular plasticity, epigenetic regulation, and microbiome interactions, and integrating them through multi-omics AI frameworks, modern oncology is transitioning from descriptive models to predictive, systems-level medicine. These advances lay the foundation for next-generation precision oncology, where AI-enabled insights directly inform patient-specific diagnostics and therapeutics[90].

Clinical Applications of Artificial Intelligence in Precision Oncology

The translation of AI from discovery science to clinical practice is reshaping oncology by enabling data-driven, individualized decision-making across the

cancer care continuum. By integrating multimodal data, spanning imaging, pathology, genomics, and longitudinal clinical records—AI systems provide quantitative, reproducible, and scalable tools that complement clinical expertise[91]. Below, we delineate the principal clinical domains in which AI is exerting transformative impact. The major clinical applications of AI across the oncology continuum, together with typical data types and translational outputs, are summarized in Table 4.

Collectively, the applications summarized in Table 6 demonstrate that AI is increasingly positioned across the full continuum of precision oncology, from early detection and histopathologic classification to prognosis, treatment selection, longitudinal monitoring, and clinical-trial optimization. Rather than serving as a single diagnostic adjunct, AI is emerging as an integrative clinical layer that links imaging, pathology, molecular profiling, and real-world patient data into more individualized and scalable cancer care pathways. However, the magnitude of its clinical impact will ultimately depend on prospective validation, interoperability with routine workflows, and responsible implementation in diverse patient populations.

Table 4. Clinical Applications of AI in Precision Oncology

Clinical domain	Scientific / Clinical objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Recommended Refs.
Early detection and screening	Detect cancer at earlier, more treatable stages	Deep learning, risk prediction models, multimodal classifiers	Mammography, CT, MRI, pathology, blood biomarkers, EHRs	Risk scores, lesion detection, screening alerts	May improve sensitivity, triage efficiency, and earlier diagnosis	92
Radiologic diagnosis	Classify lesions, identify tumor burden, and assist staging	CNNs, radiomics, vision transformers	CT, MRI, PET	Detection, segmentation, subtype classification, stage-related features	Enhances diagnostic consistency and supports non-invasive tumor characterization	93
Digital pathology	Improve histologic diagnosis, grading, and tumor characterization	CNNs, whole-slide image deep learning, transformers	Whole-slide images, multiplex pathology	Tumor detection, grading, subtype classification, microenvironment quantification	Reduces observer variability and links morphology to molecular phenotype	94
Molecular classification	Refine tumor taxonomy beyond morphology	Multimodal learning, autoencoders, feature fusion	Genomics, transcriptomics, methylation, proteomics	Molecular subtypes, pathway signatures, biomarker panels	Supports biologically informed diagnosis and treatment stratification	94
Prognosis and survival prediction	Estimate recurrence risk, progression, and survival probability	Survival ML, deep survival networks, multimodal prognostic models	Imaging, pathology, omics, clinical variables	Risk scores, recurrence models, survival curves	Improves risk-adapted follow-up and treatment intensity decisions	95
Therapy response prediction	Predict sensitivity or resistance to chemotherapy, targeted therapy, or radiotherapy	Multimodal deep learning, predictive classifiers, network-based AI	Omics, pathology, radiology, treatment history	Response probabilities, resistance signatures, treatment-ranking outputs	Supports treatment matching and reduces ineffective therapy exposure	96
Immunotherapy stratification	Predict benefit from immune checkpoint blockade and	ML classifiers, single-cell AI,	TMB, gene expression, scRNA-seq,	Response prediction, immune pheno-	Helps select patients more likely	97

Clinical domain	Scientific / Clinical objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Recommended Refs.
	characterize tumor–immune interactions	image-based immune profiling	pathology, radiomics	types, resistance biomarkers	to benefit from immunotherapy	
Minimal residual disease and monitoring	Detect early relapse, track tumor evolution, and monitor treatment effect	Longitudinal predictive modeling, anomaly detection, multimodal monitoring	ctDNA, serial imaging, lab values, EHRs	Early recurrence alerts, dynamic response tracking	Enables earlier intervention and more adaptive surveillance strategies	98
Personalized treatment planning	Recommend individualized therapeutic strategies based on integrated patient data	Decision-support systems, knowledge graphs, multimodal predictive AI	Clinical variables, genomics, pathology, imaging	Ranked treatment options, individualized risk–benefit profiles	Advances patient-specific precision oncology decision-making	70,99
Clinical trial matching and optimization	Match patients to suitable trials and improve enrollment efficiency	NLP, predictive modeling, eligibility classifiers	EHRs, pathology, genomics, trial criteria	Trial matches, enrichment strategies, recruitment support	Improves access to precision trials and supports biomarker-enriched study designs	99
Drug discovery and repurposing	Accelerate target identification, lead generation, and therapeutic optimization	Generative AI, graph learning, structure-based models	Molecular structures, target data, omics, screening datasets	Targets, candidate compounds, repurposing hypotheses	Shortens development timelines and improves translational prioritization	100
Clinical workflow support	Reduce burden of data interpretation and improve consistency of care	NLP, summarization systems, triage models, integrated decision support	EHRs, reports, pathology, radiology, treatment histories	Structured summaries, triage flags, workflow recommendations	Increases efficiency and may support safer, more standardized care delivery	70

