Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

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REVIEW

Artificial Intelligence–Enabled Multi-Omics for Predicting Immune Checkpoint Inhibitor Response and Resistance

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Abstract: Immune checkpoint inhibitors (ICIs) have reshaped oncology, yet overall response rates remain modest and resistance is common, driven by tumor heterogeneity and evolving tumor–immune crosstalk. Established biomarkers (PD-L1, tumor mutational burden, microsatellite instability) provide incomplete prediction. Multi-omics profiling across genomic, transcriptomic, proteomic, epigenomic, metabolomic and microbiomic layers offers a systems-level view of malignant and immune states, uncovering determinants of ICI efficacy such as lineage plasticity, stromal remodeling, immunometabolic reprogramming and microbiome-associated immune modulation. Artificial intelligence (AI) is uniquely positioned to fuse these heterogeneous data, learn non-linear cross-layer signatures, and enable interpretable predictions using approaches such as SHAP and Grad-CAM. Representative models link routine histology or imaging to molecular phenotypes, stratify patients beyond single biomarkers, and may nominate rational combinations that target oncogenic pathways, lactate-driven immune suppression, or the gut microbiome. In this narrative review, we synthesize recent AI–multi-omics advances for response modeling, immune-relevant tumor subtyping, and clinical translation, including radiomics/pathomics integration and liquid-biopsy–based monitoring, as well as emerging applications in toxicity risk prediction. We also discuss barriers to implementation—platform heterogeneity, limited prospective validation, bias, interpretability and cost—and outline future directions, including single-cell and spatial multi-omics integration, federated learning and generative modeling to improve robustness and equity of precision immunotherapy.

Keywords: artificial intelligence, multi-omics, immunotherapy, cancer, biomarkers

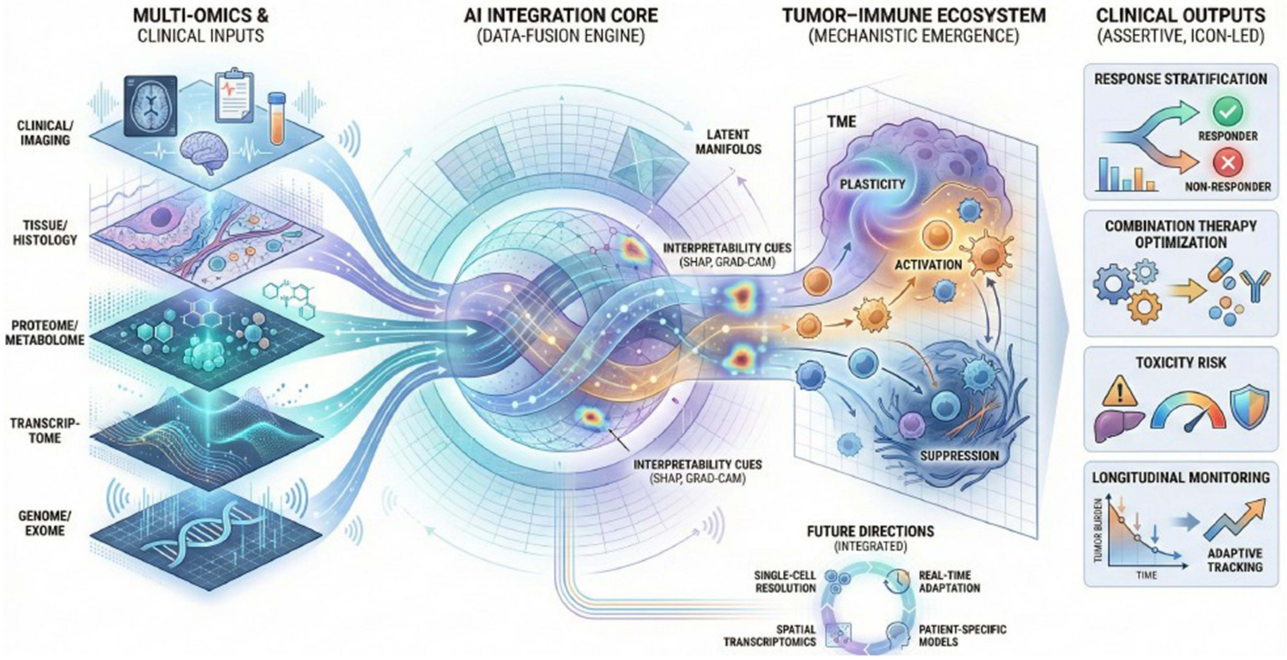
Introduction

Immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1, and CTLA-4 have reshaped oncology by restoring anti-tumor immunity, enabling durable remissions in subsets of patients with melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and other malignancies.[1–3] However, overall response rates remain modest (~20–40%), and both primary and acquired resistance are common.[1,4] These failures reflect profound tumor heterogeneity, diverse immune-evasion programs, and dynamic tumor–immune crosstalk within the tumor microenvironment (TME).[5,6] Conventional biomarkers—including tumor PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI)—provide only limited predictive accuracy and often miss the multifactorial determinants of response, motivating integrative, high-dimensional strategies for precision immunotherapy.[7,8]

Multi-omics profiling, spanning genomics, transcriptomics, proteomics, epigenomics, metabolomics, and microbiomics, offers a layered systems view of malignant cells and immune contexture and has uncovered mechanisms that shape ICI efficacy across cancer types.[8–10] In diffuse large B-cell lymphoma, genomic alterations such as TP53 and CREBBP mutations correlate with non-response, whereas responders often exhibit transcriptomic programs consistent with immune activation and cytotoxic T-cell engagement.[11,12] In NSCLC, single-cell transcriptomics has traced some tumors to alveolar type II origins and revealed lineage plasticity driven by pathways such as SOX2/WNT/YAP, fostering immunosuppressive TMEs and ICI resistance.[13,14] Epigenomic dysregulation can further promote immune escape; for

https://doi.org/10.2147/JMDH.S572089
Received: 4 October 2025
Accepted: 27 January 2026
Published: 26 February 2026

Graphical Abstract



example, enhancer activation in nasopharyngeal carcinoma upregulates oncogenic programs (eg, CACNA2D1) linked to immune evasion.[15] Metabolomic reprogramming also contributes, including lactate-associated lactylation that reinforces suppressive states.[16] The microbiome adds an additional regulatory layer: gut microbial communities can modulate systemic immunity and ICI responsiveness, with responder–non-responder differences in taxa composition (including enrichment patterns involving Bacteroides species) and consistent evidence that antibiotic-mediated microbiome disruption impairs outcomes.[17,18]

Artificial intelligence (AI), spanning machine learning (ML) and deep learning (DL), is well suited to integrating heterogeneous multi-omic data and extracting non-linear, cross-layer signatures that conventional statistics often miss.[19,20] AI-driven "pathomics" can predict MSI status in colorectal cancer with AUCs around 0.85 by linking morphologic patterns to underlying molecular programs.[21] In melanoma, a LASSO-regression model combining exome sequencing and RNA-seq outperformed TMB alone, with AUCs near 0.7 in training and ~0.64 on independent testing.[22] Importantly, interpretability tools such as SHAP and Grad-CAM can connect predictions to specific features (eg, mutations, expression programs, or informative histologic regions), improving mechanistic insight and clinical trust.

Early translational studies underscore the promise of AI-enabled multi-omics for patient stratification and therapeutic design. In NSCLC, integrative models incorporating genomic, transcriptomic, and radiomic inputs improve response prediction relative to unimodal approaches.[23,24] In hepatocellular carcinoma and bladder cancer, extreme heterogeneity and sampling constraints limit single-biopsy biomarkers, accelerating interest in multi-omic liquid biopsies for real-time monitoring of evolving disease.[25,26] Integrative AI–multi-omics frameworks aim to refine tumor subtypes and nominate tailored combinations, including pairing ICIs with targeted agents addressing FGFR/EGFR pathway alterations; research trends also highlight growing interest in multi-target strategies and microbiome modulation to overcome resistance.

