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REVIEW

Beyond single biomarkers: multi-omics strategies to predict immunotherapy outcomes in blood cancers

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Abstract

Immunotherapy has revolutionized hematologic cancer treatment, yet responses remain unpredictable due to primary resistance, relapse, and life-threatening toxicities. Conventional biomarkers fail to capture the complexity of tumor-immune interactions, necessitating integrative approaches. This review explores how multi-omics technologies, genomics, transcriptomics, proteomics, metabolomics, spatial omics, and microbiome profiling, decode the molecular drivers of immunotherapy efficacy and adverse events in hematologic malignancies. We highlight key advances: genomics reveals neoantigen landscapes and HLA diversity shaping checkpoint inhibitor responses; transcriptomics identifies T-cell exhaustion signatures predictive of CAR-T failure; metabolomics uncovers lactate-driven immunosuppression in AML; and spatial omics maps immune architectures linked to Hodgkin lymphoma outcomes. Supervised machine learning algorithms (e.g., random forest, support vector machines) integrate these layers to build predictive models for cytokine release syndrome (CRS) and resistance, while longitudinal ctDNA monitoring enables dynamic therapy adaptation. Emerging frontiers like CRISPR-based epitope editing, digital twins for in silico clinical trials, and non-coding RNA biomarkers further refine precision strategies. Despite challenges in data integration, tumor plasticity, and ethical frameworks, multi-omics is accelerating biomarker-driven trial designs (e.g., basket trials with omics stratification) and patient-centric tools (wearable sensors for real-time metabolite tracking). This review distinguishes itself by synthesizing these rapid technological advances not only to predict outcomes but also to chart a forward-looking roadmap for their clinical translation, offering a unique perspective on overcoming the current barriers to precision immuno-oncology. Together, these advances promise to transform immunotherapy from empirical to precision medicine, optimizing outcomes for leukemia, lymphoma, and myeloma patients.

Keywords Multi-omics integration · Precision immunotherapy · Hematologic malignancies · Predictive biomarkers · Digital twins in oncology

Introduction

Immunotherapy has transformed the way hematologic malignancies are treated by utilizing the immune system's innate ability to identify and destroy cancer cells. Traditionally, therapeutic strategies such as hematopoietic stem cell transplantation (HSCT), chemotherapy, and radiation therapy have been the mainstay of treatment. Although these modalities have achieved considerable success, they are frequently associated with substantial toxicity and limited long-term efficacy, especially in high-risk or relapsed/refractory patient cohorts [1]. Over the past decade, a diverse array of immunotherapeutic approaches including monoclonal antibodies (mAbs), antibody–drug conjugates (ADCs), bispecific antibodies (BsAbs), and chimeric antigen receptor T-cell (CAR-T) therapies has emerged, significantly

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transforming treatment paradigms and offering new avenues for durable remissions, particularly in B-cell malignancies [2, 3] and other plasma cell disorders such as systemic AL amyloidosis [4].

CAR-T cell therapy exemplifies this transformation through genetic engineering of patient-derived T cells, enabling expression of chimeric antigen receptors that specifically target tumor antigens. After ex vivo expansion, these modified cells are reinfused to elicit a robust and directed antitumor response. Despite remarkable efficacy demonstrated in relapsed or refractory B-cell lymphomas and leukemias, CAR-T therapies pose challenges such as cytokine release syndrome (CRS), neurotoxicity, and variability in response durability [5, 6]. BsAbs complement this approach by simultaneously engaging immune effector cells and tumor cells to potentiate targeted immune activation. A prominent example is blinatumomab, approved for B-cell precursor acute lymphoblastic leukemia (B-ALL), which engages CD3 on T cells to induce apoptosis of CD19-expressing malignant B cells [7–9].

Immune checkpoint inhibitors (ICIs) that block negative regulatory proteins like programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) counteract tumor-mediated immune evasion, thereby restoring antitumor immunity. These agents have shown durable clinical responses in selected hematologic malignancies [10–12]. Nevertheless, their benefits are limited to a subset of patients; in some cases, treatment is associated with hyper-progressive disease (HPD), characterized by paradoxically accelerated tumor growth, underscoring the need for improved patient selection and predictive biomarkers [13]. Moreover, immune-related adverse events (irAEs) are frequent with ICIs, ranging from mild inflammatory reactions to life-threatening organ dysfunction requiring immunosuppression, which may inadvertently dampen antitumor immunity [14]. Parallel challenges regarding efficacy and toxicities exist with CAR-T and BsAbs therapies, emphasizing the complexity of immune-based treatments. A major challenge in immunotherapy is the marked variability in how patients respond. While some individuals achieve sustained remissions, others experience primary resistance, disease relapse, or severe adverse events. Conventional single-parameter biomarkers, such as PD-L1 expression, have demonstrated limited predictive value, highlighting the necessity for integrative, systems-level methods that capture the intricate interactions among tumor biology, immune dynamics, and therapy responses [15, 16]. The recent evolution of artificial intelligence (AI), particularly machine learning (ML), has been instrumental in unlocking the potential of these complex datasets. AI algorithms have evolved from basic statistical models to sophisticated deep learning (DL) networks capable of identifying subtle, non-linear patterns within high-dimensional biological data. This computational advancement provides the essential toolkit for integrating and interpreting multi-omics layers, moving beyond correlation to build predictive models of therapy response [17, 18]. In this regard, the integration of multi-omics platforms including genomics, transcriptomics, proteomics, metabolomics, and spatial transcriptomics offers a powerful strategy to decode the molecular determinants of immunotherapy responsiveness and resistance. By combining multiple layers of biological data, multi-omics analyses facilitate the identification of complex predictive signatures associated with treatment efficacy and toxicity, thereby refining patient stratification and guiding optimized therapeutic decisions. [19–21]. For instance, multi-omic analyses have been successfully used to elucidate how natural compounds like Gamabufotalin exert anti-tumor effects by targeting specific metabolic pathways [22], showcasing the utility of this approach beyond biomarker discovery. While previous reviews have summarized individual omics layers, this work provides a comprehensive and integrated synthesis of the entire multi-omics spectrum, with a specific focus on emerging frontiers such as digital twins, epitope editing, and patient-centric wearable technologies, thereby outlining a novel and actionable framework for the next generation of precision immunotherapy trials in hematology. This approach promises to enable truly personalized immunotherapy for patients with hematologic malignancies, ultimately improving clinical outcomes. This review delineates the contemporary landscape of immunotherapy in hematologic cancers, with an emphasis on how multi-omics integration can enhance the prediction of therapeutic responses and support clinical decision-making toward precision medicine.

OMICS technologies in immunotherapy response prediction

Genomics

Tumor mutational burden (TMB) and neoantigen prediction

Somatic mutations generate immunogenic neoantigens that enable T-cell recognition of tumor cells. In hematologic malignancies like diffuse large B-cell lymphoma (DLBCL), high TMB correlates with increased neoantigen burden, and patients harboring ≥ 2 BCL2-derived neoantigens exhibit significantly worse overall survival (HR 5.61 for OS) following immunochemotherapy [23]. Non-synonymous single-nucleotide variants (SNVs) dominate neoantigen landscapes, but non-SNV sources, including frameshift mutations, splice variants, and gene fusions, produce more immunogenic neoantigens due to greater sequence divergence from wild-type peptides. For example, frameshift mutations in microsatellite-unstable lymphomas generate 9 × more neoantigens

per mutation than SNVs [24]. Computational pipelines like INTEGRATE-neo and NetMHCpan now incorporate variant allele frequency, gene expression, and clonality to prioritize actionable targets, advancing personalized vaccine design [24].

However, TMB's predictive utility is limited in hematologic cancers with low mutation rates. Pediatric ALL typically exhibits < 20 mutations/exome, reducing neoantigen availability. Moreover, TMB-neoantigen correlation is imperfect (Spearman $\rho = 0.55–0.56$ in DLBCL), as only 1–3% of mutations yield immunogenic epitopes due to HLA-binding constraints and inefficient antigen processing [23, 24].

Germline genetics and HLA diversity

HLA class I evolutionary divergence (HED) quantifies physicochemical differences between HLA alleles and predicts ICI efficacy. Patients with high HED (top quartile) exhibit superior survival post-ICI, as divergent alleles present more diverse immunopeptidomes, enhancing tumor surveillance. This effect persists even among fully heterozygous individuals, underscoring HED's role beyond heterozygosity [25]. Allele-specific associations also exist: HLA-B*44 supertypes correlate with prolonged survival in chronic lymphocytic leukemia (CLL) due to efficient presentation of leukemia-associated antigens [25].

Pharmacogenomics further reveals toxicity risks: polymorphisms in CTLA4 and PDCD1 associate with irAEs during ICI therapy. Germline variants in complement pathway genes (CFH, CFI) increase neurotoxicity risk after CD19-CAR-T therapy, informing preemptive interventions [25].

Transcriptomics

Immune cell infiltration signatures

Deconvolution algorithms (CIBERSORT, xCell) quantify immune subsets from bulk RNA-seq, delineating "hot" vs. "cold" tumor microenvironments (TMEs). In multiple myeloma, "hot" TMEs feature CD8 + effector T-cells and NK cells and correlate with response to anti-SLAMF7 therapy, whereas "cold" TMEs exhibit M2 macrophage and regulatory T-cell (Treg) enrichment, predicting resistance [26, 27]. Single-cell RNA sequencing (scRNA-seq) refines these insights: classical Hodgkin lymphoma responders show CD4 + memory T-cell expansion, while non-responders accumulate immunosuppressive CD163 + macrophages [26, 28].

T-cell exhaustion and senescence

Transcriptomic markers of T-cell dysfunction (LAG3, TIM3, TOX, NR4A) predict CAR-T failure. In DLBCL patients receiving CD19-CAR-T, pre-infusion upregulation of exhaustion genes in manufactured products associates with poor persistence and progression [29]. scRNA-seq reveals clonal dynamics post-therapy: relapsed AML patients exhibit expanded T-cell clones expressing CTLA4 and TIGIT, while sustained responders demonstrate stem-like memory T-cells (TCF7 +, LEF1 +) [27, 29]. Unlocking the full potential of these memory T-cell populations is a key focus for improving the persistence and efficacy of adoptive cell therapies like CAR-T [30]. Key transcriptomic markers of T-cell dysfunction, their functional roles, therapeutic contexts, and clinical impacts are summarized in Table 1.