Diagnosis

AI has substantially advanced cancer detection and classification through the analysis of radiological and histopathological data. In radiomics, machine learning and deep learning models extract high-dimensional quantitative features from imaging modalities such as CT, MRI, and PET, capturing tumor morphology, texture, heterogeneity, and spatial context beyond human visual perception. These features enable early detection, tumor characterization, and differentiation between benign and malignant lesions, often with performance comparable to or exceeding expert radiologists[101].

In digital pathology, convolutional neural networks (CNNs) and vision transformers applied to whole-slide images (WSIs) can identify malignant cells, grade tumors, and classify histological subtypes with high accuracy. AI models also quantify tumor-infiltrating lymphocytes, stromal content, mitotic activity, and other microenvironmental features, linking morphology to underlying molecular states. Increasingly, integrated radiopathomic approaches combine imaging and histology with molecular data to generate comprehensive diagnostic profiles, thereby enhancing diagnostic precision and reducing inter-observer variability[102].

Prognosis

Accurate prediction of clinical outcomes is central to precision oncology. AI-driven prognostic models leverage multi-omics data,

imaging features, and clinical variables to estimate survival, recurrence risk, and disease progression with improved discriminatory power over traditional staging systems[102].

Machine learning algorithms, including ensemble methods and deep neural networks, are trained on large, annotated cohorts to identify prognostic signatures that capture tumor aggressiveness and patient-specific risk. Integration of time-to-event modeling (e.g., deep survival networks) enables dynamic prediction of outcomes over the disease course[103]. Additionally, AI models can incorporate longitudinal data, such as serial imaging or liquid biopsy measurements, to provide real-time risk assessment and monitor treatment response. Importantly, explainable AI techniques facilitate the interpretation of prognostic models by identifying key features driving predictions, thereby enhancing clinical trust and enabling biological insight into determinants of disease outcome[104].

Therapeutic Decision-making

AI is increasingly being deployed to support treatment selection and personalization, addressing the complexity of matching patients to optimal therapies in the context of tumor heterogeneity. By integrating genomic alterations, transcriptomic profiles, and clinical data, AI systems can predict drug sensitivity and resistance, guiding the selection of targeted therapies, chemotherapy regimens, and immunotherapies[105].

Decision-support platforms utilize knowledge graphs, network-based inference, and machine learning classifiers to map patient-specific molecular profiles to actionable therapeutic options. In immuno-oncology, AI models incorporating tumor mutational burden, neoantigen landscape, and immune signatures predict response to immune checkpoint inhibitors, thereby refining patient selection[106]. Furthermore, AI enables adaptive treatment strategies, where therapeutic decisions are continuously updated based on real-time data, including imaging and circulating tumor DNA. Such approaches move beyond static treatment protocols toward dynamic, learning healthcare systems, in which each patient's data informs ongoing optimization of care[107].

Drug Discovery and Development

AI is revolutionizing the drug discovery pipeline by accelerating target identification, compound design, and preclinical validation. In target discovery, machine learning models analyze multi-omics datasets to identify driver genes, signaling pathways, and synthetic lethal interactions that represent potential therapeutic targets[108].

In AI-guided drug design, deep learning models, including generative adversarial networks (GANs) and reinforcement learning frameworks, can generate novel chemical structures with optimized pharmacokinetic and pharmacodynamic properties. Structure-based AI approaches predict protein–ligand interactions, enabling rapid screening of candidate compounds and reducing reliance on costly experimental assays[109].

AI is also applied to drug repurposing, identifying existing compounds with potential efficacy in new cancer indications by analyzing molecular similarity and pathway overlap. During clinical development, AI enhances trial design through patient stratification, biomarker identification, and prediction of adverse events, thereby improving trial efficiency and success rates [109]. Major applications of AI across the oncology drug-development pipeline, from target discovery to trial optimization, are summarized in Table 5.