This narrative review synthesizes mechanistic foundations and clinical applications of AI–multi-omics approaches for predicting ICI responses. We qualitatively integrate findings across platforms and tumor types, highlight state-of-the-art predictive models, discuss translational challenges, and outline future directions including single-cell integration paradigms, federated learning, and cross-disciplinary innovation, with explicit attention to gaps in validation and equity.

Biological Foundations of ICI Response and Multi-Omics Insights

Molecular Mechanisms of ICI Efficacy and Resistance

By blocking inhibitory signaling (PD-1/PD-L1 and CTLA-4 axes), ICIs restore cytotoxic T-cell function.[27] Efficacy nevertheless varies because tumors can induce T-cell dysfunction (exhaustion) and/or physically exclude immune cells from tumor nests, and because TMEs differ in stromal and immune composition.[28,29] In NSCLC, single-cell transcriptomics traces subsets of tumors to alveolar progenitor origins and implicates lineage plasticity driven by developmental programs such as SOX2/WNT/YAP.[30] This plasticity fosters immunosuppressive niches enriched for cancer-associated fibroblasts and macrophages whose reciprocal interactions impede T-cell infiltration and effector function, promoting immune evasion across immune-editing phases.[31] These datasets also highlight potential vulnerabilities: specific immune and stromal subsets, including $CXCL13^{+}$ $CD8^{+}$ T cells and antigen-presenting fibroblasts, are enriched in "hot," inflamed tumors and may be leveraged to strengthen anti-tumor immunity.[32]

The gut microbiome provides an additional systemic control point. In some settings, fecal microbiota transplantation from immunotherapy responders enhances anti-tumor T-cell activity in recipients, supporting a functional role for commensals and microbe-derived metabolites, while also underscoring that non-optimized transplantation could introduce or amplify immunosuppressive elements.[33,34] In NSCLC, metagenomic profiling links response to greater abundance of taxa such as Bacteroides (eg, Bacteroides caccae) and Prevotella, whereas antibiotic exposure can reduce microbial diversity and impair ICI efficacy by depleting beneficial taxa or enriching pathways that suppress immunity.[35,36]

In RCC, large transcriptomic cohorts (including datasets from >1000 patients) integrated with single-cell and spatial profiling reveal outcome-linked immune–tumor crosstalk.[37] Responders are characterized by pro-inflammatory macrophages engaging exhausted $CD8^{+}$ T cells and by patient-specific HLA allele variants that preferentially present particular neoantigens.[37] Non-responding tumors more often activate alternative immunosuppressive programs.[38] Notably, machine-learning analyses of HLA profiles identify allele "signatures" that favor high-quality neoantigen presentation and predict improved outcomes, underscoring the importance of HLA genotype and neoantigen landscape in shaping ICI success.[39]

Tumor genetics can further constrain benefit. In gastrointestinal cancers, loss-of-function alterations in CREBBP and TP53 are enriched in non-responders to PD-1 blockade, likely through effects on antigenicity and immune-related signaling, with context dependence that may vary by PD-L1 expression in the TME.[40,41] Beyond DNA sequence, epigenomic and metabolic reprogramming contributes to resistance: lactate accumulation can drive histone lactylation, inhibit T-cell function, and associate with resistance to both ICIs and radiotherapy, consistent with metabolite-to-chromatin feedback loops that reinforce immune suppression.[42,43] In bladder cancer, multi-omics assays also enable immune-relevant subclassification; for example, DNA methylation profiling from liquid biopsy samples can distinguish luminal versus basal subtypes with distinct immune landscapes and differential ICI sensitivity, informing treatment selection.[44]

Taken together, these mechanisms define a continuum from "hot" tumors—high neoantigen load, inflamed TME, and robust T-cell infiltration—to "cold" tumors that exhibit immune exclusion or suppression due to dense stroma, high cancer cell stemness, particular microbiome configurations, or immunosuppressive metabolites. Hot tumors are generally more responsive to ICIs, whereas cold tumors often require combination strategies to convert the TME into an immune-permissive state (Figure 1 and Table 1).

Tumor Heterogeneity and Cancer Stemness in Immune Evasion

Intratumoral heterogeneity enables cancers to adapt under immune pressure, as distinct subclones deploy different genetic and phenotypic escape routes, undermining uniform responses to ICIs.[55,56] Cancer stemness further amplifies resistance: stem-like tumor cells with self-renewal, quiescence, and multilineage potential can persist despite immune attack and regenerate disease.[57] Quantitative stemness metrics, including an mRNA expression–based stemness index (mRNAsi) and algorithms such as CytoTRACE, link elevated stemness to immunosuppressive microenvironments and attenuated ICI responses in pan-cancer analyses.[58]

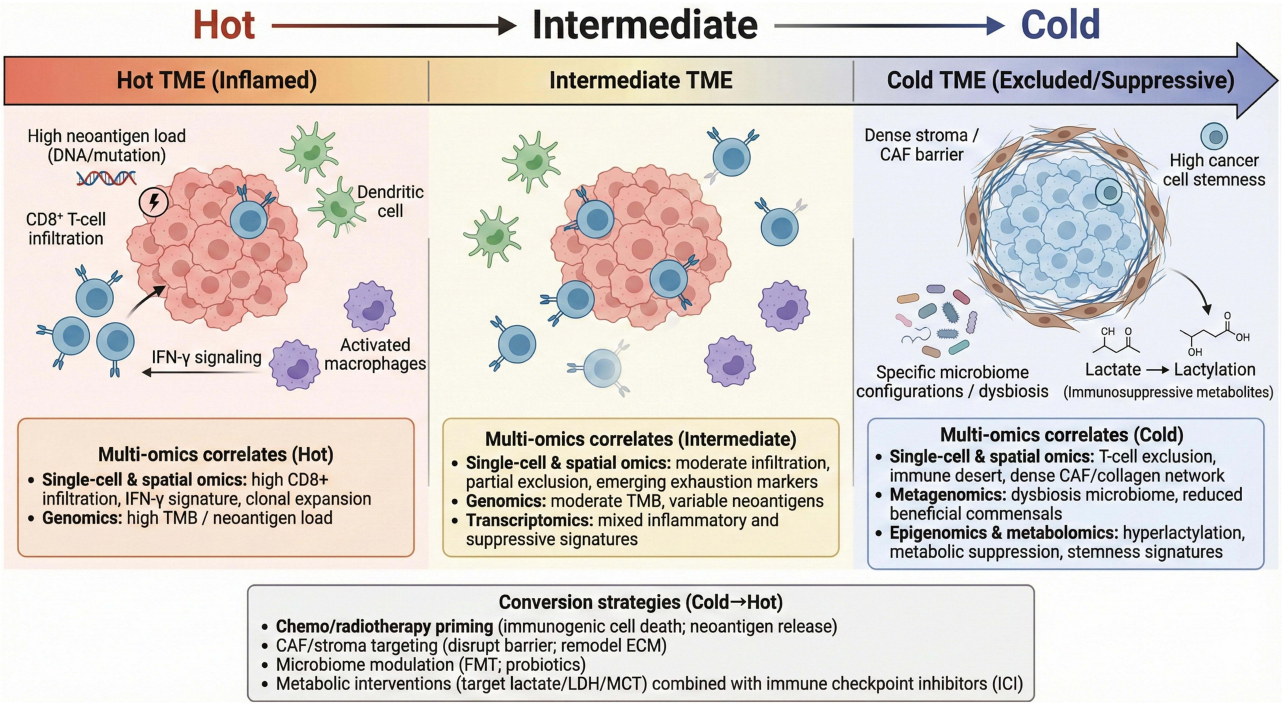


Figure 1 Hot–Intermediate–Cold tumor immune microenvironment continuum. Schematic overview of the spectrum of tumor immune microenvironments (TMEs) from hot (inflamed) to cold (excluded/suppressive). Hot TMEs feature high neoantigen load, prominent CD8β$^+$ T-cell infiltration, and IFN-γ–associated immune activation, whereas intermediate TMEs show moderate infiltration with partial exclusion and emerging exhaustion features. Cold TMEs are characterized by T-cell exclusion and immune desert phenotypes driven by dense stroma/cancer-associated fibroblast (CAF) barriers, increased tumor cell stemness, dysbiotic microbiome configurations, and immunosuppressive metabolites (eg, lactate-linked lactylation). Representative multi-omics correlates across states and candidate cold→hot conversion strategies (eg, chemo/radiotherapy priming, stromal targeting, microbiome modulation, and metabolic interventions combined with immune checkpoint inhibitors) are summarized.