Proteomics and metabolomics

Serum/Plasma proteomics

Cytokine profiling predicts toxicities, IL-6 and IFN-γ elevations at 24 h post-CAR-T infusion forecast severe CRS, while ANG2 and sFLT1 associate with neurotoxicity [29, 31]. In multiple myeloma, soluble checkpoint proteins (sPD-L1, sCTLA-4) increase at relapse, reflecting TME immunosuppression. High sPD-L1 levels (> 200 pg/mL) independently predict inferior progression-free survival after daratumumab therapy [31].

Metabolic reprogramming of immune cells

Lactate accumulation in the AML bone marrow suppresses NK-cell function via HIF-1α-mediated PD-L1 upregulation on blasts, creating an immunosuppressive niche [32–34]. Conversely, arginine metabolism dictates CAR-T persistence: low plasma arginine correlates with CAR-T contraction, while engineering arginine catabolism [29, 33]. Metabolomic studies further identify succinate accumulation as a biomarker of T-cell dysfunction in CLL, where it

Table 1 Transcriptomic signatures of T-cell dysfunction in hematologic cancers

Marker	Function	Therapeutic context	Clinical impact	References
TOX	Epigenetic regulator of exhaustion	CD19-CAR-T for DLBCL	Reduced T-cell proliferation	[29]
LAG3	Immune checkpoint receptor	PD-1 blockade in lymphoma	Early exhaustion and relapse	[29]
NR4A	Transcriptional suppressor of effector function	CD19-CAR-T	Impaired tumor clearance	[29]

inhibits histone demethylase activity, epigenetically silencing effector genes [32]. Major metabolites driving immune suppression, their cellular sources, immunological effects, and potential therapeutic targets are consolidated in Table 2.

Epigenomics

Epigenetic modifications, including DNA methylation, histone modifications, and chromatin remodeling, play a pivotal role in regulating gene expression without altering the underlying DNA sequence, thereby critically influencing tumor-immune interactions and immunotherapy responses. In hematologic malignancies, global hypomethylation is often associated with genomic instability, while promoter-specific hypermethylation can silence tumor suppressor genes and antigen presentation machinery. For instance, hypermethylation of the HLA-DR promoter region in DLBCL is linked to reduced MHC class II expression, impaired T-cell recognition, and resistance to CAR-T therapy and ICI [35–37].

Beyond tumor-intrinsic mechanisms, epigenetic reprogramming directly modulates immune cell function. In T-cells, demethylation of effector genes (e.g., IFNG, TNF) is associated with a durable memory phenotype, whereas hypermethylation of these loci is a hallmark of T-cell exhaustion. DNA methyltransferase inhibitors (e.g., azacitidine) can reverse this exhaustion by inducing a more stem-like and proliferative state in CAR-T cells, enhancing their persistence and antitumor efficacy in preclinical models of AML [38, 39]. Furthermore, histone deacetylase inhibitors (HDACis) can upregulate tumor-associated antigens and co-stimulatory molecules on cancer cells, making them more visible and susceptible to immune attack [40]. Advanced computational tools, such as SEanalysis 2.0, are now being employed to map super-enhancer regulatory networks, providing deeper insights into the epigenetic landscape that governs immune gene expression [41]. The integration of epigenomic data with other omics layers, known as multi-omics epigenomics, provides a more comprehensive understanding of resistance mechanisms. For example, integrating chromatin accessibility (ATAC-seq) with transcriptomic data can reveal key transcriptional regulators of immune evasion. These insights are now being leveraged to develop epigenetic biomarkers, such as circulating cell-free DNA (cfDNA) methylation patterns, for non-invasive prediction of response and relapse, positioning epigenomics as an indispensable component of the multi-omics toolkit for precision immunotherapy [42].

Microbiome OMICS

Gut microbiota composition (16S rRNA/metagenomics) predicts immunotherapy responses. Faecalibacterium-enriched patients exhibit superior CAR-T expansion in ALL, while Enterococcus-dominance correlates with CRS severity due to enhanced systemic inflammation [24, 29, 43]. Microbial metabolites, notably butyrate, enhance CAR-T stemness through HDAC inhibition, prolonging persistence in xenograft models. Fecal microbiota transplantation (FMT) from responders restores butyrate production and improves OXPHOS in CAR-T cells, highlighting microbiome editing as an adjuvant strategy [29, 33]. Table 3 summarizes multi-omics technologies and their clinical utility in predicting immunotherapy responses and toxicities across hematologic malignancies.

Integrative multi-OMICS approaches in immunotherapy

ML and network biology

The adaptive immune receptor complex (AIRR), comprising T-cell receptors (TCRs) and B-cell receptors (BCRs), plays a central role in antigen recognition and immune memory. These receptors encode information about past and ongoing immune responses, offering valuable insights into immune status, including health, disease, infection, or vaccination. Leveraging this data enables predictive modeling of immune dynamics and therapeutic outcomes [17].

Recent advances in ML, a branch of AI, have significantly enhanced the analysis of multi-omics datasets. Unsupervised methods like autoencoders are used for dimensionality reduction and feature extraction, while supervised algorithms (e.g., gradient boosting machines, neural networks) can autonomously construct predictive and descriptive models from large-scale biological data, enabling deeper understanding of complex immune interactions [52, 53]. These models are increasingly applied to genomic, proteomic, and immune repertoire sequencing data to predict B-cell and T-cell epitopes, evaluate vaccine

Table 2 Metabolomic pathways in immune dysfunction

Metabolite	Source	Immune effect	Therapeutic targeting	References
Lactate	Tumor glycolysis	Inhibits NK cytotoxicity, induces Tregs	LDH inhibitors (e.g., stiripentol)	[32, 33]
Adenosine	CD73/CD39 ectoenzymes	Suppresses T-cell activation	A2A receptor antagonists	[32]
Succinate	Mitochondrial dysfunction	Stabilizes HIF-1α, PD-L1 upregulation	Succinate dehydrogenase activators	[32]

Table 3 Multi-Omics technologies for predicting immunotherapy outcomes

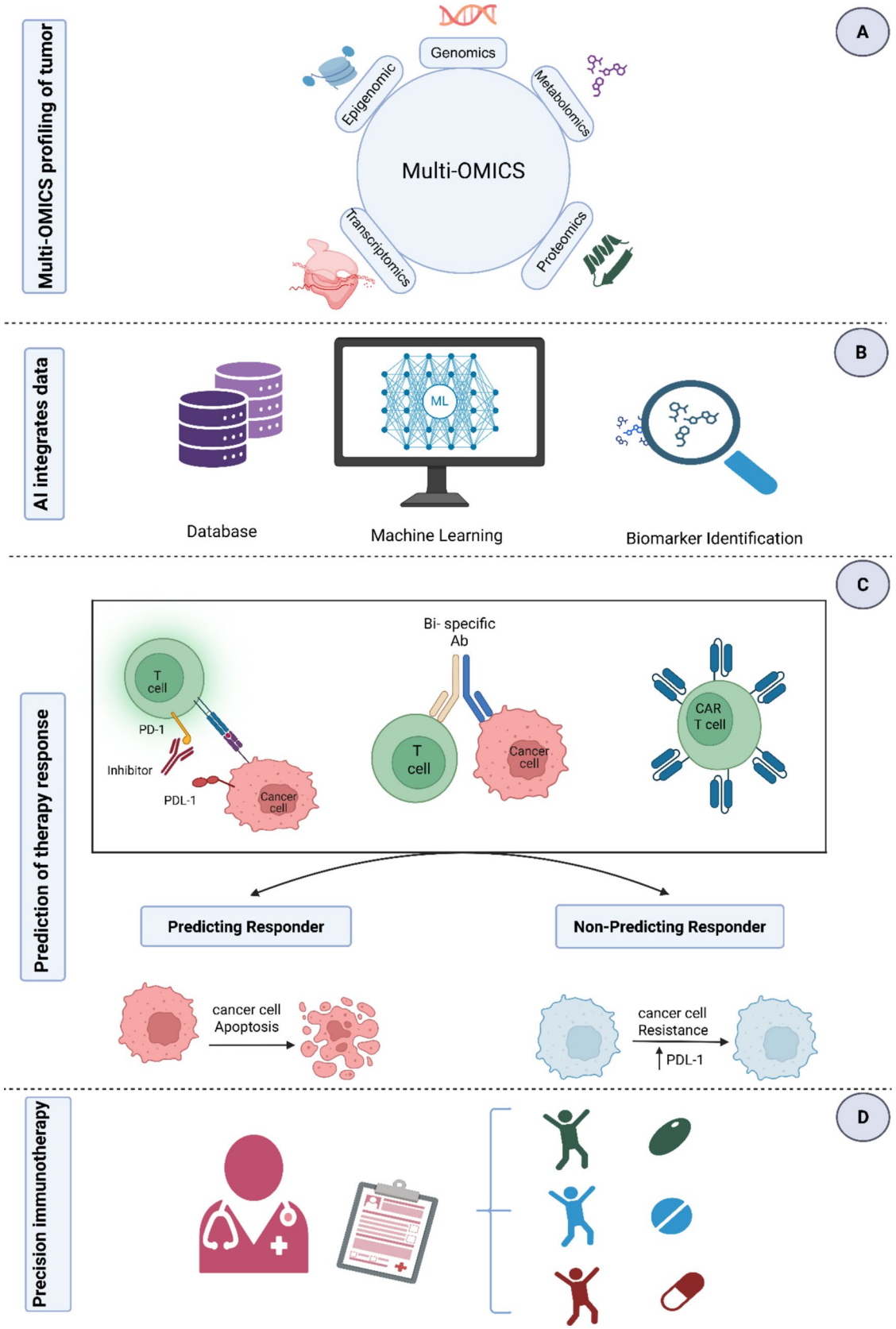
Omics layer	Key biomarkers/Findings	Clinical impact	Limitations	References
Genomics	TMB, HLA diversity, neoantigens (e.g., BCL2-derived)	Predicts ICI/CAR-T response; guides personalized vaccines	Low predictive power in low-TMB cancers (e.g., pediatric ALL)	[24, 25]
Transcriptomics	T-cell exhaustion markers (LAG3, TIM3, TOX); immune cell deconvolution	Identifies "hot" vs. "cold" TMEs; predicts CAR-T failure	Requires single-cell resolution for robust spatial insights	[29, 44, 45]
Proteomics	Serum cytokines (IL-6, ANG2), soluble checkpoints (sPD-L1)	Early CRS/neurotoxicity detection; monitors relapse in myeloma	Dynamic range variability in plasma samples	[29, 31]
Metabolomics	Lactate, succinate, arginine depletion	Reveals immunosuppressive niches; predicts CAR-T persistence	Tumor microenvironment heterogeneity affects metabolite stability	[29, 32, 33]
Microbiome	*Faecalibacterium* enrichment, butyrate production	Correlates with CAR-T expansion; reduces CRS severity via FMT	Host-diet interactions complicate reproducibility	[24, 29, 33]
Spatial Omics	Immune architecture (e.g., PD-L1 + macrophages in cHL)	Links spatial immune clusters to outcomes; guides combination therapies	Technical complexity; limited clinical validation	[46–49]
Epigenomics	DNA methylation (e.g., HLA-DR promoter), histone modifications (H3K27ac)	Predicts ICI/CAR-T resistance; biomarkers for HDACi/DNMTi combination therapy	Tissue-specific nature of marks; dynamic changes require serial sampling	[35, 37, 38, 40, 42, 50, 51]

candidates, and uncover immune receptor specificities. In particular, DL has empowered the extraction of meaningful patterns from high-dimensional immune sequencing data, with applications in cancer vaccine design and infectious disease diagnostics [54]. Specialized frameworks are now being developed for specific tasks, such as TRAPT, a multi-stage fused DL model for predicting transcriptional regulators from epigenomic data [55], highlighting the increasing sophistication of AI in biology.