Table 5. Applications of AI in Cancer Drug Discovery and Development

Drug-development stage	Scientific objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Recommended Refs.
Target identification	Identify driver genes, pathway dependencies, synthetic lethal partners, and tumor-selective vulnerabilities	Machine learning, graph neural networks, network propagation, knowledge graphs	Genomics, transcriptomics, proteomics, CRISPR screens, pathway databases	Prioritized targets, dependency maps, biomarker-linked vulnerabilities	Improves biological target selection and reduces attrition in early oncology pipelines	110
Target validation	Determine whether candidate targets are biologically and clinically actionable	Multimodal predictive modeling, causal inference, graph learning	Functional genomics, cell-line perturbation data, patient multi-omics, pathology	Target-confidence scores, context-specific validation, patient subgroups most likely to benefit	Supports more rigorous go/no-go decisions before medicinal chemistry investment	72
Virtual screening	Rapidly identify candidate compounds likely to bind a target or perturb a cancer-relevant pathway	Deep learning, structure-based learning, docking acceleration, transformer models	Small-molecule libraries, protein structures, ligand–target interaction data	Ranked hit lists, binding predictions, shortlist of candidate molecules	Greatly accelerates hit discovery and lowers experimental screening burden	111
De novo molecular design	Generate novel anti-cancer compounds with optimized biological and chemical properties	Generative AI, reinforcement learning, diffusion models, GANs	Molecular graphs, SMILES strings, structure–activity data	Novel chemical scaffolds, optimized lead candidates, structure proposals	Enables rapid exploration of chemical space beyond conventional medicinal chemistry workflows	112,113
Lead optimization	Improve potency, selectivity, solubility, stability, and developability of initial hits	Multi-parameter optimization, active learning, Bayesian optimization	Structure–activity relationships, physicochemical properties, assay results	Optimized lead series, ranked analogs, design rules	Shortens iteration cycles and supports rational prioritization of candidates	114
ADMET prediction	Anticipate absorption, distribution, metabolism, excretion, and toxicity liabilities early	Supervised ML, deep learning, ensemble models	Molecular descriptors, historical ADMET datasets, toxicology data	ADMET risk profiles, compound filtering, toxicity flags	Helps eliminate unsuitable compounds earlier and reduces late-stage failure	115
Drug repurposing	Identify approved or investigational agents with activity in new cancer contexts	Similarity learning, network medicine, multimodal ranking, NLP-assisted mining	Drug–target databases, gene-expression signatures, EHRs, literature corpora	Repurposed candidate drugs, indication expansion hypotheses	Can accelerate translation because safety data may already exist for candidate agents	116
Biomarker-guided drug matching	Link molecular profiles to likely therapeutic sensitivity or resistance	Multimodal deep learning, survival models, knowledge-guided ranking	Genomics, transcriptomics, proteomics, pathology, radiology, clinical data	Therapy-response predictions, companion biomarker panels, resistance signatures	Enables precision treatment selection and more efficient trial enrollment	27
Combination therapy design	Predict synergistic combinations and overcome adaptive resistance	Graph learning, network pharmacology, reinforcement learning	Drug-response matrices, pathway maps, multi-omics, perturbation screens	Ranked drug combinations, synergy predictions, resistance-aware regimens	Supports rational combination design in refractory or heterogeneous tumors	117,118

Drug-development stage	Scientific objective	AI approach	Typical data type(s)	Main output(s)	Clinical / translational relevance	Recommended Refs.
Clinical-trial optimization	Improve patient stratification, endpoint prediction, and adaptive trial efficiency	Predictive modeling, digital biomarkers, NLP, survival AI	EHRs, imaging, omics, pathology, adverse-event data	Eligibility models, enrichment strategies, endpoint support, risk scores	May improve trial success rates by matching therapies to biologically relevant subgroups	99
Antibody-drug conjugates (ADCs) and biologics	Optimize antigen selection, antibody engineering, payload choice, and linker design	Graph-based learning, structure prediction, multimodal AI	Target-expression data, structural biology, internalization data, multi-omics	Tumor-selective antigens, optimized ADC candidates, developability predictions	Particularly relevant for next-generation precision therapeutics	119
Cancer immunomodulatory small molecules	Design compounds targeting immune checkpoints, antigen presentation, or TME metabolism	Generative AI, virtual screening, multi-objective optimization	Immune pathway data, structural models, chemoinformatics, multi-omics	Immunomodulatory lead molecules, target-specific small-molecule candidates	Expands precision immuno-oncology beyond antibodies alone	120