Across tumor types, specific mediators of stemness correlate with immune exclusion. The chaperonin CCT5 is frequently overexpressed in proliferative, stem-like cancer cells and associates with "cold" TMEs marked by sparse tumor-infiltrating lymphocytes and reduced CD8$^+$ T-cell presence.[59,60] Single-cell and spatial multi-omics suggest that CCT5 supports DNA repair and stress-response programs, and its overexpression correlates with inferior ICI outcomes across cohorts.[59] In lung adenocarcinoma, stem-like subpopulations enriched for proliferation markers such as MKI67 and STMN1 contribute to intratumoral heterogeneity and are associated with cold immune profiles (minimal CD8$^+$ infiltration) and poor ICI response; cohort analyses further link high stemness to reduced T-cell infiltration on immunofluorescence and worse outcomes after checkpoint blockade.[48,61]

Other malignancies show parallel biology. In nasopharyngeal carcinoma, Epstein–Barr virus–associated enhancer activation upregulates stemness-linked oncogenes such as CACNA2D1; experimental inhibition of CACNA2D1 reduces stem-like properties and increases immune vulnerability.[50,62] In breast cancer, emerging PANoptosis-based subtypes differ in immune infiltration, and high stemness in aggressive subtypes aligns with pathways that exclude or suppress immune cells.[63] In colorectal cancer, an immune-excluded subtype features a dominant stromal compartment that physically and biochemically blocks T-cell entry into the tumor core, yielding T-cell absence despite antigen presence and associating with poor differentiation, high heterogeneity, and MSI-related genomic instability patterns.[64,65]

Single-cell multi-omics further clarifies the niche logic of resistance. In urothelial carcinoma, combined bulk and single-cell RNA sequencing implicates myeloid-rich microenvironments in PD-1/PD-L1 resistance, consistent with niches that nurture stem-like, immune-evasive tumor states.[66,67] Moreover, rare tumor subsets undergoing epithelial–mesenchymal transition can enter persister states expressing stem-cell markers (eg, Snail1), appear intrinsically resistant to PD-1 blockade, survive treatment, and drive relapse.[68] Figure 1 and Table 1 summarize these pathways and representative multi-omic correlates of ICI efficacy and resistance.

Table 1 Key Biological Mechanisms and Multi-Omics Insights Across Cancers

Cancer Type	Mechanism of Resistance/ Efficacy	Multi-Omics Layer Involved	Key Biomarkers/ Genes	Reference
NSCLC	Lineage plasticity via SOX2/WNT/YAP; immunosuppressive TME with fibroblast-macrophage crosstalk	Single-cell transcriptomics, spatial omics	CXCL13+ CD8+ T cells, antigen-presenting fibroblasts (apCAFs)	Elucidating cellular origins and TME dynamic evolution in NSCLC through multi-omics technologies.[45]
Melanoma	T-cell exhaustion; microbiome modulation via FMT	Metagenomics, transcriptomics	Bacteroides caccae, Prevotella copri; HLA neoantigen footprints	Exploring fecal microbiota signatures associated with immune response and antibiotic impact in NSCLC: insights from metagenomic and machine learning approaches.[46]
RCC	Proinflammatory macrophages and exhausted CD8+ T cells; neoantigen-favoring HLAs	Bulk/single-cell transcriptomics, genomics	TP53/CREBBP mutations; HLA repertoires	Multi-omics analysis and response prediction of PD-1 monoclonal antibody containing regimens in patients with relapsed/refractory diffuse large B-cell lymphoma;[47] A spatial architecture-embedding HLA signature to predict clinical response to immunotherapy in renal cell carcinoma.[37]
HCC	Intra-tumoral heterogeneity; stemness-linked cold TMEs	Genomics, epigenomics	CCT5 overexpression; MKI67/STMN1 stem markers	Single-cell and multi-omics analysis reveals the role of stem cells in prognosis and immunotherapy of lung adenocarcinoma patients;[48] Chaperonin containing TCP1 subunit 5 as a novel pan-cancer prognostic biomarker for tumor stemness and immunotherapy response: insights from multi-omics data, integrated machine learning, and experimental validation.[49]
Bladder Cancer	Luminal vs basal subtypes; methylation-driven immune profiles	Epigenomics (methylation assays), liquid biopsies	EBV-induced CACNA2D1 activation	AI-Driven Drug Target Screening Platform Identified Oncogene CACNA2D1 Activated by Enhancer Infestation in Epstein-Barr Virus-Associated Nasopharyngeal Carcinoma.[50]
Colorectal Cancer	Stromal dominance in immune-excluded subtypes; poor differentiation linked to MSI	Pathomics, genomics/ transcriptomics	PANoptosis genes; enhancer activation	Development and interpretation of a pathomics-based model for the prediction of microsatellite instability in Colorectal Cancer;[51] Multi-omics indicators of long-term survival benefits after immune checkpoint inhibitor therapy;[52] Unveiling the role of PANoptosis-related genes in breast cancer: an integrated study by multi-omics analysis and machine learning algorithms;[53] Comprehensive characterization of tumor microenvironment in colorectal cancer via molecular analysis.[54]

Note: Biomarkers/signatures are representative examples reported in the cited studies and may vary by cohort, assay platform, and sampling strategy (bulk vs single-cell /spatial).

Abbreviations: NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; TME, tumor microenvironment; CAF, cancer-associated fibroblast; FMT, fecal microbiota transplantation; MSI, microsatellite instability.

AI-Driven Multi-Omics Integration for Biomarker Discovery

AI Algorithms in Multi-Omics Data Processing

Machine learning and deep learning are well suited to the dimensionality and heterogeneity of multi-omics datasets. Techniques such as LASSO regression, random forests, support vector machines, and deep neural networks (including convolutional neural networks) can integrate diverse feature types into robust predictors.[23,24] In colorectal cancer, an

ensemble multiple instance learning approach combined whole-slide histopathology with genomic and transcriptomic data to predict MSI status with an AUC of ~0.85, connecting subtle histologic patterns to mutation burden and immune pathway activation signatures.[21,69] Such models can be adapted across cohorts via transfer learning, improving generalizability while retaining biologically interpretable signals.[21,69]

Deep learning is particularly useful for imaging–molecular integration. In NSCLC, a DenseNet-based network extracted radiomic features from routine CT scans and combined them with blood inflammatory markers to predict ICI outcomes, achieving AUCs >0.80 in training and ~0.86 in independent validation cohorts.[24,70] Interpretability methods such as Grad-CAM have been applied to localize tumor regions driving predictions, providing imaging correlates of immune-active versus immune-suppressive biology.[71] For microbiome data, random forest classifiers trained on fecal metagenomic profiles identified gut microbial patterns associated with ICI responsiveness; in that analysis, enrichment of certain Bacteroides species aligned with response, whereas antibiotic-associated loss of microbial diversity aligned with non-response.[17,18]

Beyond response prediction, AI enables cross-domain data fusion for safety and target discovery.[72] In cardio-oncology, AI has integrated genomic, proteomic, and clinical data to identify multi-omics biomarkers that may predict ICI-related cardiotoxicity.[73] In nasopharyngeal carcinoma, an AI platform integrating genomic, epigenomic, and transcriptomic profiles prioritized driver candidates and highlighted CACNA2D1 as activated by EBV-related enhancers; laboratory validation supported a role in immune evasion, and inhibition reduced tumor growth, nominating CACNA2D1 as a therapeutic target.[15,50] Bibliometric analyses of recent literature further indicate accelerating growth of AI–multi-omics applications in immunotherapy biomarker research, consistent with a broader shift toward data-driven precision medicine.[74]