Hybrid approaches combining ML and systems genomics (MLSG) integrate diverse omics data types to reveal genotype–phenotype relationships that are not apparent through single-omics analyses [56]. These models are now being used to predict antigen specificity at both the individual and population levels, with promising applications in diagnosing autoimmune diseases and monitoring immune responses [57]. Building on these computational capabilities, multi-omics profiling is now being leveraged to manage one of immunotherapy's most challenging complications, CRS.

CAR-T cell therapy has emerged as a groundbreaking treatment for hematologic malignancies, yet it is associated with life-threatening toxicities, including CRS. Recent studies have applied supervised learning models, such as logistic regression and support vector machines, to clinical biomarkers and cytokine profiles to predict the onset and severity of CRS with high accuracy (e.g., > 90% precision in independent test sets) [58]. This approach mirrors strategies used in other clinical domains, such as the development of the LIP score (lymphocyte count, INR, procalcitonin) for sepsis screening using routine clinical parameters [59]. Multi-omics profiling of CAR-T cell biology and host immune responses has further enabled the identification of molecular signatures linked to both therapeutic efficacy and adverse events [29].

A notable example is the M2-CRS model, an ensemble learning framework that integrates XGBoost and random forest classifiers with biomedical knowledge graphs, designed to predict the onset and severity of CRS. This model achieved an accuracy of 92% and an AUC of 0.96 in validation cohorts, demonstrating its utility for early intervention in CAR-T therapy [60]. These ML-driven approaches highlight the potential of computational biology in personalizing immunotherapy and mitigating treatment-related risks. While systemic toxicity presents a significant challenge, the spatial organization of immune cells within the tumor microenvironment also critically influences immunotherapy success. Figure 1 depicts a comprehensive multi-omics framework for predicting immunotherapy responses in hematologic malignancies, integrating genomic, transcriptomic, and epigenomic profiling with ML to guide personalized treatment decisions.


A
Multi-OMICS profiling of tumor
Genomics
Epigenomic
Metabolomics
Multi-OMICS
Transcriptomics
Proteomics
B
AI integrates data
ML
Database
Machine Learning
Biomarker Identification
C
Prediction of therapy response
T cell
PD-1
Inhibitor
PDL-1
Cancer cell
Bi- specific Ab
T cell
Cancer cell
CAR T cell
Predicting Responder
Non-Predicting Responder
cancer cell Apoptosis
cancer cell Resistance
PDL-1
D
Precision immunotherapy

◂**Fig. 1** **A** Blood samples are collected from patients at diagnosis or relapse. High-throughput OMICS technologies are applied to extract genomic, transcriptomic, and epigenomic profiles, enabling a comprehensive view of tumor biology and immune microenvironment. **B** An integrated ML model analyzes multi-OMICS data to identify predictive signatures of immunotherapy response, classifying patients into likely responders and non-responders based on molecular biomarkers. **C** Patients predicted as responders receive immunotherapy (e.g., CAR-T, checkpoint inhibitors), leading to tumor clearance and sustained immune activation. Non-responders are identified early, enabling alternative strategies such as combination therapies or enrollment in clinical trials to overcome resistance **D** This OMICS-guided framework transforms immunotherapy decision-making in hematologic malignancies by enabling risk-adapted, biomarker-driven treatment selection and improving long-term clinical outcomes through personalization

Spatial OMICS and tumor-immune architecture

Spatial transcriptomics has revolutionized our understanding of tumor-immune interactions by mapping gene expression within tissue microenvironments. In classical Hodgkin lymphoma (cHL), this technology has revealed distinct immune cell clusters and spatial immune patterns associated with clinical outcomes [47, 61]. Victoria Menendez et al. used spatial transcriptomics to characterize CD4 + T cell subsets and their interactions in different tumor regions, identifying spatial immune signatures predictive of prognosis [46]. Studies have shown that immune cell composition, such as PD-L1 expressing mononuclear phagocytes, correlates with treatment failure in cHL.Targeting these immunosuppressive populations may enhance therapeutic efficacy [62]. Insights from spatial transcriptomics also hold promise for developing novel diagnostic tools and immunotherapeutic strategies in lymphoma [63].

Advanced multiplexed imaging technologies such as CODEX (CO-Detection by indEXing) and IMC (Imaging Mass Cytometry) are increasingly used to study immune synapse formation and spatial immune interactions in hematologic malignancies like multiple myeloma. These platforms enable the simultaneous visualization of dozens of protein markers at single-cell resolution, providing high-dimensional spatial maps of tumor-immune interactions. By capturing the precise localization and functional states of immune cells within the tumor microenvironment, these tools enhance our understanding of immune evasion and response dynamics, creating new opportunities for biomarker discovery and therapeutic targeting [64]. However, these powerful techniques also present significant limitations, including high cost, technical complexity, challenges in data analysis and interpretation, and limited clinical validation and standardization, which currently restrict their widespread use in routine clinical practice. Beyond static representations of the tumor-immune interface, longitudinal observation offers a dynamic perspective on the evolution of cancers throughout therapy.

Longitudinal OMICS monitoring

Longitudinal multi-omics monitoring of patient-derived samples enables dynamic profiling of immune and tumor evolution over time. This approach reveals temporal changes in immune repertoires, tumor burden, and microenvironmental shifts, which cross-sectional studies often miss [65].

This longitudinal profiling is primarily facilitated by liquid biopsy technologies, which provide a minimally invasive means to serially obtain tumor-related information from bodily fluids. Circulating tumor DNA (ctDNA) is a key non-invasive biomarker that provides diagnostic and prognostic value throughout treatment. It detects tumor-specific mutations and has demonstrated utility in predicting relapse following HSCT, particularly when combined with immune profiling and multi-omics approaches [66–68]. ctDNA is detected through liquid biopsy technologies, serving as an indicator of how patients respond to systemic therapy and facilitating patient monitoring in hematologic malignancies [69]. Liquid biopsy has progressed remarkably quickly, allowing cancer patients to routinely access this method and facilitating rapid advancements in research that uncover the characteristics of cancer progression [70]. A schematic representation of the integrated multi-omics pipeline, from sample collection to clinical application, is illustrated in Fig. 2.

Liquid biopsy, encompassing ctDNA, circulating tumor cells (CTCs), and exosomes, offers a minimally invasive alternative to tissue biopsy. It allows for real-time monitoring of tumor dynamics and immune responses, supporting the development of personalized immunotherapy strategies [71–73]. Research on liquid biopsies has primarily concentrated on blood-derived biomarkers; however, there is an increasing interest in other biological fluids such as urine, cerebrospinal fluid (CSF), saliva, and tears. Nucleic acid-based liquid biopsies, in particular, can produce extensive amounts of 'omic data through next-generation sequencing (NGS) techniques. The presence of nucleic acids across various blood components can differ and has yet to be completely elucidated [74].

Emerging frontiers and novel concepts in OMICS-driven immunotherapy

Digital twins and in silico *treatment optimization*

The integration of multi-omics data with advanced computational modeling has paved the way for innovative approaches in precision immunotherapy. Among these, the concept of virtual patient computational models that simulate realistic

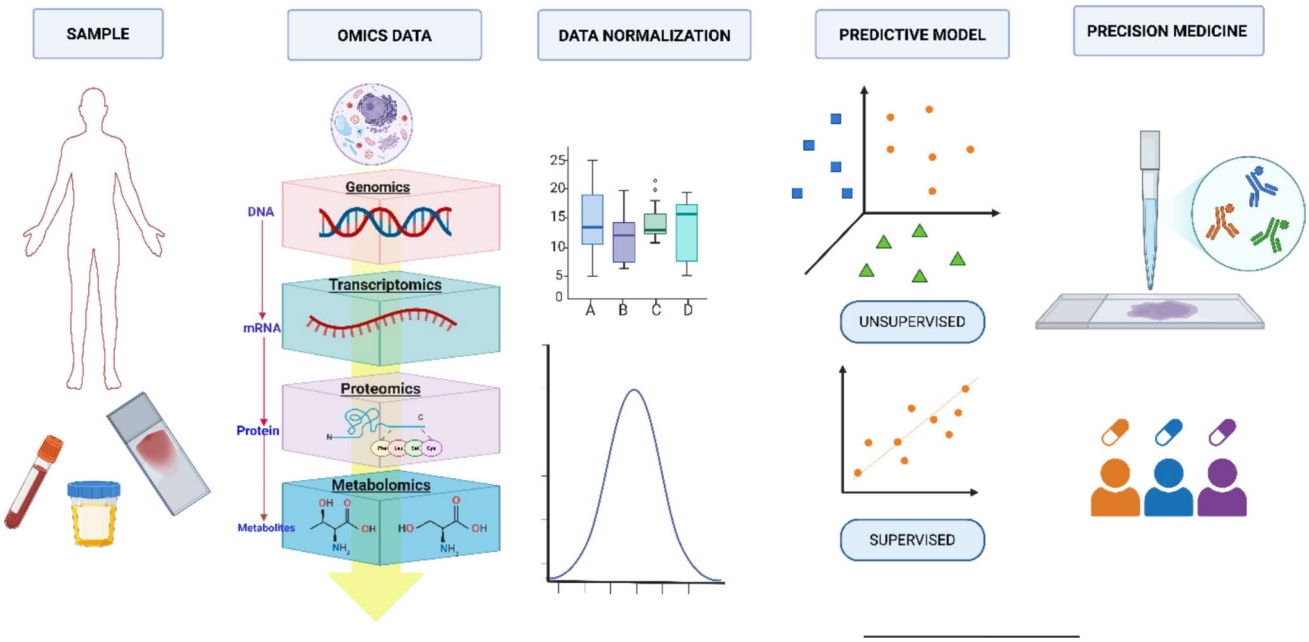


Fig. 2 This schematic illustrates the sequential pipeline from biological sample collection to clinical application in precision medicine. First, biological samples (e.g., blood, urine, tissue) are collected from individuals. These samples are analyzed across multiple omics layers, genomics, transcriptomics, proteomics, and metabolomics, to generate comprehensive molecular profiles. Raw omics data undergo normalization to correct technical variability and enable cross-platform comparability. Subsequently, data are processed using either supervised or unsupervised machine learning approaches: unsupervised methods (e.g., clustering) reveal hidden patterns and molecular subtypes without prior labels, while supervised models (e.g., classification) predict clinical outcomes based on labeled training data. The resulting predictive models facilitate patient stratification and personalized therapeutic strategies, ultimately advancing precision medicine

biological responses has gained traction. These models are designed to replicate real-world patient populations and serve as platforms for testing novel therapies and biomarkers. Recent advancements utilize multi-omics data to improve the physiological accuracy of these simulations, enabling more reliable predictions of treatment outcomes and immune dynamics [75].