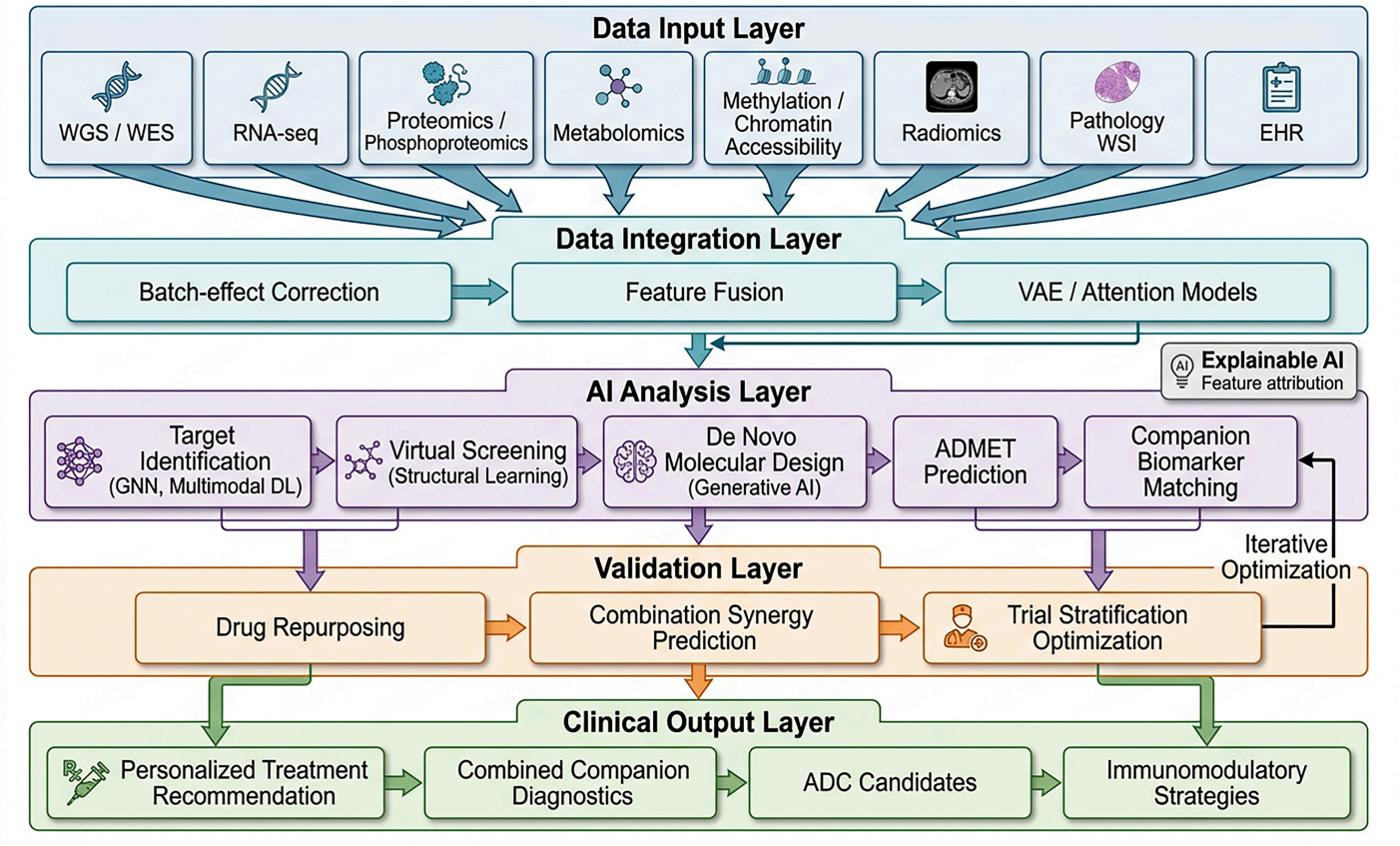


Figure 4. Multi-Omics Integration Pipeline in AI-Based Oncology. Illustrates an end-to-end AI-driven multi-omics workflow integrating molecular, structural, imaging, and real-world clinical data to support target prioritization, candidate optimization, efficacy prediction, clinical-trial design, and ultimately individualized treatment.AI, artificial intelligence; WGS, whole-genome sequencing; WES, whole-exome sequencing; WSI, whole-slide imaging; EHR, electronic health records; VAE, variational autoencoder; GNN, graph neural network; DL, deep learning; ADMET, absorption, distribution, metabolism, excretion, and toxicity; ADC, antibody–drug conjugate.

Collectively, these applications show that AI is no longer confined to isolated prediction tasks but is increasingly embedded across the full oncology drug-development continuum. By integrating molecular profiling, structural biology, pharmacology, and clinical data, AI

can improve target prioritization, accelerate candidate optimization, refine biomarker-linked therapy selection, and support more adaptive and efficient clinical development [121].

Across diagnosis, prognosis, therapeutic decision-making, and drug discovery, AI is redefining the clinical landscape of oncology. By transforming heterogeneous biomedical data into actionable knowledge, AI bridges the gap between molecular complexity and clinical application. As these technologies mature and integrate with routine clinical workflows, they hold the promise of delivering truly personalized, data-driven cancer care, thereby advancing the realization of next-generation precision oncology.

Challenges and Limitations

Despite the transformative promise of AI in oncology, its translation into routine clinical practice remains constrained by substantial methodological, technical, ethical, and regulatory challenges. These limitations are not merely operational obstacles but fundamental issues that shape the reliability, generalizability, and clinical legitimacy of AI-enabled precision oncology. A critical appraisal of these challenges is therefore essential if AI is to move beyond proof-of-concept studies toward robust, equitable, and clinically trustworthy implementation. The major translational barriers facing AI in oncology, together with practical mitigation strategies, are summarized in Table 4.