Predictive Models for ICI Response

Capitalizing on patterns extracted by AI, multiple predictive models have been constructed to forecast ICI benefit, frequently outperforming single biomarkers such as TMB or PD-L1 expression alone.[75] Artificial neural networks and ensemble methods (eg, gradient-boosted decision trees) commonly integrate mutations, immune transcripts, immune-cell abundance, imaging-derived features, and clinical variables into composite predictors of response probability.[76]

In melanoma, a LASSO model fusing exome sequencing features with RNA-seq immune transcripts achieved an AUC of ~0.70 in training and ~0.64 in an independent test set, outperforming conventional mutational metrics such as non-synonymous TMB.[19,77] In relapsed DLBCL, an ANN incorporating tumor PD-L1 score, patient age, and recurrent mutations (including TP53 and CREBBP) achieved AUCs of 0.97 (training) and 0.94 (testing) for anti–PD-1 response prediction.[78] Analyses of model weights indicated that features reflecting spatial immune cell organization (eg, immune-cell proximity and localization patterns derived from pathology) were strongly linked to predicted outcomes, suggesting that the ANN learned clinically meaningful connections between tissue architecture and immunotherapy efficacy.[12,78]

In advanced gastroesophageal cancers, AI-derived genomic mutation signatures have been reported to predict overall survival after immunotherapy with high sensitivity and stable performance across cohorts, outperforming TMB and PD-L1 status as prognostic indicators.[40,79] Such models can also propose combination strategies; one framework nominated the MEK inhibitor trametinib for “high-risk” patients based on an inverse correlation between signature score and trametinib IC50 in model systems.[79] Stemness-associated modeling provides additional biologic resolution. In LUAD, a prognostic model combining CoxBoost and elastic net evaluated stem cell–associated genes (eg, MKI67 and STMN1) with immune markers and stratified ICI response with modest accuracy (AUC ~0.65); high stemness scores aligned with reduced CD8+ T-cell infiltration and worse outcomes, consistent with a cold tumor microenvironment.[48,58]

In HCC, an AI model integrating SNP variants, gene expression, and clinical factors has been used to predict ICI response and guide conversion strategies (eg, adding locoregional therapies) for patients unlikely to respond to ICIs alone.[80,81] In NSCLC, multi-omics predictors have been extended to the neoadjuvant setting: integrating radiomic features with genomic and transcriptomic data can forecast pathologic response (eg, major pathological response) to neoadjuvant immunochemotherapy and inform perioperative decision-making.[24] Reported performance across cancer types is summarized in Table 2, with several models externally validated.

Table 2 Performance of AI Predictive Models for ICI Response

Model Type	Cancer Type	Key Features/ Algorithms	Performance Metrics	Validation	Reference
Ensemble MIL	Colorectal Cancer	Histopathology images correlated with genomics/ transcriptomics	AUC 0.88–0.85	Multicenter cohorts	Development and interpretation of a pathomics-based model for the prediction of microsatellite instability in Colorectal Cancer.[51]
LASSO-based	Melanoma	Exome/RNA-seq integration; SHAP interpretability	AUC 0.7 (training), 0.64 (testing)	TCGA/GEO	AI Model for Predicting Anti-PD1 Response in Melanoma Using Multi-Omics Biomarkers.[82]
ANN	DLBCL	PD-L1 scores, age, TP53/CREBBP mutations	AUC 0.97/0.94	Spatial profiling	Multi-omics analysis and response prediction of PD-1 monoclonal antibody containing regimens in patients with relapsed/refractory diffuse large B-cell lymphoma.[47]
DenseNet	NSCLC	CT radiomics + inflammatory indices; Grad-CAM	AUC >0.8	Multicenter (AUC 0.865/0.823)	Deep learning and inflammatory markers predict early response to immunotherapy in unresectable NSCLC: A multicenter study.[70]
CoxBoost +Enet	LUAD	Stem cell genes (MKI67/STMN1); immune infiltration	AUC >0.65	Seven cohorts, immunofluorescence	Single-cell and multi-omics analysis reveals the role of stem cells in prognosis and immunotherapy of lung adenocarcinoma patients.[48]
					Multi-omics characterization and machine learning of lung adenocarcinoma molecular subtypes to guide precise chemotherapy and immunotherapy.[83]
Consensus Clustering	HNSCC	Differentiation genes; CMPIS signature	C-index 0.666	TCGA/GEO	Molecular Subtypes Based on Cell Differentiation Trajectories in Head and Neck Squamous Cell Carcinoma: Differential Prognosis and Immunotherapeutic Responses.[84]
					Integrating immune multi-omics and machine learning to improve prognosis, immune landscape, and sensitivity to first- and second-line treatments for head and neck squamous cell carcinoma.[85]
					Integrated multiomics analysis and machine learning refine molecular subtypes and prognosis for thyroid cancer.[86]
Random Forest	NSCLC (microbiome)	Metagenomic profiles (Bacteroides caccae)	Not specified (predictive taxa identified)	Metagenomic cohorts	Exploring fecal microbiota signatures associated with immune response and antibiotic impact in NSCLC: insights from metagenomic and machine learning approaches.[46]
					Mapping the rapid growth of multi-omics in tumor immunotherapy: Bibliometric evidence of technology convergence and paradigm shifts.[74]

Note: Reported performance metrics are quoted as described in the referenced articles and are not directly comparable across studies because of differences in endpoints (response vs survival), cohorts, imaging/omics preprocessing, and validation design.

Abbreviations: ICI, immune checkpoint inhibitor; AUC, area under the receiver operating characteristic curve; MIL, multiple instance learning; ANN, artificial neural network; SHAP, Shapley Additive Explanations; Grad-CAM, gradient-weighted class activation mapping; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; LUAD, lung adenocarcinoma; HNSCC, head and neck squamous cell carcinoma.

Subtype Classification and Patient Stratification

Beyond predicting binary response, AI and multi-omics have been used to classify tumors into subtypes with distinct immunotherapy sensitivities, guiding selection of ICIs alone versus combination regimens.[87] In HNSCC, unsupervised clustering of differentiation-related gene expression revealed three robust subtypes characterized by stromal/

mesenchymal features, metabolic programs, or immune activation.[88] Low-differentiation (dedifferentiated, mesenchymal-like) tumors tended to be immune-inflamed and respond better to anti–PD-1/PD-L1, whereas more differentiated tumors were often immune-cold.[89]

Machine learning has extended these stratifications into prognostic signatures. A composite immunotherapy sensitivity signature (CMPIS) for HNSCC achieved a concordance index of ~0.66 and suggested treatment tailoring: hot tumors (low differentiation score, high immune infiltration) benefit more from ICIs or chemotherapy, whereas cold tumors (high differentiation score, low infiltration) may respond better to radiotherapy or EGFR-targeted agents.[19,85] In melanoma, integrative analyses of TCGA and GEO datasets identified subtypes with different immunotherapy outcomes; one subtype with low signature scores corresponded to highly immunogenic hot tumors enriched for interferon-γ programs and active T-cell infiltration, associated with improved outcomes on ICIs.[90]

In NSCLC, multi-omics stratification has refined LUAD taxonomy; one subgroup driven by lineage plasticity and oncogenic pathways showed an immune-excluded microenvironment and resistance to both immune checkpoint blockade and tyrosine kinase inhibitors, implying a need for alternative or dual strategies.[13,30] In bladder cancer, emerging work integrates genomic and transcriptomic profiles with liquid-biopsy features (circulating tumor DNA and circulating tumor cells) to infer luminal versus basal phenotypes noninvasively and predict ICI benefit.[91] Metabolic–epigenomic integration is also expanding: models incorporating lactylation patterns suggest a lactate-driven immune-evasion state that may benefit from rational combinations such as immunotherapy plus radiotherapy.[42]

Figure 2 schematizes the integrated AI–multi-omics workflow: genomics, transcriptomics, epigenomics, metabolomics, microbiomics, pathomics, and radiomics feed into an AI core using feature selection and representation learning (LASSO, random forests, DenseNet-class networks, multiple instance learning). Outputs include biomarker/target prioritization (eg, TP53, CREBBP, CACNA2D1), predictive response models summarized by ROC curves and interpreted with SHAP-like attribution, and immune-relevant subtype calls distinguishing immune-inactive tumors, hot inflamed tumors, and strongly immunosuppressive subtypes to support patient stratification and treatment tailoring.