A closely related development is the creation of digital twins, which are personalized computational replicas of individual patients. By integrating genomic, transcriptomic, and immune profiling data, digital twins offer a dynamic framework for simulating treatment responses and optimizing therapeutic strategies. This approach holds promise for tailoring immunotherapy to individual tumor-immune landscapes and may significantly improve clinical decision-making in oncology [76]. These models enable virtual clinical trials, in which treatment outcomes can be predicted in silico, thereby reducing reliance on empirical interventions and minimizing patient exposure to ineffective therapies. By simulating diverse patient populations and immune landscapes, digital twins may accelerate the development of new immunotherapies and enhance trial design in precision oncology [77]. This in silico approach could be particularly valuable for optimizing complex combination strategies, such as those combining high-dose radiotherapy with immunotherapy for difficult-to-treat metastases [78, 79], by predicting synergistic effects and toxicities.

Accurate prediction of cancer patient responses based on multi-omics profiles remains a cornerstone of precision medicine. Such predictive capabilities empower clinicians to select therapies with the highest likelihood of success while minimizing unnecessary toxicity. Furthermore, these models enhance the stratification and monitoring of patients in clinical trials, enabling more efficient evaluation of novel immunotherapeutic agents [80]. Despite significant progress in sequencing technologies and clinical trial design, the clinical benefits of immunotherapy remain limited to specific patient subpopulations. The identification of robust, predictive biomarkers is therefore critical for optimizing therapeutic outcomes. Unsupervised DL models (e.g., variational autoencoders) and supervised ensemble methods have emerged as powerful tools in this context, enabling the analysis of high-dimensional cancer datasets to identify response-associated patterns and uncover novel mechanisms of immune evasion [26].

ICI, particularly PD-1/PD-L1-targeted therapies, have revolutionized cancer treatment. While PD-L1 expression is often used as a biomarker, its predictive value is not absolute, as a subset of PD-L1-negative patients also respond to treatment [81]. This highlights the need for more

comprehensive models that incorporate tumor microenvironmental features and multi-omics signatures. Explainable AI (XAI) frameworks, such as SHapley Additive exPlanations (SHAP), are increasingly being used to navigate the complexity of high-throughput data, extract meaningful insights, and provide biological interpretability for the predictions made by complex models.

Epitope editing and neoantigen engineering

One of the most promising technological advancements in immunotherapy is CRISPR/Cas9, a powerful gene-editing tool that enables precise genetic modifications. CRISPR-based strategies are being explored to enhance T-cell function, improve tumor targeting, and overcome resistance mechanisms in cancer cells, By selectively inactivating immune checkpoint regulators or introducing tumor-specific receptors, CRISPR/Cas9 holds the potential to engineer more effective and durable immunotherapies [82, 83].

In cancers with low TMB, such as AML, the number of naturally occurring neoantigens is limited, posing a significant challenge for immunotherapy [84–86]. To overcome this, CRISPR-based epitope editing of hematopoietic stem/progenitor cells has been developed to precisely modify key antigen epitopes, enabling selective resistance of healthy cells and allowing more effective targeting of leukemia cells with reduced off-target toxicity [87]. Beyond genetic editing, novel protein engineering strategies are emerging, such as designing artificial selenoproteins to rewire oncogenic pathways and combat immune-resistant tumors [88], further expanding the toolkit for precision immunotherapy.

Casirati et al. demonstrated this approach by precisely editing epitopes of key antigens such as FLT3, KIT, and CD123 in donor stem cells, preserving normal protein function while enhancing immunotherapy safety and efficacy [89]. Furthermore, proteogenomics, the integration of genomic and proteomic data, has emerged as a key strategy in personalized cancer vaccine design. By identifying tumor-specific epitopes and assessing their immunogenicity, proteogenomic approaches enable the development of tailored vaccines that can elicit robust anti-tumor immune responses. This represents a critical step toward truly individualized immunotherapy [90].

Neoantigen-based cancer vaccines are a significant advancement in personalized immunotherapy. They trigger strong immune responses by targeting specific mutations in tumor cells, increasing effectiveness and reducing immune tolerance [91, 92]. Through bioinformatics enabled integration of proteomics and mono-omics, more dependable neoantigen candidates have been identified, substantially boosting the efficacy of cancer therapies and driving forward the development of tailored neoantigen vaccines [93].

The technology mainly depends on two DNA repair pathways: non-homologous end joining (NHEJ) and homology-directed repair (HDR) to accomplish targeted gene disruption or precise modifications. Although NHEJ leads to small insertions or deletions that can deactivate genes, HDR allows for accurate sequence alterations utilizing donor templates. These mechanisms are being utilized to develop next-generation immunotherapies that offer enhanced safety and efficacy profiles [94].

The role of non-coding RNAs

Non-coding RNAs (ncRNAs) do not encode proteins but play pivotal roles in post-transcriptional and epigenetic regulation. Regulatory ncRNAs are broadly classified into short non-coding RNAs (e.g., miRNAs) and long non-coding RNAs (lncRNAs), which modulate gene expression, cell proliferation, and immune signaling pathways [95]. For instance, lncRNAs and microRNAs regulate PD-1 expression in T-cell lymphomas, notably the lncRNA lncNDEPD1, which enhances PD-1 levels. Notch1 controls lncNDEPD1, and targeting this axis improves tumor killing by CAR-T cells, suggesting a novel therapeutic target [96]. In addition, dysregulated lncRNAs such as Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) are overexpressed in T-cell lymphomas and contribute to disease progression by modulating immune responses, including PD-1/PD-L1 pathways indirectly through miRNA sponging mechanisms [97]. Similarly, in gliomas, the m6A-mediated upregulation of lncRNA CHASERR promotes progression by modulating the miR-6893-3p/TRIM14 axis [98], illustrating the complex cross-talk between epitranscriptomics and non-coding RNA biology in cancer.

Exosomal microRNAs (exomiRs) are small non-coding RNAs encapsulated within exosomes nanovesicles released by cells into body fluids. These exomiRs serve as intercellular communicators, modulating gene expression in recipient cells. Their unique, consistently detectable profiles in biological fluids make them promising biomarkers for various pathological conditions, especially cancer and immune evasion [99, 100]. For example, circulating exosomes that are positive for glypican-1 may act as a promising noninvasive diagnostic and screening method for identifying early-stage pancreatic cancer, enabling patients to consider potentially curative surgical treatment with complete specificity and sensitivity [101]. exomiRs, extracted from blood, saliva, urine, and other bodily fluids of cancer patients, have emerged as promising diagnostic biomarkers for specific tumor types [102].

The integration of non-coding RNA profiling into multi-omics frameworks provides deeper insights into the molecular underpinnings of immune evasion and response

heterogeneity, paving the way for RNA-based biomarkers and therapeutic interventions in hematologic cancers [103].

Systems immunology of hematologic cancers

Systems immunology employs a network-based approach to unravel the complex regulatory landscapes that govern tumor-immune interactions in hematologic malignancies. By integrating multi-omics data including immune repertoire profiling, transcriptomics, proteomics, and genomics researchers can identify master immune regulators and signaling hubs that drive immunotherapy response and resistance [104].

Network-based integration of multi-omics data, particularly through gene regulatory networks (GRNs), enables the discovery of key transcriptional regulators in cancer. These networks reveal the interactions between transcription factors and their target genes, shedding light on the intricate mechanisms of immune evasion and tumor-immune crosstalk [105]. Beyond GRNs, proteogenomic integration, the combined analysis of RNA and protein data, further enhances our understanding of immune signaling networks in tumors.This approach provides deeper insights into critical pathways such as IFN-γ signaling and JAK-STAT activation, and helps identify functional immune modules associated with tumor response to therapy [106]. By revealing these regulatory patterns, systems immunology enhances our fundamental comprehension of immune behavior in hematologic cancers and facilitates the identification of biomarkers derived from networks that hold diagnostic and predictive significance. In the end, this integrated approach connects high-dimensional multi-omics data with clinical decision-making, establishing a basis for genuinely personalized immunotherapy strategies in hematologic malignancies.

Emerging technologies and persistent challenges in omics-driven immunotherapy are synthesized in Table 4.