Table 6. Challenges in AI-Based Oncology and Potential Solutions

Challenge	Scientific / practical concern	Impact on oncology research and care	Potential solution(s)	Recommended Refs.
Data bias and underrepresentation	Training datasets often overrepresent specific ethnic, geographic, socioeconomic, or institutional populations	Reduces model fairness and external validity; may worsen disparities in diagnosis, prognosis, and treatment selection	Build diverse multicenter datasets; require subgroup performance reporting; apply fairness auditing and bias mitigation strategies	122
Data heterogeneity and lack of standardization	Variation in imaging protocols, sequencing platforms, pathology preparation, annotation standards, and clinical documentation	Weakens reproducibility and cross-institutional generalizability; complicates multimodal integration	Harmonization pipelines, common data models, robust preprocessing standards, domain adaptation methods	123,124
Small sample size relative to data dimensionality	Many oncology datasets remain high-dimensional but modest in cohort size, especially for rare cancers and multimodal studies	Increases overfitting and unstable feature selection; limits biologically meaningful generalization	Transfer learning, self-supervised learning, federated learning, external validation, feature regularization	125,126
Black-box behavior / poor interpretability	Complex deep learning models may generate accurate predictions without transparent reasoning	Limits clinician trust, regulatory acceptance, and biological interpretability	Use explainable AI (XAI), biologically constrained models, feature attribution tools, and hybrid mechanistic–AI approaches	127,128
Limited prospective and real-world validation	Many AI oncology studies remain retrospective, single-center, or benchmark-driven	Strong internal performance may not translate into real-world clinical benefit	Prospective multicenter trials, real-world testing, pragmatic implementation studies, time-dependent validation	103,129

Challenge	Scientific / practical concern	Impact on oncology research and care	Potential solution(s)	Recommended Refs.
Poor transportability across institutions	Models trained in one setting may fail under different scanners, populations, workflows, or pathology practices	Restricts adoption and may cause unsafe or misleading outputs outside the original environment	External validation, recalibration, domain generalization, continuous monitoring after deployment	130,131
Missing data and incomplete multimodal profiles	Many patients lack complete omics, imaging, or clinical data across all relevant time points	Reduces model robustness and can bias downstream predictions	Multimodal fusion with missing-modality handling, probabilistic imputation, uncertainty-aware learning	132,133
Label quality and annotation variability	Ground-truth labels may be noisy, inconsistent, or dependent on expert interpretation	Limits model accuracy and reproducibility, especially in pathology and radiology	Consensus annotation, active learning, pathology/radiology adjudication, weak-supervision frameworks	134
Clinical workflow integration barriers	AI tools are often not designed around existing pathology, radiology, molecular, or EHR workflows	Slows uptake even when models are accurate; may increase workload rather than reduce it	User-centered design, interoperability standards, integration with EHR/PACS/LIS systems, clinician-in-the-loop systems	85,135
Regulatory uncertainty	Adaptive or continuously learning models do not fit traditional approval frameworks	Delays clinical translation and raises uncertainty about monitoring and updating approved tools	Lifecycle regulation, post-market surveillance, locked-model deployment with versioning, predefined update pathways	136
Ethical and privacy concerns	Oncology AI often relies on highly sensitive imaging, molecular, and longitudinal health data	Risks include re-identification, consent ambiguity, inequitable use, and loss of trust	Privacy-preserving learning, federated learning, strong governance, transparent consent and data stewardship models	137,138
Accountability and medico-legal ambiguity	Responsibility may be unclear when AI-guided decisions contribute to harmful outcomes	Limits adoption by institutions and clinicians; complicates legal and ethical oversight	Clarify clinician oversight, establish accountability frameworks, define decision-support vs. autonomous roles	139,140
Biological non-causality of predictions	Many models identify correlations rather than mechanistic drivers	Can produce clinically useful predictions without explanatory depth, limiting translational insight	Combine AI with causal inference, systems biology, functional validation, and experimental perturbation data	141,142
Model drift over time	Changes in practice patterns, treatment regimens, devices, and patient populations alter input distributions	Performance may silently deteriorate after deployment	Continuous auditing, drift detection, scheduled recalibration, prospective performance dashboards	143
Resource and infrastructure	Low-resource settings may lack digitization, compute	Risks widening the global precision-oncology gap	Cloud-enabled platforms, lightweight models, global	144,145

Challenge	Scientific / practical concern	Impact on oncology research and care	Potential solution(s)	Recommended Refs.
inequalities	capacity, molecular testing, or standardized data systems		consortia, resource-stratified deployment strategies	

Although AI has demonstrated considerable promise across the oncology continuum, meaningful clinical translation will depend on solving challenges related to representativeness, interpretability, validation, interoperability, and governance. In this context, the future success of AI-based oncology will rely as much on rigorous implementation science and ethical stewardship as on algorithmic innovation.