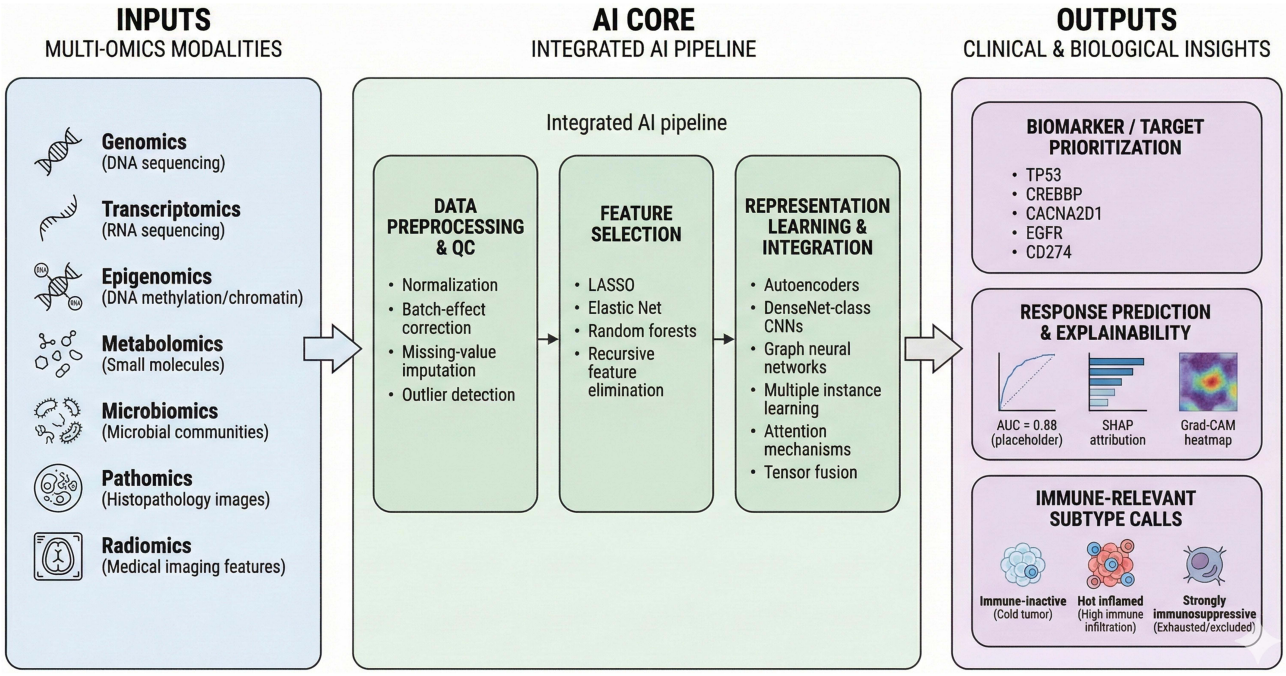


Figure 2 Integrated AI pipeline for multi-omics integration and clinical outputs. End-to-end workflow linking multi-omics inputs (genomics, transcriptomics, epigenomics, metabolomics, microbiomics, pathomics, and radiomics) to an AI core composed of data preprocessing/quality control (normalization, batch-effect correction, missing-value imputation, and outlier detection), feature selection (eg, LASSO, elastic net, random forests, recursive feature elimination), and representation learning/integration (eg, autoencoders, CNNs, graph neural networks, multiple-instance learning, attention mechanisms, and tensor fusion). The pipeline outputs clinically actionable results, including biomarker/target prioritization, treatment response prediction with explainability (eg, AUC/ROC, attribution scores, and heatmap-based localization), and immune-relevant subtype calls (immune-inactive/cold, hot inflamed, and strongly immunosuppressive exhausted/excluded) to support patient stratification.

Clinical Applications and Translational Challenges

Predicting Therapeutic Outcomes and Guiding Combination Therapies

AI–multi-omics frameworks are increasingly used to anticipate ICI outcomes before, or early during, treatment and to guide selection of monotherapy versus combination regimens.[23,77] In melanoma, an integrative model combining tumor exome and transcriptome features predicts anti–PD-1 efficacy with an AUC of about 0.7 and stratifies patients by expected benefit from combination approaches.[77] Low predicted response scores often correspond to immune-cold tumors with limited T-cell infiltration; such patients can be triaged to ICI plus cytotoxic chemotherapy to induce tumor inflammation, whereas high-score patients may proceed with ICI monotherapy.[13,19] Early trials guided by this logic suggest improved outcomes when chemotherapy is added for low-score patients, illustrating how model-based stratification can individualize intensity of care.[3,92]

In advanced gastroesophageal cancers, AI-driven genomic signatures have been used to forecast overall survival benefit from ICIs and to identify patients unlikely to benefit from immunotherapy alone.[40,79] Tumors classified as high risk displayed profiles consistent with sensitivity to targeted agents, leading to the MEK inhibitor trametinib as a candidate partner for ICIs in this subgroup and motivating follow-up studies.[40,79] In another setting, immunogenomic modeling of treatment-resistant cancers has suggested HSP90 inhibitors as ICI partners, weakening resistance and improving antigen presentation.[93] These analyses generate mechanistically plausible, trial-testable hypotheses for overcoming immune escape.

Rational combination strategies extend beyond drug–drug pairing to include modulation of the microbiome and tumor metabolism. In non-small-cell lung cancer (NSCLC), fecal microbiota transplantation (FMT) is being explored to shift the gut microbiome toward states associated with improved ICI responsiveness.[18,36] AI analyses of microbiome profiles have identified taxa associated with better outcomes, including *Prevotella copri*, suggesting that enriching such commensals through FMT or probiotics may be beneficial.[17] Early clinical studies indicate that transferring stool from an ICI responder to a non-responder can sometimes induce responses in the recipient, but safety, donor selection, and microbiome profiling remain crucial and could be strengthened by AI-guided matching.[34,94]

On the metabolic front, multi-omics integration has implicated lactylation-linked programs in resistance.[95] Models combining epigenomic and transcriptional features can identify tumors most driven by lactylation-associated regulatory patterns, motivating strategies that reduce lactate production or block lactate transport and signaling (for example, LDH inhibition or lactate-transporter blockade) alongside ICIs.[16,43] These approaches are being evaluated to sensitize resistant tumors and to synergize immunotherapy with radiotherapy.

AI-based stratification can also inform modality choice and sequencing. In head and neck squamous cell carcinoma (HNSCC), the CMPIS immunotherapy sensitivity signature helps distinguish patients likely to do well with immunotherapy or conventional chemotherapy (immune-hot tumors with low risk scores) from those more likely to benefit from alternative options such as radiotherapy or EGFR-targeted inhibitors (immune-cold tumors with high risk scores).[19,75] In hepatocellular carcinoma (HCC), models integrating tumor genomics with liquid-biopsy features are being explored to guide conversion strategies, in which patients predicted not to respond to ICIs alone may receive locoregional therapies (such as transarterial chemoembolization or radiofrequency ablation) alongside immunotherapy to reduce tumor burden and promote immune recognition.[80,96]

In NSCLC, multi-omics AI systems are being implemented in neoadjuvant immunotherapy-plus-chemotherapy trials to predict major pathologic response or pathologic complete response before surgery.[24,70] Patients with low predicted probability of deep response can be triaged to alternative or intensified regimens, whereas those predicted to respond well can proceed without unnecessary additions that increase toxicity.[24,97] Overall, these examples illustrate how AI–multi-omics can enable adaptive, response-guided immunotherapy, but prospective validation remains the decisive requirement for clinical uptake.