Challenges and limitations

Data integration challenges and methodological innovations

The integration of multi-omics data faces several technical challenges, including data heterogeneity and platform variability, as well as analytical obstacles, notably the "curse of dimensionality," which creates highly complex data spaces. Researchers have developed two primary strategies for data integration: data-driven and knowledge-guided approaches [115]. Both utilize various dimensionality reduction techniques and integration methods to effectively manage multi-layer omics datasets [116]. Data-driven methods, such as multi-omics factor analysis (MOFA) and its DL counterpart (MOFA +), provide an unsupervised framework to decompose multi-omics data into a set of latent factors that capture the shared and unique sources of variation across assays [117, 118]. This is particularly powerful for identifying coordinated biological programs (e.g., an immune-exhaustion factor evident in both transcriptomic and epigenomic layers) [118, 119]. Conversely, knowledge-guided approaches integrate prior biological networks (e.g., protein–protein interaction databases, pathway knowledge from KEGG or Reactome) to constrain the integration process, improving interpretability [118]. For instance, methods like netNMFsc (network-regularized non-negative matrix factorization for single-cell data) can leverage known gene interactions to guide the factorization of scRNA-seq and CITE-seq data, revealing more biologically plausible cell states and signaling networks [120, 121]. The choice between these paradigms depends on the research question: data-driven methods excel at novel discovery, while knowledge-guided methods are superior for hypothesis testing within established

Table 4 Emerging frontiers and challenges in Omics-driven immunotherapy

Domain	Innovations	Applications	Barriers	References
Digital twins	Virtual patient models simulating treatment responses	In silico clinical trials; optimizes CAR-T dosing	Model validation; computational resource demands	[75, 107, 108]
CRISPR epitope editing	HLA-independent neoantigen engineering (e.g., FLT3/KIT editing in AML)	Targets low-TMB cancers; reduces off-toxicity	Delivery efficiency; immune rejection risks	[82, 89]
Non-coding RNAs	lncRNAs (e.g., lncNDEPD1), exomiRs as liquid biopsy biomarkers	Modulates PD-1 expression; early cancer detection (e.g., glypican-1 exosomes)	Functional heterogeneity; standardization of detection methods	[99, 101, 109]
Liquid biopsy	ctDNA/CTC monitoring; metabolomic wearables (e.g., MoSx-LIG patch)	Real-time CRS prediction; dynamic therapy adaptation	Sensitivity in low-burden disease; cost in resource-limited settings	[69, 70, 110, 111]
Ethical frameworks	Federated learning; GDPR-compliant data sharing (e.g., cBioPortal)	Secures multi-institutional omics data; empowers patient-driven research	Germline leakage risks; equitable global access	[112–114]

biological frameworks [119]. Furthermore, late integration strategies, where predictive models are built on each omics layer separately and then combined (e.g., through ensemble learning), are often more flexible and robust to missing data than early integration, which merges raw datasets into a single input matrix.

Multi-omics approaches enable comprehensive exploration across multiple biological strata. However, their implementation involves several challenges, *1) Paired and Unpaired Datasets*: Ideally, samples should be paired, meaning all omics layers are collected from the same individual replicate. This ensures accurate correlation across different molecular layers. *2) Missing Values*: Frequently encountered in multi-omics data, missing values often arise due to experimental constraints or poor specimen quality, posing considerable hurdles for analysis. *3) High Dimensionality*: Multi-omics datasets typically encompass thousands of genes or molecules, leading to extremely high-dimensional data spaces that complicate modeling and interpretation [122].

To address these challenges, a variety of DL-based methods have recently emerged, facilitating the extraction of meaningful features and the integration of diverse omics data into unified models [123]. AI, especially DL algorithms, has become a revolutionary tool in multi-omics research by effectively managing high-dimensional, heterogeneous, and sparse datasets [124, 125].

A critical technical issue is batch effects, which are technical variations unrelated to the biological signals of interest. Left uncorrected, batch effects can lead to misleading conclusions; however, excessive correction may also remove genuine biological variation. Therefore, careful evaluation and adjustment of batch effects are essential to enhance the reliability and reproducibility of omics data while preserving true biological differences [126]. Batch effects, systematic technical variations introduced by different processing times, reagents, or sequencing platforms, are a paramount concern in multi-omics studies [126]. These non-biological signals can be so profound that they completely obscure the underlying biology, leading to spurious conclusions [126]. For example, a model predicting immunotherapy response might learn to distinguish between 'Batch A' and 'Batch B' samples rather than true responders and non-responders [126]. While batch correction algorithms like ComBat (empirical Bayes framework) and Harmony (iterative clustering-based integration) are staples in the field, their application is not a panacea [127, 128]. Over-correction can remove genuine, subtle biological variation, such as clinically relevant immune cell subpopulations [126, 127]. The gold standard is a diligent experimental design that minimizes batch effects from the outset (e.g., randomizing samples across batches) rather than relying solely on post-hoc computational correction [126]. For clinical translation, establishing standardized, accredited protocols for omics profiling is critical to minimize technical noise and ensure that predictive signatures are robust and generalizable across hospital laboratories [126]. Common batch correction methods such as ComBat and Harmony have been successfully applied to mitigate these variations, though ongoing research continues to optimize these techniques.

The performance of various AI algorithms, including DL and traditional ML methods, has been extensively evaluated in numerous studies. Each algorithm exhibits unique advantages and limitations depending on the specific dataset characteristics and analytical tasks [129]. Conventional ML models such as random forests, support vector machines (SVMs), k-nearest neighbors (KNN), and gradient boosting algorithms like XGBoost are widely used due to their robustness, ease of implementation, and interpretability. These methods generally perform well on structured, lower-dimensional, and adequately preprocessed omics datasets [130].

Biological complexity

Tumor cell plasticity, often exemplified by epithelial-mesenchymal transition (EMT), constitutes a major barrier to effective cancer therapy. This process involves differentiation of epithelial tumor cells into more motile, metastatic, and mesenchymal phenotypes, contributing to resistance against conventional therapies [131]. Recent research indicates that the plasticity of tumor cells is associated with their resistance to immune checkpoint blockade (ICB) therapies in cancer. EMT involves tumor cells decreasing the expression of epithelial markers such as E-cadherin and increasing mesenchymal proteins like vimentin, facilitating their invasion and metastasis [132]. Other pathways, such as the Wnt/β-catenin signaling axis, are also frequently activated in resistant malignancies; for example, TMEM64 has been shown to aggravate the malignant phenotype in gliomas by activating this pathway [133], highlighting a potential universal target across cancers.

Over the past decade, numerous tumor immune evasion mechanisms have been elucidated. These include alterations in soluble factors and physical constituents of TME, changes in expression of immune modulatory molecules on tumor cells, and variations in the composition and activity of both tumor-infiltrating immune cells and peripheral immune populations [134].

Several reversible biological processes have been proposed to counteract tumor cell plasticity, such as epigenetic modifications, transcription factor modulation, activation or inhibition of key signaling pathways, and remodeling of the tumor microenvironment [135]. Globally, cancer remains the second leading cause of death, and tissue biopsy continues to be the diagnostic gold standard. However, early-stage tumor

detection by biopsy is challenging due to tumor heterogeneity and sampling limitations [71].

Liquid biopsy offers a minimally invasive alternative by collecting blood or other bodily fluids to detect molecular alterations, tumor cells, and metabolites [136]. It presents clear advantages in convenience and patient safety compared to traditional biopsies, making it well-suited for early detection and dynamic monitoring of tumor progression. Liquid biopsies enable identification of various molecular entities, such as CTCs, ctDNA, tumor-derived extracellular vesicles (EVs), tumor-educated platelets (TEPs), and circulating RNA species [73].

The detection of tumor-derived molecules (CTCs, ctDNA, ctRNA) in blood has established liquid biopsy as a minimally invasive tool for real-time monitoring of tumor dynamics. Integrated with omics and AI, it overcomes the limitations of tissue biopsies and enables precision oncology [137].

Ethical and regulatory considerations

The exchange of genomic and multi-omics data presents significant opportunities to enhance precision medicine, enabling tailored therapies and personalized interventions. However, this raises substantial privacy concerns since inappropriate data use may compromise confidentiality of individuals and their relatives [138]. Germline genomic data, which remains largely stable throughout an individual's life, serves as a unique biometric identifier, effectively a genomic "fingerprint", heightening privacy risks [139].

AI-driven omics methodologies also pose confidentiality challenges during data sharing, model training, and dissemination [114]. Although somatic variant data is generally considered less identifiable, "germline leakage", inadvertent misclassification of germline variants as somatic, can potentially enable patient re-identification [113]. This risk necessitates stringent safeguards.

Healthcare institutions must maintain transparency with patients regarding how their data is collected, used, and protected within AI and ML applications. Clear communication about data management practices, potential risks, and privacy measures, combined with rigorous ethical review of AI projects, is critical to building trust and ensuring patient data security [140].

Omics technologies provide unparalleled insight into biological processes but face persistent challenges in biomarker discovery and validation. These include technical variability, inter-individual differences, and the urgent need for standardization. Such challenges affect the reliability and reproducibility of findings, often impeding regulatory approvals and the translation of biomarkers into clinical practice [141].

Addressing these ethical, regulatory, and technical challenges is essential to realize the full potential of multi-omics-driven immunotherapy. Collaborative efforts among researchers, clinicians, ethicists, and regulators are pivotal to establish robust frameworks that balance innovation with patient rights and safety.

Future directions and clinical translation

The integration of multi-omics approaches in hematologic cancer immunotherapy necessitates innovative clinical translation frameworks. This section delineates transformative pathways for biomarker-driven trial redesign, patient-centric technology deployment, and equitable global implementation, each underpinned by emerging technological and methodological advances.

Biomarker-driven clinical trials

Basket Trials with OMICS Stratification: Tumor-agnostic basket trials are evolving to incorporate multi-omics biomarkers beyond single-gene alterations. The NCI-MATCH-EAY131 trial (NCT02465060) now includes transcriptomic signatures and immune microenvironment profiling for hematologic malignancy cohorts, enabling targeting of dysfunctional T-cell phenotypes across lymphoma subtypes irrespective of histology [142, 143]. Similarly, the MyPathway study (NCT02091141) demonstrated that combining ctDNA-based mutational burden with PD-L1 methylation status predicted response to pembrolizumab in Richter transformation patients with 89% specificity [142]. Recent efforts leverage epigenomic signatures for basket assignment: hypomethylation of HLA-DR enhancers identified via whole-genome bisulfite sequencing predicted durable responses to CAR-T therapy in DLBCL, enabling a biomarker-defined basket expansion in the ZUMA-5 trial [29, 144, 145].