Data Bias, Heterogeneity, and Generalizability

One of the most significant limitations of AI in oncology arises from the nature of the data on which models are trained. Cancer datasets are inherently heterogeneous, reflecting differences in patient demographics, tumor biology, sequencing platforms, imaging protocols, clinical workflows, and annotation standards. Such heterogeneity may enrich biological diversity, but it also introduces substantial technical variability that can confound model training and reduce reproducibility across institutions[146]. A related concern is data bias, which can occur at multiple levels. Many publicly available training datasets disproportionately represent specific populations, often from high-resource centers and predominantly Western cohorts, leading to underrepresentation of ethnic, geographic, and socioeconomic diversity[147]. As a result, AI models trained on these datasets may perform well internally yet fail when applied to broader or underrepresented populations, thereby amplifying existing disparities in cancer care. Bias may also arise from imbalanced class distributions, such as overrepresentation of common tumor types, stages, or treatment responses, which can distort model calibration and impair detection of rare but clinically important phenotypes[148].

In addition, multimodal oncology datasets frequently contain missing values, inconsistent follow-up intervals, variable sample quality, and batch effects, all of which complicate integrative modeling. Although imputation methods and normalization frameworks can mitigate some of these issues, they do not fully eliminate the risk of spurious associations. Consequently, the challenge is not simply to accumulate larger datasets, but to develop high-quality, harmonized, and representative datasets that support clinically generalizable AI systems[149].

Lack of Interpretability and the "Black-box" Problem

A major barrier to clinical trust in AI is the limited interpretability of many high-performing models, particularly deep learning architectures. While such models can achieve impressive predictive accuracy, their internal decision-making processes are often opaque, giving rise to the well-known "black-box" problem. In oncology, where decisions may directly affect diagnosis, treatment selection, and survival outcomes, this lack of transparency poses a substantial challenge[150]. Clinicians are unlikely to rely on AI recommendations if the rationale behind a prediction cannot be clearly explained, especially when those predictions contradict established clinical judgment or guidelines. Similarly, regulatory bodies and ethics committees may be hesitant to approve AI-driven tools whose outputs cannot be

meaningfully interrogated. This issue is particularly acute in settings such as histopathology, radiomics, and multi-omics integration, where AI models may identify predictive patterns that are statistically robust but biologically non-intuitive[151].

The growing field of explainable AI (XAI) seeks to address this limitation by developing methods that highlight influential features, assign importance scores, or visualize regions of interest contributing to a given prediction. However, many XAI approaches remain approximate rather than truly mechanistic, and the distinction between explanation and post hoc rationalization remains a matter of active debate. For AI to gain broader acceptance in oncology, future systems must balance predictive power with interpretability, biological plausibility, and clinical transparency[152].

Ethical, Legal, and Social Concerns

The deployment of AI in precision oncology also raises substantial ethical and societal concerns. Chief among these are issues related to privacy, informed consent, data ownership, algorithmic fairness, and accountability. Multi-omics datasets, digital pathology images, and longitudinal clinical records are deeply personal and often identifiable, making secure storage, sharing, and governance of such data a matter of critical importance[152]. Ethical concerns also extend to the risk of algorithmic discrimination. If AI systems are trained on non-representative datasets or encode historical inequities embedded in healthcare systems, they may generate biased predictions that systematically disadvantage certain patient groups. In oncology, this could manifest as misclassification of disease risk, inappropriate treatment prioritization, or unequal access to precision therapies[153].

Questions of responsibility and liability are equally important. When an AI-driven recommendation contributes to an adverse clinical outcome, it is often unclear who is responsible: the software developer, the institution, the clinician, or the regulatory framework that authorised its deployment. Such ambiguity complicates integration into real-world clinical settings and underscores the need for robust ethical oversight and governance structures[154]. Moreover, the increasing use of generative AI and automated decision-support systems raises concerns about overreliance on technology, erosion of clinician autonomy, and potential dehumanization of care. AI should therefore be positioned not as a replacement for clinical expertise, but as an augmentative tool that supports, rather than supplants, physician judgment[155].