Real-World Evidence and Multicenter Validation

As AI–multi-omics models move toward clinical use, validation in real-world patient populations and across multiple centers is essential to avoid overfitting to a single cohort, platform, or workflow. In NSCLC, a model combining CT

imaging features with peripheral inflammatory markers achieved AUCs of 0.865 and 0.823 in two external hospital-based validation sets, supporting reproducibility.[24,70] In diffuse large B-cell lymphoma, an artificial neural network model predicting anti–PD-1 response achieved about 94% AUC in an independent cohort, closely mirroring training performance; concordant spatial immune-profiling results provided biological support for its predictions.[78,98]

Cross-cohort consistency has also been reported for genomic models in gastrointestinal cancers, where mutation-signature predictors maintained prognostic accuracy across multiple cohorts and outperformed tumor mutational burden in predicting overall survival after immunotherapy.[40,79] Large consortia and public resources further enable validation: melanoma immune subtypes and machine-learning signatures initially derived from TCGA were reproduced in independent datasets and clinical-trial cohorts, confirming that immune-hot programs (including interferon signaling and T-cell–inflamed expression) associate with better outcomes under ICIs.[19] In lung adenocarcinoma, stemness-based stratification applied to multiple independent cohorts consistently separated patients into risk groups, with predicted immune-cold cases showing low CD8 T-cell infiltration on immunofluorescence, consistent with the model's biological premise.[48,58]

Another translational advantage is the potential to reduce invasive procedures through noninvasive monitoring. In bladder cancer, multicenter studies are evaluating AI-enhanced liquid-biopsy approaches that measure tumor DNA or methylation markers in urine and blood.[44,99] Early results suggest that machine learning can detect recurrence or evolving resistance patterns without repeated cystoscopy or serial tissue biopsies, enabling earlier treatment adjustment while reducing patient burden.[61,100]

Validation efforts also reveal biases that must be addressed. Models trained in cohorts from specific geographic regions, care settings, or ancestral backgrounds may not generalize elsewhere without recalibration, underscoring the need for diverse training data and systematic external testing. Overall, multicenter evidence supports feasibility and sets the stage for embedding these tools into prospective trials and routine practice.

Challenges in Implementation

Despite promise, several barriers impede routine clinical use. Data heterogeneity is a dominant issue: multi-omics inputs arise from different platforms and protocols (sequencing chemistries, imaging devices, sample-processing methods, and analytic pipelines), and even modest variation can alter readouts and degrade model performance.[23,101] Pre-analytical variability is particularly problematic for liquid biopsies, motivating efforts to harmonize specimen handling, establish quality-control standards, and implement shared normalization procedures so that models remain portable across laboratories.[102]

Tumor heterogeneity and evolving resistance further complicate prediction. In HCC, high mutational complexity and multiple resistance pathways, including angiogenesis programs and WNT/β-catenin signaling, limit the utility of static biomarkers.[103,104] Maintaining accuracy may require longitudinal sampling, incorporation of on-treatment dynamics, and periodic model updating to reflect tumor evolution. Moreover, some AI-derived biomarkers are not easily actionable: a high-risk classification may reflect complex multi-gene patterns without a clear therapeutic lever, emphasizing the need for interpretable modeling and experimentally validated mechanisms.[105]

The black-box nature of many algorithms remains a hurdle for clinicians and regulators. Interpretability techniques, including SHAP-based feature attribution, attention visualization, and multi-omics correlation analysis, are essential to connect predictions to established biology and to support trust.[71,106] For example, in colorectal cancer, deep-learning pathomics models predicting microsatellite instability gain credibility when attention maps are presented and linked to mismatch-repair alterations and immune infiltration, offering a plausible biological rationale for the output.[21]

Prospective evidence is still limited. Most results remain retrospective, and few trials are designed to test AI-guided treatment strategies as the intervention.[107] Prospective studies are beginning—for example, neoadjuvant NSCLC programs such as CAMEL that incorporate multi-omics and AI for subgroup analyses of response determinants—but definitive evidence may require randomized designs comparing AI-guided selection with standard decision-making, measuring outcomes, toxicity, and resource use.[70] Such trials also demand prespecified decision rules, timely data turnaround, and clear accountability for how recommendations are applied.

Equity and global representativeness are additional concerns. AI–omics research is concentrated in a limited number of countries and centers, raising risks of population bias and limited applicability.[108] Expanding datasets to under-

represented groups and tumor types, strengthening international collaboration, and using privacy-preserving approaches such as federated learning are critical to avoid widening disparities.[109,110]

Finally, cost and workflow integration must be addressed. Comprehensive multi-omics profiling can be expensive and slow;[111] the field must demonstrate that added predictive value justifies cost or develop streamlined assays (for example, focused panels) that preserve performance while improving feasibility.[112] Outputs must be clinically usable and timely, delivered as clear risk scores with interpretation at decision points and integrated into clinical decision-support systems. Regulatory pathways are evolving, and harmonized validation protocols will be needed before guideline-level endorsement becomes routine.[113]

Many of these challenges are summarized in Figure 3, which depicts the path from AI–multi-omics discovery to clinical application, emphasizing the need for real-world validation and solutions to heterogeneity, interpretability, and governance. Addressing these barriers will determine whether AI–multi-omics becomes routine in oncology practice and sets the stage for forthcoming technologies that further enhance predictive utility.

Future Directions and Emerging Technologies

Advanced AI–Multi-Omics Paradigms

A major frontier is the integration of single-cell and spatial omics with AI. Single-cell RNA sequencing and spatial transcriptomics can resolve the tumor microenvironment (TME) at cellular and micro-architectural scales, capturing heterogeneity and dynamic tumor–immune interactions that bulk profiling obscures.[30,114] AI models that ingest spatio-temporal structure may better predict response trajectories that vary across tumor regions and evolve during therapy.[115] In non-small-cell lung cancer (NSCLC), single-cell multi-omics has revealed spatial niches characterized by lineage plasticity and immune suppression linked to SOX2/WNT/YAP signaling.[30,116] Incorporating such heterogeneity into AI frameworks could support spatially resolved predictions and suggest when and where adjunct interventions—such as