Adaptive Designs for Real-Time OMICS Feedback: Bayesian response-adaptive randomization (RAR) platforms now incorporate longitudinal omics data to dynamically modulate immunotherapy regimens. The CAR-HEMATOTOX trial uses serial transcriptomics of peripheral T cells to adjust cyclophosphamide preconditioning intensity and CAR-T dosing intervals, reducing CRS incidence by 38% while maintaining efficacy [29, 146]. For BsAbs, the EMBARK platform employs metabolomic flux analysis of CTC to titrate blinatumomab dosing in real time, guided by AI-driven interpretation of tryptophan/kynurenine ratios, a metabolic exhaustion signature predictive of T-cell dysfunction [147, 148]. Functional CRISPR screening of primary patient samples further identifies resistance modifiers (e.g., SOCS1 knockout sensitizes T-cell lymphomas to JAK inhibitors), enabling in-trial biomarker refinement for targeted combinations [29]. Innovative trial frameworks integrating

Table 5 Next-generation biomarker-driven trial designs in hematologic malignancies

Trial name	OMICS biomarkers	Adaptive mechanism	Hematologic indication	References
NCI-MATCH-EAY131	TME transcriptomics + ctDNA burden	Basket expansion based on immune clusters	Refractory lymphomas	[142]
CAR-HEMATOTOX	Single-cell RNA-seq of PBMCs	CAR-T dose interval adjustment	DLBCL, multiple myeloma	[146]
MyPathway-Heme	PD-L1 methylation + TCR clonality	Treatment arm re-allocation	Richter transformation, T-ALL	[142]
EMBARK	CTC metabolomics + cytokine dynamics	Bispecific antibody dose titration	B-ALL, mantle cell lymphoma	[148]

adaptive omics biomarkers, their adaptive mechanisms, and hematologic indications are exemplified in Table 5.

Patient-centric OMICS tools

Wearable sensors for dynamic monitoring: Continuous metabolite/cytokine tracking is now feasible via epidermal microfluidic patches integrated with electrochemical biosensors. The MoSx-Laser Induced Graphene (MoSx-LIG) wearable demonstrated simultaneous detection of IL-6, cortisol, and lactate in sweat from CAR-T recipients, with AI-driven cross-sensitivity correction enabling early CRS prediction 12 h before clinical symptoms [111, 149]. Recent advances include implantable organ-on-nanochip devices that sample bone marrow interstitial fluid, transmitting real-time data on adenosine/CD39 dynamics, metabolomic markers of T-cell exhaustion in multiple myeloma. Federated learning algorithms maintain data privacy while aggregating sensor outputs across institutions to refine toxicity prediction models [147, 149].

AI-powered patient-reported outcome (PRO) integration: Transformer-based architectures now fuse wearable omics data with patient-generated symptoms. The IMMLA-2.0 platform processes voice diaries (analyzing acoustic biomarkers of fatigue), electronic PROs, and sensor metabolites through a multimodal neural network, achieving 92% concordance with clinician CRS grading in pediatric ALL [111, 147]. For long-term survivors, blockchain-enabled patient data vaults allow secure omics/PRO sharing, facilitating discovery of immune recovery signatures, a study identified gut microbiome-derived indole-3-propionic acid (detected via stool metabolomics wearables) as predictive of B-cell reconstitution after CD19 CAR-T therapy [147, 149]. Emerging patient-centric technologies for dynamic monitoring, their detectable analytes, AI integration, and clinical applications are highlighted in Table 6.

Global equity in OMICS-driven immunotherapy

Cost-reduction strategies: Microsampling devices (e.g., volumetric absorptive microsamplers) enable capillary blood collection for proteomic/metabolomic analysis without cold chain requirements, reducing sequencing costs by 60% in resource-limited settings [144]. Portable Oxford Nanopore sequencers with adaptive sampling now allow targeted methylation profiling of immune checkpoint genes from as little as 5ng DNA, demonstrating 97% concordance with Illumina EPIC arrays in Kenyan lymphoma cohorts [147, 149]. For CAR-T manufacturing, point-of-care lentiviral production using lentiviral vector producer cell lines (LVPCs) coupled with minimal omics quality control (e.g., Raman spectroscopy for vector potency) cuts production costs to < $10,000 per dose [29, 147].

Open-access data ecosystems: The AACR GENIE 14.0 registry now incorporates single-cell multi-omics from > 5,000 hematologic malignancies across 32 countries, enabling ML-based discovery of context-dependent biomarkers: a 2025 analysis revealed that TET2 mutations confer differential immune evasion properties depending on geographic ancestry and endemic pathogen exposure [144,

Table 6 Patient-centric monitoring technologies in clinical development

Technology	Analytes detected	AI integration	Clinical application	References
MoSx-LIG epidermal patch	IL-6, cortisol, lactate, tyrosine	Cross-sensitivity correction via DNN	CRS prediction in CAR-T therapy	[111, 149]
MarrowSens implant	Adenosine, CD39, kynurenine	Federated learning for multi-center calibration	Exhaustion monitoring in myeloma	[147, 149]
IMMLA-2.0 platform	Voice biomarkers + metabolites + ePROs	Multimodal transformer networks	Real-time toxicity grading	[111, 147]
GutBiome wearable	Fecal IPA, butyrate, LPS	Reinforcement learning-based alert system	B-cell reconstitution prediction	[147, 149]

147]. cBioPortal's new federated analysis module allows GDPR-compliant cross-border queries of somatic-genomic/transcriptomic data while retaining local data governance. Citizen science initiatives like Patients CANcer Omics (PCANO) empower patients to directly upload wearable omics data into research repositories, accelerating discovery of rare toxicity signatures, Venezuelan patients with Chagas cardiomyopathy, for example, were found to have unique IL-1Ra dynamics after CAR-T infusion, necessitating adapted toxicity management [142, 149].

Sustained equity requires embedded capacity building: the WHO's HEMATOMICS initiative establishes micro-credential courses for local bioinformaticians, coupled with containerized analysis suites (OmicsBox-Africa) that perform offline variant calling and immune repertoire reconstruction on low-bandwidth networks [147, 149].

Conclusion

Immunotherapy has irrevocably altered the therapeutic landscape for hematologic malignancies, yet its full potential remains constrained by unpredictable efficacy, resistance, and toxicity. This review underscores how multi-omics integration, spanning genomics, transcriptomics, proteomics, metabolomics, spatial biology, and microbiome profiling, transcends the limitations of single biomarkers to decode the complex interplay between tumors, immune cells, and therapy. By revealing molecular drivers of response, resistance, and adverse events, these layered approaches illuminate actionable pathways for intervention: from CRISPR-engineered epitopes that overcome antigenic paucity in AML, to microbiome-derived metabolites that enhance CAR-T persistence, and spatial immune architectures dictating Hodgkin lymphoma outcomes. Furthermore, advances in prodrug engineering, enabling precise molecular tailoring for stable delivery and rapid activation [150], complement these biological strategies in the overarching mission of personalizing cancer treatment.

ML and AI act as catalytic forces, transforming high-dimensional omics data into predictive digital twins, dynamic toxicity biomarkers, and adaptive clinical trial designs. Innovations like wearable sensors for real-time metabolite tracking and federated learning for global data equity are already bridging the gap between bench discoveries and patient-centric care. Despite challenges, data heterogeneity, tumor plasticity, and ethical imperatives, the convergence of multi-omics with immunotherapy heralds a paradigm shift: from empirical treatment to precision immuno-oncology. As basket trials incorporate omics stratification and liquid biopsies enable longitudinal monitoring, these strategies promise to optimize outcomes across leukemia, lymphoma, and myeloma. The future lies not in isolated biomarkers, but in integrative biological networks that personalize immunotherapy for every patient, turning heterogeneity from a barrier into a blueprint for cure.

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References

1. Lanier OL, et al. Immunotherapy approaches for hematological cancers. iScience. 2022. https://doi.org/10.1016/j.isci.2022.105326.
2. Zhang X, et al. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. Front Immunol. 2022;13:927153.
3. Soleimani Samarkhazan H, et al. Targeting acute myeloid leukemia through antibody engineering: innovations in immunotherapy and combination regimens. Clin Exp Med. 2025;25(1):215.
4. Moreno V, et al. Current and emerging immunotherapies for systemic AL amyloidosis. Discov Med. 2024;36(188):1761–71.
5. Zhang C, et al. Engineering car-t cells. Biomarker Res. 2017;5:1–6.
6. Rehman M, et al. Enhancing CAR T cells function: role of immunomodulators in cancer immunotherapy. Clin Exp Med. 2024;24(1):180.
7. Ma J, et al. Bispecific antibodies: from research to clinical application. Front Immunol. 2021;12:626616.