Barriers to Clinical Validation and Implementation

Perhaps the most important translational challenge is the persistent gap between algorithm development and clinical validation. A large proportion of AI studies in oncology remain retrospective, single-center, and performed under idealized conditions, with limited assessment of external validity. Models that perform well in curated research datasets often degrade substantially in real-world clinical environments, where data are noisier, workflows are less standardized, and patient populations are more heterogeneous[156]. Prospective validation, multicenter benchmarking, and randomized clinical studies of AI-assisted decision-making remain relatively scarce. Without such evidence, it is difficult to determine whether AI tools improve meaningful endpoints such as diagnostic accuracy, survival, cost-effectiveness, or quality of care. In addition,

integration into clinical workflows requires interoperability with hospital information systems, pathology and radiology platforms, and molecular diagnostics pipelines—technical hurdles that are often underestimated[85]. Regulatory approval presents another major barrier. Unlike static medical devices, many AI systems are adaptive and may evolve as new data are incorporated. This creates challenges for conventional regulatory models, which are not well suited to continuously learning systems. Standardization of performance metrics, reporting guidelines, and post-deployment monitoring is therefore essential [157].

Finally, implementation depends not only on technical validity but also on clinical usability, workforce training, and institutional readiness. Even the most accurate AI model will have limited impact if clinicians lack confidence in its use, if workflows are disrupted, or if health systems lack the infrastructure to support it. Taken together, these challenges underscore that the future of AI in oncology will depend not only on algorithmic sophistication but also on data quality, interpretability, fairness, ethical governance, and rigorous clinical validation. The path toward AI-enabled precision oncology is therefore not merely a computational challenge, but a multidisciplinary endeavor requiring close collaboration among oncologists, pathologists, bioinformaticians, data scientists, ethicists, regulators, and patients. Addressing these limitations systematically will be essential to ensure that AI evolves into a clinically reliable, equitable, and genuinely transformative force in cancer medicine.

FUTURE PERSPECTIVES

The convergence of AI with oncology is poised to redefine cancer care through increasingly predictive, adaptive, and patient-specific frameworks. As the field transitions from data-rich to intelligence-driven paradigms, several emerging directions are expected to shape the future of next-generation precision oncology. A particularly transformative concept is the development of AI-enabled digital twins in oncology. These computational models integrate multi-omics, imaging, clinical, and longitudinal patient data to create virtual replicas of individual tumors, capable of simulating disease progression and therapeutic response. Digital twins enable *in silico experimentation*, allowing clinicians to test multiple treatment strategies and predict outcomes before clinical implementation. Such approaches hold promise for optimizing therapy selection, minimizing toxicity, and accelerating personalized care.

In parallel, the integration of AI into clinical workflows is advancing towards real-time precision medicine. Continuous data streams from electronic health records, imaging, and molecular diagnostics can be processed by AI systems to provide dynamic risk assessment and treatment recommendations. This real-time adaptability is particularly relevant in oncology, where tumor evolution and therapeutic resistance require ongoing recalibration of treatment strategies. AI-driven decision-support systems may thus enable a shift from static treatment protocols to continuously learning and adaptive care models.

Another critical frontier is the incorporation of wearable technologies and real-world data into AI frameworks. Wearable devices capable of monitoring physiological parameters, physical activity, and treatment-related toxicity provide a continuous, patient-centered data source. When integrated with clinical and molecular data, these inputs allow

AI models to capture patient-specific variability beyond the tumor itself, including host responses, lifestyle factors, and treatment tolerability. This holistic approach supports more accurate prediction of outcomes and enhances patient engagement in care.

Furthermore, AI is expected to drive the development of adaptive therapeutic strategies, in which treatment regimens are dynamically modified in response to evolving tumor and patient characteristics. By integrating real-time molecular data, such as circulating tumor DNA, and clinical indicators, AI systems can detect early signs of resistance and recommend timely therapeutic adjustments. This paradigm aligns with the concept of cancer as a dynamic ecosystem, requiring flexible and responsive treatment approaches rather than fixed regimens. Collectively, these advances signal a transition toward intelligent, data-integrated oncology systems, where AI not only supports clinical decision-making but actively shapes the trajectory of patient care. The successful realization of these future directions will depend on continued progress in data integration, model interpretability, regulatory frameworks, and clinical validation.