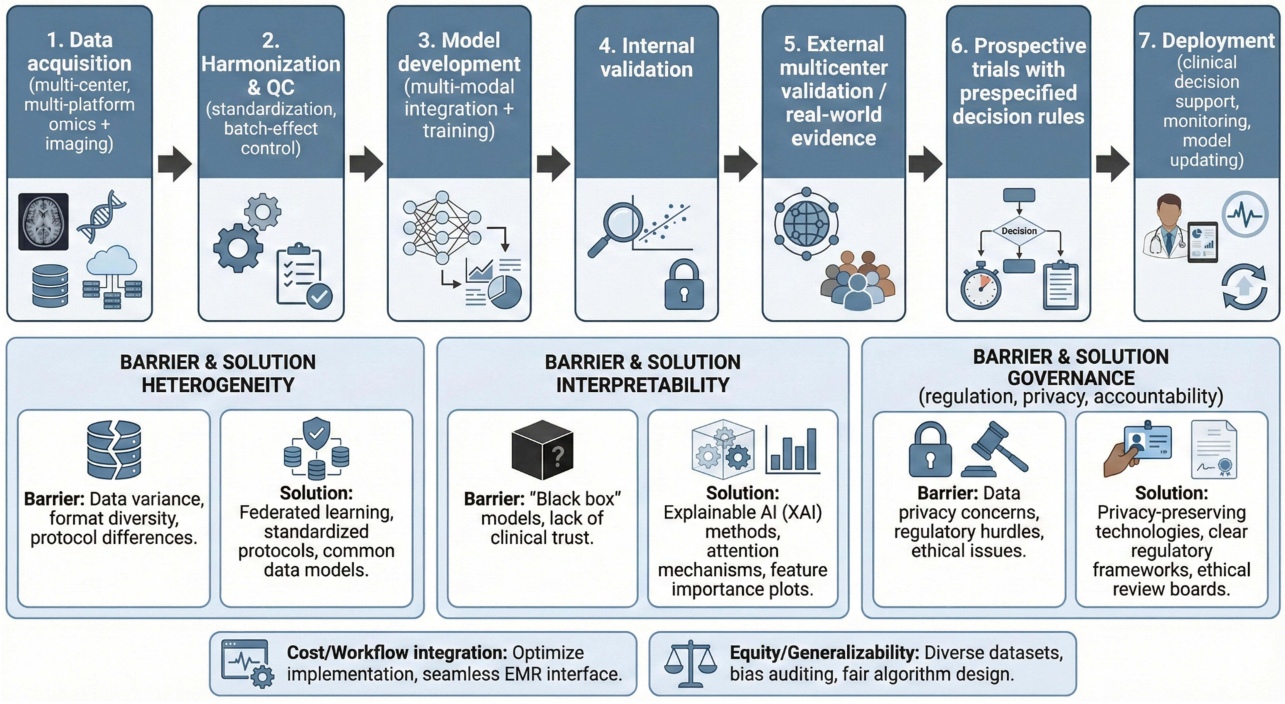


Figure 3 Translational roadmap for clinical deployment of AI–multi-omics models. Stepwise framework for moving AI–multi-omics models from development to real-world implementation: multicenter data acquisition (multi-platform omics and imaging), harmonization and QC (standardization and batch control), multimodal model development and training, internal validation, external multicenter validation/real-world evidence, prospective trials with prespecified decision rules, and deployment within clinical decision support with continuous monitoring and model updating. Key "barrier–solution" pairs are highlighted, including heterogeneity (federated learning, standardized protocols, common data models), interpretability and clinical trust ("black-box" concerns addressed by explainable AI), and governance (privacy-preserving technologies, regulatory frameworks, and ethical oversight), alongside practical considerations of cost/workflow integration and equity/generalizability.

https://doi.org/10.2147/JMDH.S572089

adding an immune agonist or targeting specific sites with radiotherapy—might convert "cold" regions to "hot" and improve overall response.[117,118]

Federated learning is an increasingly relevant paradigm for multi-center immunotherapy modeling. In federated settings, data remain within the originating institutions while model updates are shared and aggregated, addressing privacy and governance barriers that limit pooled multi-omics studies.[119,120] In pharmacogenomics, federated AI has already demonstrated the feasibility of discovering chemotherapy-response biomarkers across hospitals without centralizing raw patient data.[121] Applying analogous infrastructure to immunotherapy could enable global consortia to jointly train ICI response predictors on diverse populations, thereby improving generalizability and reducing bias while maintaining confidentiality.[122]

Generative AI offers a complementary strategy to increase effective sample size, particularly for rare cancers, uncommon resistance phenotypes, and underpowered trials. Generative adversarial networks and diffusion models can synthesize multi-omics samples that preserve essential properties of real tumors.[118,123] For single-cell data, synthetic immune-cell profiles can expand coverage of tumor-infiltrating states and improve robustness of downstream predictors.[124] Early diffusion-based approaches have simulated realistic tumor gene-expression patterns and immune-cell distributions, providing a pragmatic route to strengthen model training when real examples are limited.[125,126]

Hardware and algorithmic innovation may further extend feasibility at the scale demanded by multi-omics. Quantum computing is being explored for its potential to address the combinatorial complexity of ultra-high-dimensional datasets.[127] Although practical oncology applications remain nascent, quantum algorithms are hypothesized to accelerate pattern recognition and optimization, potentially enabling faster exploration of interactions among tens of thousands of features.[127,128] If realized, these capabilities could speed simulation of TME interaction networks under different perturbations and help prioritize candidate resistance drivers for experimental follow-up.[129]

Parallel advances in pathomics and radiomics are moving the field toward more integrated and interpretable multimodal models. Pathomics is progressing through ensemble deep learning and transfer learning approaches that correlate whole-slide histology with genomic and transcriptomic programs, including prediction of microsatellite instability, with improving robustness across scanners and staining protocols.[51,130] Radiomics is evolving through fused models that combine CT representations with multi-omic biomarkers; in NSCLC, architectures such as DenseNet-based encoders have been paired with interpretability methods (eg, Grad-CAM) to highlight radiographic regions driving predictions and to connect imaging features to underlying gene-expression patterns or immune-cell densities.[131,132] Such alignment between model outputs and biological signals is likely to increase clinical acceptance.

Beyond efficacy prediction, AI–multi-omics is extending to survivorship and adverse-event management. In cardio-oncology, integrating genomic predisposition, blood biomarker trajectories, and clinical risk factors has revealed multi-omic patterns associated with increased risk of ICI-associated myocarditis and other cardiotoxicities.[133,134] Predicting toxicity risk could enable proactive monitoring, earlier intervention, and risk-adapted treatment strategies, expanding the translational value of AI from selecting therapy to managing long-term safety.[135]

Personalized Medicine and Biomarker Validation

A central near-term objective is truly personalized immunotherapy paired with rigorous biomarker validation. As mechanistic understanding deepens, personalization is expected to extend beyond choosing therapy to optimizing dose, schedule, sequencing, and adaptive modification over time based on evolving tumor biology and immune state.

Liquid biopsy is likely to be pivotal for personalization because it can capture tumor evolution through serial, minimally invasive sampling. Circulating tumor DNA, circulating tumor cells, and epigenetic signals such as methylation can indicate molecular response, minimal residual disease, and emerging resistance, sometimes earlier than conventional imaging.[25,26] In bladder cancer, AI-enhanced liquid biopsy strategies are being evaluated to detect recurrence or resistance patterns and to reduce reliance on repeated cystoscopies or tissue biopsies.[44] More broadly, integrating longitudinal liquid-biopsy signals with multi-omics and clinical features could support earlier therapy switching, escalation, or de-escalation, provided prospective trials confirm clinical benefit.[25]

Prospective validation remains decisive. Retrospective discrimination—however impressive—does not establish that model-guided decisions improve outcomes. In melanoma, multi-omics predictors integrating mutational profiles and

immune signatures have outperformed tumor mutational burden in retrospective analyses, yet larger prospective studies are required to test whether biomarker-guided treatment selection improves survival, reduces toxicity, and is cost-effective.[77,87] Accordingly, trial designs are evolving: umbrella and platform trials increasingly incorporate biomarker-defined arms in which AI-derived signatures determine stratification, and neoadjuvant studies provide early, quantifiable endpoints such as major pathological response and pathologic complete response.[9,10]

Biomarker pipelines are also being refined into integrated discovery–validation loops. AI can screen multi-omics for outlier signals and pathway connectivity, prioritize candidates with plausible actionability, and accelerate experimental confirmation.[9] In nasopharyngeal carcinoma, AI-driven screening has highlighted targets such as CACNA2D1 by connecting multi-omic anomalies to known pathways before laboratory validation.[50] In ovarian cancer, multi-omics analyses have identified stemness-related expression programs and genetic alterations associated with ICI response; machine-learning models have then been strengthened by experimental validation in cell lines and organoids.[57,58] Increasing integration of epigenomic assays (eg, chromatin accessibility or enhancer mapping) is expected to expand discovery of regulatory elements that drive resistance and to support development of epigenetic or transcriptional combination strategies.[15]

Neoadjuvant personalization is advancing in parallel. In NSCLC, multi-omics AI systems are being evaluated to predict pathological response to neoadjuvant immunotherapy and to interpret resistance through features such as radiomic signatures and DNA repair mutations, informing escalation, de-escalation, alternative sequencing, or earlier surgery.[24,70] In hepatocellular carcinoma, where one or two driver alterations may dominate, AI tools are being developed to standardize how single-gene status—such as TP53 mutation status—should be combined with broader omics context to guide decisions between immunotherapy and targeted agents, moving from prognostic associations toward actionable guidance.[80,81]

Personalization will also increasingly involve longitudinal physiologic data. Wearables and digital health platforms provide continuous measures (heart rate, activity, symptom reporting) that can be synchronized with laboratory trends and omics readouts.[9,10] In principle, AI systems could detect subtle early patterns suggestive of cytokine release syndrome or autoimmune toxicity and trigger earlier evaluation, dosing adjustments, or supportive interventions, thereby enabling dynamic management rather than static dosing.[9,73]

The immunotherapy landscape is also broadening to engineered modalities such as CAR-T cells and bispecific T-cell engagers. AI is being applied to predict which construct designs or target combinations may maximize tumor control while limiting toxicity by integrating tumor multi-omics with patient T-cell state and host factors.[9,72] Similar integration of host polymorphisms, baseline cytokines, and clinical features is being used to forecast severe adverse events, including neurotoxicity and cytokine storms, supporting risk-adapted monitoring and design of safer therapeutic strategies.[73,81]

Bibliometric analyses suggest continued momentum in AI-enabled biomarker discovery while emphasizing the need for prospective, well-designed studies and regulatory-grade validation.[9,74] In the near term, AI–multi-omics may guide trial enrollment by enriching predicted responder or resistant populations to test mechanistic hypotheses efficiently.[10] Over time, such models could function as companion diagnostics paired with newly approved immunotherapies, potentially as co-developed drug–test strategies, contingent on reproducibility, clinical utility, and regulatory evaluation.