8. Jain T, Litzow MR. No free rides: management of toxicities of novel immunotherapies in ALL, including financial. Blood Adv. 2018;2(22):3393–403.
9. Rajabi L, et al. Aqueous and ethanolic extracts of Moringa oleifera leaves induce selective cytotoxicity in Raji and Jurkat cell lines by activating the P21 pathway independent of P53. Mol Biol Rep. 2025;52(1):102.
10. Choudhery MS, et al. Car-T-cell-based cancer immunotherapies: potentials, limitations, and future prospects. J Clin Med. 2024;13(11):3202.
11. Topalian SL, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54.
12. Soleimani Samarkhazan H, et al. The AML immune paradox: decoding escape pathways and pioneering checkpoint, vaccine, and combination strategies. Clin Exp Med. 2025;25(1):240.
13. Ding P, et al. Mechanism underlying the immune checkpoint inhibitor-induced hyper-progressive state of cancer. Cancer Drug Resistance. 2022;5(1):147.
14. Chen M, et al. Divergent tumor and immune cell reprogramming underlying immunotherapy response and immune-related adverse events in lung squamous cell carcinoma. J Immunother Cancer. 2023;11(10):e007305.
15. Cho U, Im S, Park HS. Exploring histological predictive biomarkers for immune checkpoint inhibitor therapy response in non–small cell lung cancer. J Pathol Transl Med. 2024;58(2):49–58.
16. Khagi Y, Kurzrock R, Patel SP. Next generation predictive biomarkers for immune checkpoint inhibition. Cancer Metastasis Rev. 2017;36:179–90.
17. Pavlović M, et al. The immuneML ecosystem for machine learning analysis of adaptive immune receptor repertoires. Nat Mach Intell. 2021;3(11):936–44.
18. Torres-Martos Á, et al. Omics data preprocessing for machine learning: a case study in childhood obesity. Genes. 2023. https://doi.org/10.3390/genes14020248.
19. Chen C, et al. Applications of multi-omics analysis in human diseases. MedComm. 2023;4(4):e315.
20. Yan J, et al. Network approaches to systems biology analysis of complex disease: integrative methods for multi-omics data. Brief Bioinform. 2018;19(6):1370–81.
21. Subramanian I, et al. Multi-omics data integration, interpretation, and its application. Bioinform Biol Insights. 2020;14:1177932219899051.
22. Zheng P, et al. A multi-omic analysis reveals that Gamabufotalin exerts anti-hepatocellular carcinoma effects by regulating amino acid metabolism through targeting STAMBPL1. Phytomedicine. 2024;135:156094.
23. Paulson J, et al. S845 predicted neoantigens provide prognostic insight in DLBCL. HemaSphere. 2019;3(S1):377.
24. De Mattos-Arruda L, et al. Neoantigen prediction and computational perspectives towards clinical benefit: recommendations from the ESMO precision medicine working group. Ann Oncol. 2020;31(8):978–90.
25. Chowell D, et al. Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy. Nat Med. 2019;25(11):1715–20.
26. Li Y, et al. Informing immunotherapy with multi-omics driven machine learning. NPJ Digit Med. 2024;7(1):67.
27. Di Giacomo AM, et al. Perspectives on the role of "-Omics" in predicting response to immunotherapy. Eur J Cancer. 2025;220:115393.
28. Raoufi A, et al. Macrophages in graft-versus-host disease (GVHD): dual roles as therapeutic tools and targets. Clin Exp Med. 2025;25(1):73.
29. Yang J, et al. Advancing CAR T cell therapy through the use of multidimensional omics data. Nat Rev Clin Oncol. 2023;20(4):211–28.
30. Sun D-Y, et al. Unlocking the full potential of memory T cells in adoptive T cell therapy for hematologic malignancies. Int Immunopharmacol. 2025;144:113392.
31. Bonaroti J, et al. Plasma proteomics reveals early, broad release of chemokine, cytokine, TNF, and interferon mediators following trauma with delayed increases in a subset of chemokines and cytokines in patients that remain critically ill. Front Immunol. 2022;13:1038086.
32. Sun L, et al. Metabolic reprogramming in immune response and tissue inflammation. Arterioscler Thromb Vasc Biol. 2020;40(9):1990–2001.
33. Hu T, et al. Metabolic regulation of the immune system in health and diseases: mechanisms and interventions. Signal Transduct Target Ther. 2024;9(1):268.
34. Zhang F, et al. "Beyond CAR-T: engineered NK cell therapies (CAR-NK, NKCEs) in next-generation cancer immunotherapy." Crit Rev Oncol Hematol. 2025. https://doi.org/10.1016/j.critrevonc.2025.104912.
35. Zugasti I, et al. Car-T cell therapy for cancer: current challenges and future directions. Signal Transduct Target Ther. 2025;10(1):210.
36. Aghayan AH, et al. "Extracellular vesicle-based biomarkers in diffuse large B-Cell lymphoma: a systematic review and meta-analysis." Crit Rev Oncol Hematol. 2025. https://doi.org/10.1016/j.critrevonc.2025.104884.
37. Prinzing B, et al. Deleting DNMT3A in CAR T cells prevents exhaustion and enhances antitumor activity. Sci Transl Med. 2021;13(620):eabh0272.
38. Stone ML, et al. Epigenetic therapy activates type I interferon signaling in murine ovarian cancer to reduce immunosuppression and tumor burden. Proc Natl Acad Sci U S A. 2017;114(51):E10981-e10990.
39. Abdar Esfahani M, et al. The epigenetic revolution in hematology: from benchside breakthroughs to clinical transformations. Clin Exp Med. 2025;25(1):230.
40. Topper MJ, et al. The emerging role of epigenetic therapeutics in immuno-oncology. Nat Rev Clin Oncol. 2020;17(2):75–90.
41. Qian F-C, et al. SEanalysis 2.0: a comprehensive super-enhancer regulatory network analysis tool for human and mouse. Nucleic Acids Res. 2023;51(W1):W520–7.
42. Moss J, et al. Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. Nat Commun. 2018;9(1):5068.
43. Soleimani Samarkhazan H, et al. "The microbiome in graft-versus-host disease: a tale of two ecosystems." J Transl Med. 2025;23(1):832.
44. Di Giacomo AM, et al. Perspectives on the role of "-Omics" in predicting response to immunotherapy. Eur J Cancer. 2025;220:115393.
45. Li Y, et al. Informing immunotherapy with multi-omics driven machine learning. NPJ Digit Med. 2024;7(1):67.
46. Menéndez V, et al. Mapping the spatial dynamics of the CD4+ T cell spectrum in classical Hodgkin lymphoma. Mod Pathol. 2024;37(9):100551.
47. Pickard K, et al. Location, location, location: mapping the lymphoma tumor microenvironment using spatial transcriptomics. Front Oncol. 2023;13:1258245.
48. Stewart BJ, et al. Spatial and molecular profiling of the mononuclear phagocyte network in classic Hodgkin lymphoma. Blood. 2023;141(19):2343–58.
49. van Bladel DAG, et al. Novel approaches in molecular characterization of classical Hodgkin lymphoma. Cancers (Basel). 2022. https://doi.org/10.3390/cancers14133222.
50. Abdar Esfahani M, et al. The epigenetic revolution in hematology: from benchside breakthroughs to clinical transformations. Clin Exp Med. 2025;25(1):230.

51. Aghayan AH, et al. Extracellular vesicle-based biomarkers in diffuse large B-cell lymphoma: a systematic review and meta-analysis. Crit Rev Oncol Hematol. 2025;215:104884.
52. Torres-Martos A, et al. Omics data preprocessing for machine learning: a case study in childhood obesity. Genes. 2023;14(2):248.
53. Li R, et al. Machine learning meets omics: applications and perspectives. Brief Bioinform. 2022;23(1):bbab460.
54. Katayama Y, et al. Machine learning approaches to TCR repertoire analysis. Front Immunol. 2022;13:858057.
55. Zhang G, et al. TRAPT: a multi-stage fused deep learning framework for predicting transcriptional regulators based on large-scale epigenomic data. Nat Commun. 2025;16(1):3611.
56. Lin E, Lane H-Y. Machine learning and systems genomics approaches for multi-omics data. Biomarker Res. 2017;5:1–6.
57. Mason DM, Reddy ST. Predicting adaptive immune receptor specificities by machine learning is a data generation problem. Cell Syst. 2024;15(12):1190–7.
58. Wei Z, et al. Prediction of severe CRS and determination of biomarkers in B cell-acute lymphoblastic leukemia treated with CAR-T cells. Front Immunol. 2023;14:1273507.
59. Liu B, et al. Developing a new sepsis screening tool based on lymphocyte count, international normalized ratio and procalcitonin (LIP score). Sci Rep. 2022;12(1):20002.
60. Bogatu A, et al. Meta-analysis informed machine learning: supporting cytokine storm detection during CAR-T cell therapy. J Biomed Inform. 2023;142:104367.
61. van Bladel DA, et al. Novel approaches in molecular characterization of classical Hodgkin lymphoma. Cancers. 2022;14(13):3222.
62. Stewart BJ, et al. Spatial and molecular profiling of the mononuclear phagocyte network in classic Hodgkin lymphoma. Blood, J Am Soc Hematol. 2023;141(19):2343–58.
63. Fortner A, Bucur O. Multiplexed spatial transcriptomics methods and the application of expansion microscopy. Front Cell Dev Biol. 2024;12:1378875.
64. Zhao C, Germain RN. Multiplex imaging in immuno-oncology. J Immunother Cancer. 2023;11(10):e006923.
65. Babu M, Snyder M. Multi-omics profiling for health. Mol Cell Proteomics. 2023;22(6):100561.
66. Cheng F, Su L, Qian C. Circulating tumor DNA: a promising biomarker in the liquid biopsy of cancer. Oncotarget. 2016;7(30):48832.
67. Lu C, et al. Applications of circulating tumor DNA in immune checkpoint inhibition: emerging roles and future perspectives. Front Oncol. 2022;12:836891.
68. Al-Showbaki L, et al. Changes in circulating tumor DNA and outcomes in solid tumors treated with immune checkpoint inhibitors: a systematic review. J Immunother Cancer. 2023;11(2):e005854.
69. Filis P, et al. Longitudinal ctDNA profiling in precision oncology and immuno-oncology. Drug Discov Today. 2023;28(4):103540.
70. Qureshi Z, et al. Liquid biopsies for early detection and monitoring of cancer: advances, challenges, and future directions. Ann Med Surg. 2025;87(6):3244–53.
71. Vaidyanathan R, et al. Cancer diagnosis: from tumor to liquid biopsy and beyond. Lab Chip. 2019;19(1):11–34.
72. Li W, et al. Liquid biopsy in lung cancer: significance in diagnostics, prediction, and treatment monitoring. Mol Cancer. 2022;21(1):25.
73. Ma L, et al. Liquid biopsy in cancer: current status, challenges and future prospects. Signal Transduct Target Ther. 2024;9(1):336.
74. Tivey A, et al. Mining nucleic acid "omics" to boost liquid biopsy in cancer. Cell Rep Med. 2024. https://doi.org/10.1016/j.xcrm.2024.101736.
75. Michelson S. The impact of systems biology and biosimulation on drug discovery and development. Mol Biosyst. 2006;2(6–7):288–91.
76. Wang H, et al. From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modeling. NPJ Digit Med. 2024;7(1):189.
77. Wang Y, et al. TWIN-GPT: digital twins for clinical trials via large language model. ACM Trans Multimedia Comput Commun Appl. 2024. https://doi.org/10.1145/3674838.
78. Anton SC, et al. State of the art in melanoma brain metastatic treatment and evidence of combined high-dose radiotherapy and immunotherapy approach. ARNM. 2024. https://doi.org/10.36922/arnm.3499.
79. Chen Y, et al. Oxygen-independent radiodynamic therapy: radiation-boosted chemodynamics for reprogramming the tumor immune environment and enhancing antitumor immune response. ACS Appl Mater Interfaces. 2024;16(17):21546–56.
80. Azuaje F. Computational models for predicting drug responses in cancer research. Brief Bioinform. 2017;18(5):820–9.
81. Mei T, Wang T, Zhou Q. Multi-omics and artificial intelligence predict clinical outcomes of immunotherapy in non-small cell lung cancer patients. Clin Exp Med. 2024;24(1):60.
82. Vimal S, et al. CRISPR/Cas9: role of genome editing in cancer immunotherapy. Oral Oncol Rep. 2024;10:100251.
83. Noormohamadi H, et al. CRISPR/Cas technologies in pancreatic cancer research and therapeutics: recent advances and future outlook. Discov Oncol. 2025;16(1):1530.
84. Jardim DL, et al. The challenges of tumor mutational burden as an immunotherapy biomarker. Cancer Cell. 2021;39(2):154–73.
85. Soleimani Samarkhazan H, et al. C-type lectin-like molecule-1 as a diagnostic, prognostic, and therapeutic marker in leukemia. Mol Biol Rep. 2025;52(1):464.
86. Soleimani Samarkhazan H, et al. Unveiling the potential of CLL-1: a promising target for AML therapy. Biomark Res. 2025;13(1):28.
87. Casirati, G., *Epitope editing of hematopoietic stem cells enables adoptive immunotherapies for acute myeloid leukemia.* 2023.
88. You, W., et al., 2025 *From foe to friend: Rewiring oncogenic pathways through artificial selenoprotein to combat immune-resistant tumor.* J Pharm Anal, p. 101322.
89. Casirati G, et al. Epitope editing enables targeted immunotherapy of acute myeloid leukaemia. Nature. 2023;621(7978):404–14.
90. Rodriguez H, et al. The next horizon in precision oncology: proteogenomics to inform cancer diagnosis and treatment. Cell. 2021;184(7):1661–70.
91. Ahmed S, Mazhar MS, Shabbir MF. Neoantigen-based cancer vaccines: current innovations, challenges and future directions in personalized immunotherapy. Cancer Immunol Connect. 2024;1(1):1–10.
92. Zehtabcheh S, et al. Insights into KMT2A rearrangements in acute myeloid leukemia: from molecular characteristics to targeted therapies. Biomark Res. 2025;13(1):73.
93. Ren Y, et al. Proteogenomics offers a novel avenue in neoantigen identification for cancer immunotherapy. Int Immunopharmacol. 2024;142:113147.
94. Doudna JA. The promise and challenge of therapeutic genome editing. Nature. 2020;578(7794):229–36.
95. He X, et al. Epigenetic modifications in radiation-induced non-targeted effects and their clinical significance. Biochimica et Biophysica Acta (BBA)-General Subjects. 2023;1867(8):130386.
96. Cheng S, et al. Long noncoding RNA lncNDEPD1 regulates PD-1 expression via miR-3619-5p in CD8+ T cells. J Immunol. 2022;208(6):1483–92.
97. Zhang C, et al. Long non-coding RNA MALAT1 in hematological malignancies and its clinical applications. Chin Med J. 2024;137(10):1151–9.