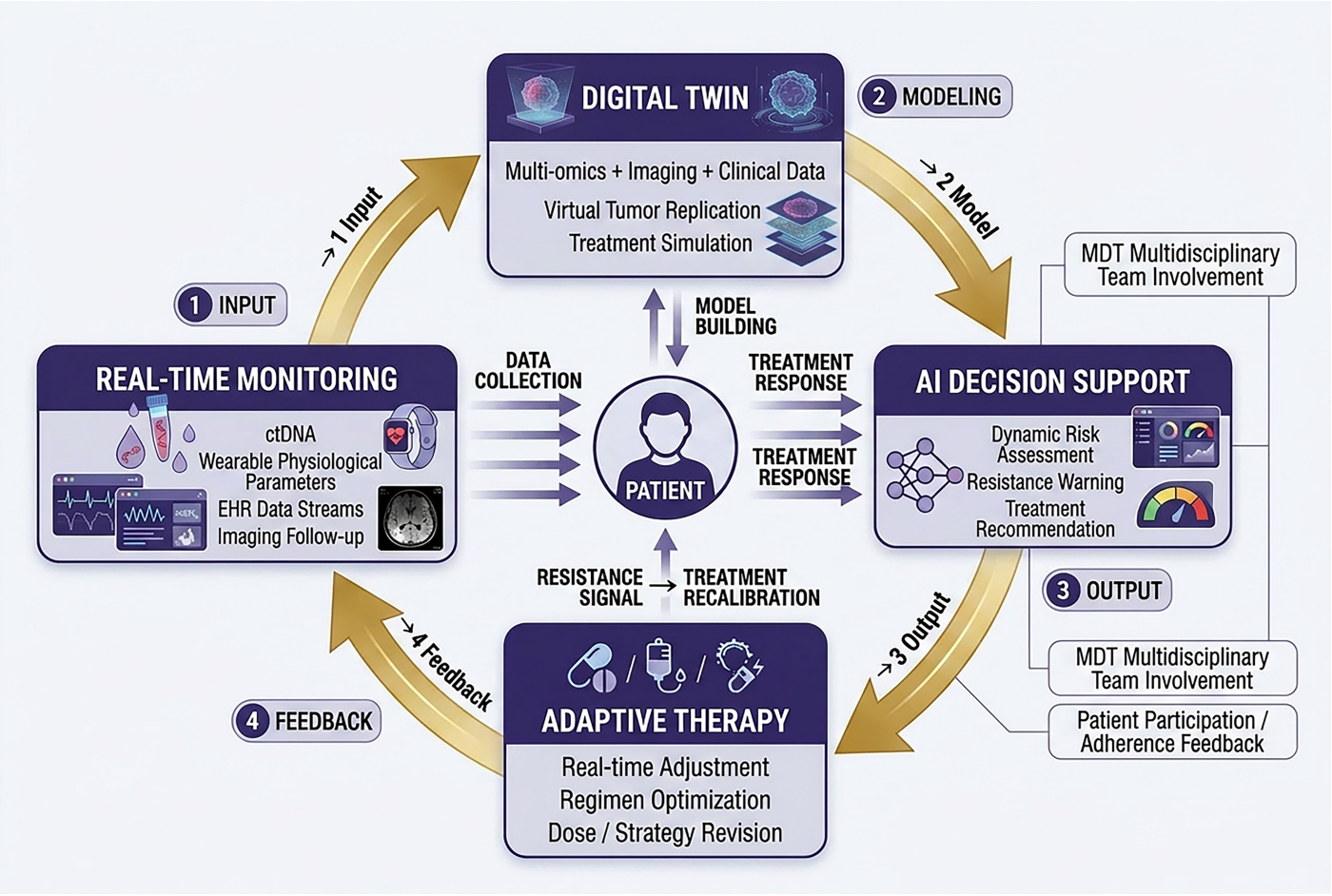


Figure 5. Next-Generation Precision Oncology: AI, Digital Twins, and Adaptive Therapies. Presents a closed-loop precision-oncology model in which a patient-specific digital twin integrates multi-omics, imaging, and clinical data; AI provides risk and treatment recommendations; adaptive therapy modifies treatment in real time; and ctDNA, wearable, and EHR monitoring continuously feed new information back into the decision system. AI, artificial intelligence; MDT, multidisciplinary team; EHR, electronic health record; ctDNA, circulating tumor DNA.

CONCLUSION

Artificial intelligence has emerged as a transformative force in oncology, offering unprecedented capabilities to decode the complexity underlying the hallmarks of cancer. By integrating high-dimensional, multimodal

data, AI enables the transition from descriptive models of tumor biology to predictive, systems-level frameworks that capture the dynamic interplay of genetic, epigenetic, cellular, and microenvironmental factors. The evolution of the hallmarks framework from a set of static biological traits to a dynamic, interconnected network of processes aligns closely with the strengths of AI-driven approaches. Through multi-omics integration, network modeling, and real-time analytics, AI facilitates the translation of hallmark-based concepts into clinically actionable insights, bridging the gap between molecular mechanisms and patient outcomes. Looking forward, the integration of AI with emerging paradigms such as digital twins, adaptive therapies, and real-world data streams is expected to further advance the field toward next generation precision oncology. However, the realization of this vision will require careful attention to challenges related to data quality, interpretability, ethical governance, and clinical validation. In this context, AI should be viewed not merely as a technological tool but as a conceptual framework that reshapes our understanding of cancer—from a static disease defined by discrete hallmarks to a dynamic, evolving system amenable to intelligent intervention.

DECLARATIONS

Data Availability Statement

No new data were generated or analyzed in this review article.

Funding

The authors declare that no funding was received for this work.

Ethics Approval and Consent to Participate

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

Use of Generative AI

Generative AI tools were used only for language improvement and proofreading. The authors reviewed and approved the final content and take full responsibility for the manuscript.

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