Interdisciplinary Integration

The next phase of progress will be driven by deeper interdisciplinary integration across immunology, oncology, pathology, bioinformatics, data science, engineering, and related domains. A prominent axis is the microbiome–metabolism–immune interface. Gut microbes shape systemic metabolites (including short-chain fatty acids and tryptophan-derived products) that modulate immune-cell function and influence ICI response.[17] In NSCLC, integrating fecal metagenomics with serum metabolomics and tumor transcriptomics, then analyzing the combined dataset with machine learning, has clarified how microbial taxa may modulate systemic immune pathways relevant to ICI efficacy.[24,36] Such models could ultimately inform individualized microbial or metabolic interventions, ranging from donor selection in fecal microbiota transplantation to targeted probiotic or dietary strategies, if safety and efficacy are prospectively established.

Metabolism and epigenetics are converging in clinically relevant ways. Lactylation exemplifies a metabolic–epigenetic mark linked to immune evasion and resistance.[16] AI can support patient selection for combinations in which metabolic agents (such as lactate dehydrogenase inhibitors or lactate-transport inhibitors) are paired with ICIs by integrating metabolic gene-expression programs, lactate-associated measures from serum or imaging surrogates, and immune signatures.[23,43] This integration can generate rational hypotheses for overcoming resistance and help define subgroups most likely to benefit from metabolic add-ons.

Spatial biology further illustrates the value of cross-field collaboration. In diffuse large B-cell lymphoma, combining spatial proteomics platforms (eg, GeoMX or CODEX) with genomics and machine learning has revealed immune-escape architectures—such as tumor cells surrounded by macrophages and fibroblasts—that pure genomics would miss.[9,12] Similar cross-modal integration has enabled compound biomarkers that combine genetic context with spatial immune organization; in renal cell carcinoma, "spatial HLA signatures" that integrate HLA genotype with spatial T-cell distribution exemplify how genetic and spatial information can jointly improve response prediction.[10,37]

Interdisciplinary interpretation is crucial for converting machine-learned subtypes into treatment strategies. In head and neck squamous cell carcinoma, integrating metabolic measures (hypoxia and glycolysis), stemness indices, and immune profiles has defined subtypes with therapeutic implications, requiring joint interpretation from oncologists, metabolic specialists, and data scientists.[9,85] In melanoma, single-cell immune states gain clinical value when integrated with pathology and clinical covariates to guide whether to prioritize ICIs or alternative immune modalities.[90] In lung adenocarcinoma, stemness-based stratification of "cold" tumors has motivated combination strategies that target cancer stemness pathways or epigenetic modulators alongside immunotherapy, illustrating how computational subtyping can yield mechanistically grounded treatment hypotheses when interpreted collaboratively.[48,58]

Looking ahead, proposed directions include broader global consortia enabled by federated learning to ensure equitable performance across ancestries and care settings, and deeper mechanistic simulations that couple AI with emerging computing paradigms, including speculative links to quantum biology. Synthesis frameworks commonly emphasize needs in data handling, validation, interpretability, therapeutic expansion, and interdisciplinary cooperation. Ultimately, the field's trajectory will be defined by whether increasingly sophisticated AI–multi-omics models can be operationalized into timely, interpretable, and prospectively validated tools that measurably improve outcomes in precision immunotherapy (Table 3).

Table 3 Challenges and Future Directions in AI-Multi-Omics Integration

Category	Current Challenges	Proposed Future Directions	Potential Impact	Reference
Data Handling	Heterogeneity, standardization gaps, pre-analytical variability	Federated learning; multi-omics AI paradigms (eg, diffusion models)	Improved privacy, robustness for rare cancers	Elucidating cellular origins and TME dynamic evolution in NSCLC through multi-omics technologies.[45] Current AI technologies in cancer diagnostics and treatment.[136]
Validation	Scarce prospective trials; biases in global research	Large multicenter RCTs; biomarker pipelines with AI-screening	Enhanced equity, clinical-grade validation	AI Model for Predicting Anti-PD1 Response in Melanoma Using Multi-Omics Biomarkers.[82] Trends and hotspots in research related to tumor immune escape: bibliometric analysis and future perspectives.[137] Neoadjuvant camrelizumab, nab-paclitaxel, and carboplatin in patients with stage IB-IIIA non-small cell lung cancer (NANE-LC): a study protocol of prospective, single-arm, multicenter, Phase II study.[138]

(*Continued*)

Table 3 (Continued).

Category	Current Challenges	Proposed Future Directions	Potential Impact	Reference
Interpretability	Black-box models; ethical issues	SHAP/Grad-CAM; multi-omics correlations	Better clinical translation, personalized dosing	Development and interpretation of a pathomics-based model for the prediction of microsatellite instability in Colorectal Cancer.[51] Deep learning and inflammatory markers predict early response to immunotherapy in unresectable NSCLC: A multicenter study.[70]
Therapeutic Expansion	Resistance mechanisms; cost-effectiveness	Microbiome modulation, lactylation-targeted synergies; wearable AI monitoring	Adaptive therapies, comorbidity management	Exploring fecal microbiota signatures associated with immune response and antibiotic impact in NSCLC: insights from metagenomic and machine learning approaches.[46] Next-Generation Immunotherapy: Advancing Clinical Applications in Cancer Treatment.[139]
Interdisciplinary	Limited microbiome-immune links	AI with quantum biology; global consortia for diverse data	Pathway simulations, precision immunotherapy	Multi-omics analysis and response prediction of PD-1 monoclonal antibody containing regimens in patients with relapsed/refractory diffuse large B-cell lymphoma.[47] Combining multi-omics analysis with machine learning to uncover novel molecular subtypes, prognostic markers, and insights into immunotherapy for melanoma.[140] Single-cell and multi-omics analysis reveals the role of stem cells in prognosis and immunotherapy of lung adenocarcinoma patients.[48] Molecular Subtypes Based on Cell Differentiation Trajectories in Head and Neck Squamous Cell Carcinoma: Differential Prognosis and Immunotherapeutic Responses.[84]

Note: Items listed under "Proposed Future Directions" reflect commonly recommended solutions in the cited literature; feasibility and clinical impact depend on data governance, regulatory requirements, and prospective validation in diverse patient populations.
Abbreviations: QC, quality control; RCT, randomized controlled trial; SHAP, Shapley Additive Explanations; Grad-CAM, gradient-weighted class activation mapping.

Data Sharing Statement

This manuscript is a narrative review based on publicly available literature and data sources. No original datasets were generated or analyzed in this study. All data supporting the conclusions (such as performance metrics, model details, and outcome statistics) are derived from the cited studies and are accessible through those publications or public databases. Additional details or materials related to the review are available from the corresponding author upon reasonable request.

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Author Contributions

All authors contributed significantly to this work and meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. Xiaodong Wang: Conceptualization, Methodology, Writing – original draft (Introduction and Biological Foundations sections), Writing – review & editing. Jing He: Methodology, Investigation (literature search and data curation for multi-omics insights), Writing – original draft (AI Integration section), Writing – review & editing. Gouping Ding: Investigation (literature search for AI algorithms and predictive models), Writing – original draft (Clinical Applications and Challenges sections), Writing – review & editing. Yixuan Tang: Visualization (figure and table preparation), Writing – original draft (Abstract and Keywords), Writing – review & editing. Qianqian Wang: Conceptualization, Supervision, Project administration, Writing – original draft (integrating all sections and Future Directions), Writing – review & editing. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no competing interests in this work.

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