98. Wu X, et al. M(6)A-mediated upregulation of lncRNA CHASERR promotes the progression of Glioma by modulating the miR-6893-3p/TRIM14 axis. Mol Neurobiol. 2024;61(8):5418–40.
99. Alotaibi F. Exosomal micrornas in cancer: potential biomarkers and immunotherapeutic targets for immune checkpoint molecules. Front Genet. 2023;14:1052731.
100. Zhu M, et al. Exosomal miRNA as biomarker in cancer diagnosis and prognosis: a review. Medicine (Baltimore). 2024;103(42):e40082.
101. Melo SA, et al. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature. 2015;523(7559):177–82.
102. Yang P, et al. Exosomal microrna signature acts as an efficient biomarker for non-invasive diagnosis of gallbladder carcinoma. iScience. 2022. https://doi.org/10.1016/j.isci.2022.104816.
103. Salido-Guadarrama I, Romero-Cordoba SL, Rueda-Zarazua B. Multi-omics mining of lncRNAs with biological and clinical relevance in cancer. Int J Mol Sci. 2023;24(23):16600.
104. Yu J, Peng J, Chi H. Systems immunology: integrating multi-omics data to infer regulatory networks and hidden drivers of immunity. Curr Opin Syst Biol. 2019;15:19–29.
105. Pop RT, et al. Gene regulatory network integration with multi-omics data enhances survival predictions in cancer. Brief Bioinform. 2025. https://doi.org/10.1093/bib/bbaf315.
106. Shi, W., et al., *Pan-cancer proteogenomic network analysis uncovers immune microenvironment and prognostic biomarkers.* medRxiv, 2025: p. 2025.01. 15.24319471.
107. Wang H, et al. From virtual patients to digital twins in immuno-oncology: lessons learned from mechanistic quantitative systems pharmacology modeling. NPJ Digit Med. 2024;7(1):189.
108. Wang S, Ju D, Zeng X. Mechanisms and clinical implications of human gut microbiota-drug interactions in the precision medicine era. Biomedicines. 2024. https://doi.org/10.3390/biomedicines12010194.
109. Cheng S, et al. Long noncoding RNA lncNDEPD1 regulates PD-1 expression via miR-3619-5p in CD8(+) T cells. J Immunol. 2022;208(6):1483–92.
110. Ma L, et al. Liquid biopsy in cancer current: status, challenges and future prospects. Signal Transduct Target Ther. 2024;9(1):336.
111. Shajari S, et al. The emergence of AI-based wearable sensors for digital health technology: a review. Sensors (Basel). 2023. https://doi.org/10.3390/s23239498.
112. Naik N, et al. Legal and ethical consideration in artificial intelligence in healthcare: who takes responsibility? Front Surg. 2022;9:862322.
113. Sendorek DH, et al. Germline contamination and leakage in whole genome somatic single nucleotide variant detection. BMC Bioinformatics. 2018;19(1):28.
114. Zhou J, Huang C, Gao X. Patient privacy in AI-driven omics methods. Trends Genet. 2024;40(5):383–6.
115. Sahoo K, Sundararajan V. Methods in DNA methylation array dataset analysis: a review. Comput Struct Biotechnol J. 2024;23:2304–25.
116. Lu J, et al. Multi-omics decodes host-specific and environmental microbiome interactions in sepsis. Front Microbiol. 2025;16:1618177.
117. Argelaguet R, et al. Multi-omics factor analysis-a framework for unsupervised integration of multi-omics data sets. Mol Syst Biol. 2018;14(6):e8124.
118. Argelaguet R, et al. MOFA+: a statistical framework for comprehensive integration of multi-modal single-cell data. Genome Biol. 2020;21(1):111.
119. Omran MM, et al. Comparative analysis of statistical and deep learning-based multi-omics integration for breast cancer subtype classification. J Transl Med. 2025;23(1):709.
120. Elyanow R, et al. netNMF-sc: leveraging gene-gene interactions for imputation and dimensionality reduction in single-cell expression analysis. Genome Res. 2020;30(2):195–204.
121. Li W, et al. Knowledge-guided learning methods for integrative analysis of multi-omics data. Comput Struct Biotechnol J. 2024;23:1945–50.
122. Ballard JL, et al. Deep learning-based approaches for multi-omics data integration and analysis. BioData Min. 2024;17(1):38.
123. Picard M, et al. Integration strategies of multi-omics data for machine learning analysis. Comput Struct Biotechnol J. 2021;19:3735–46.
124. Ali H. Artificial intelligence in multi-omics data integration: advancing precision medicine, biomarker discovery and genomic-driven disease interventions. Int J Sci Res Arch. 2023;8(1):1012–30.
125. Mohr AE, et al. Navigating challenges and opportunities in multi-omics integration for personalized healthcare. Biomedicines. 2024. https://doi.org/10.3390/biomedicines12071496.
126. Yu Y, et al. Assessing and mitigating batch effects in large-scale omics studies. Genome Biol. 2024;25(1):254.
127. Yu Y, et al. Correcting batch effects in large-scale multiomics studies using a reference-material-based ratio method. Genome Biol. 2023;24(1):201.
128. Arevalo J, et al. Evaluating batch correction methods for image-based cell profiling. Nat Commun. 2024;15(1):6516.
129. Wang WJ, et al. Droplet digital PCR for BCR/ABL(P210) detection of chronic myeloid leukemia: a high sensitive method of the minimal residual disease and disease progression. Eur J Haematol. 2018;101(3):291–6.
130. Srivastava R. Advancing precision oncology with AI-powered genomic analysis. Front Pharmacol. 2025;16:1591696.
131. Derynck R, Weinberg RA. EMT and cancer: more than meets the eye. Dev Cell. 2019;49(3):313–6.
132. Horn LA, Fousek K, Palena C. Tumor plasticity and resistance to immunotherapy. Trends Cancer. 2020;6(5):432–41.
133. Yang H, et al. TMEM64 aggravates the malignant phenotype of glioma by activating the Wnt/β-catenin signaling pathway. Int J Biol Macromol. 2024;260:129332.
134. Friedrich M, et al. Tumor-induced escape mechanisms and their association with resistance to checkpoint inhibitor therapy. Cancer Immunol Immunother. 2019;68(10):1689–700.
135. Shi Z-D, et al. Tumor cell plasticity in targeted therapy-induced resistance: mechanisms and new strategies. Signal Transduct Target Ther. 2023;8(1):113.
136. Pandey S, Yadav P. Liquid biopsy in cancer management: integrating diagnostics and clinical applications. Pract Lab Med. 2025;43:e00446.
137. Amelio I, et al. Liquid biopsies and cancer omics. Cell Death Discov. 2020;6(1):131.
138. Erlich Y, Narayanan A. Routes for breaching and protecting genetic privacy. Nat Rev Genet. 2014;15(6):409–21.
139. Bonomi L, Huang Y, Ohno-Machado L. Privacy challenges and research opportunities for genomic data sharing. Nat Genet. 2020;52(7):646–54.
140. Naik N, et al. Legal and ethical consideration in artificial intelligence in healthcare: who takes responsibility? Front Surg. 2022;9:862322.
141. Thiele M, et al. Opportunities and barriers in omics-based biomarker discovery for steatotic liver diseases. J Hepatol. 2024;81(2):345–59.
142. Fountzilas E, et al. Tumor-agnostic baskets to N-of-1 platform trials and real-world data: transforming precision oncology clinical trial design. Cancer Treat Rev. 2024;125:102703.
143. Kasim A, et al. Basket trials in oncology: a systematic review of practices and methods, comparative analysis of innovative

methods, and an appraisal of a missed opportunity. Front Oncol. 2023;13:1266286.
144. Teleanu M-V, et al. Celebrating Ulrik Ringborg: multi-omics-based patient stratification for precision cancer treatment. Biomolecules. 2025;15(5):693.
145. Jacobson CA, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23(1):91–103.
146. Rejeski K, et al. CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499–513.
147. Dong H, et al. Mapping the rapid growth of multi-omics in tumor immunotherapy: bibliometric evidence of technology convergence and paradigm shifts. Hum Vaccin Immunother. 2025;21(1):2493539.
148. *LBA02–09 EMBARK: A phase 3 randomized study of enzalutamide or placebo plus leuprolide acetate and enzalutamide monotherapy in high-risk biochemically recurrent prostate cancer.* J Urol, 2023. **210**(1): p. 224–226.
149. Vidanagamachchi SM, Waidyarathna K. Opportunities, challenges and future perspectives of using bioinformatics and artificial intelligence techniques on tropical disease identification using omics data. Front Digit Health. 2024;6:1471200.
150. Feng C, et al. Precisely tailoring molecular structure of doxorubicin prodrugs to enable stable nanoassembly, rapid activation, and potent antitumor effect. Pharmaceutics. 2024;16(12):1582.