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Original Article

Integrative Multi-Omics in Precision Medicine: From Molecular Interconnectivity to Single-Cell Resolution

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ABSTRACT

The convergence of high-throughput omics technologies has ushered in a new era of precision medicine, enabling the comprehensive characterization of disease biology and the development of individualized treatment strategies. Traditionally, omics layers such as genomics, transcriptomics, proteomics, and metabolomics were analysed in isolation, limiting their clinical utility. However, recent advances in integrative computational approaches and biological modelling have shifted the paradigm toward systems biology, where multi-omics data are collectively analysed to capture dynamic, multilayered regulatory networks. This evolution has transformed our understanding of disease pathogenesis, therapeutic response, and resistance mechanisms. This review presents a detailed exploration of how multi-omics is being applied in modern precision medicine, with a particular focus on the growing importance of single-cell and spatial omics technologies. These modalities offer cell-type-specific and spatially resolved molecular insights, revealing hidden heterogeneity and functional interactions that influence drug efficacy. We discuss the mechanistic role of each omics layer, the interplay among layers, and emerging computational methods, including AI-based models and causal inference frameworks, that enable actionable insights from complex datasets. Furthermore, we highlight clinical case studies and translational advances demonstrating multi-omics applications in cancer therapy, immunotherapy, and microbiome modulation. Challenges related to data integration, standardization, privacy, and inclusion are also examined, along with future directions such as real-time liquid biopsy analysis and decision-support platforms. By tracing the transition from fragmented data analysis to unified, patient-centric frameworks, this review highlights the pivotal role of the multi-omics in shaping the next generation of personalized healthcare.

Keywords: multi-omics, precision medicine, drug response, single-cell omics, spatial transcriptomics, clinical decision support, systems biology

INTRODUCTION

Precision medicine represents a transformative shift in healthcare, aiming to tailor treatment and prevention strategies to the unique biological makeup of each individual. This approach recognizes that diseases, particularly complex disorders such as cancer, autoimmune conditions, and metabolic syndromes, are not monolithic entities but rather heterogeneous processes shaped by genomic, molecular, environmental, and lifestyle factors. Central to the success of precision medicine is the ability to unravel this heterogeneity at multiple biological scales, a task increasingly enabled by multi-omics technologies.[1] Multi-omics refers to the integrative analysis of diverse omics data types, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, and others, to provide a comprehensive view of cellular and physiological processes. Each omics layer captures distinct dimensions of biological regulation: the genome provides the blueprint, the epigenome modulates gene accessibility, the transcriptome reflects dynamic gene activity, the proteome encodes functional effectors, and the metabolome represents the biochemical state of the cell. When combined, these layers offer synergistic insights into disease mechanisms, treatment response, and systems-level interactions that cannot be inferred from any single modality alone.[2] Historically, the analysis of omics data has been siloed, with each layer investigated independently due to technological limitations, data incompatibility, and lack of integrative frameworks. Genomic studies have identified mutations linked to disease susceptibility and potential therapy targets,

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while transcriptomics has revealed gene expression signatures associated with prognosis. However, such isolated analyses often failed to account for downstream regulatory events, post-translational modifications, and metabolic alterations that critically influence phenotype. The emergence of integrative bioinformatics tools, advances in sequencing and mass spectrometry, and the establishment of public consortia such as TCGA, CPTAC, and ICGC have collectively catalysed a shift toward truly multi-dimensional analysis.[3] In parallel, novel experimental technologies—most notably single-cell omics and spatial transcriptomics—have enabled the dissection of molecular heterogeneity at unprecedented resolution. These tools enable researchers to capture cell-type-specific and location-specific molecular profiles, revealing how the tumour microenvironment, immune landscape, and intercellular interactions influence treatment outcomes. Such insights are increasingly informing the design of adaptive therapies, combination regimens, and biomarker-driven clinical trials.[4] This review aims to provide an in-depth synthesis of the current state and future directions of multi-omics in precision medicine. We begin by examining the biological contributions and limitations of individual omics layers, followed by a discussion of their interconnections through systems biology and trans-omics approaches. Subsequent sections explore the landscape of computational integration strategies, AI-driven predictive models, and case studies where multi-omics has informed clinical decision-making. Special emphasis is placed on single-cell and spatial technologies, the microbiome, and time-series omics, as well as the ethical, legal, and social dimensions of implementing these tools in real-world settings. By offering a holistic overview grounded in both mechanistic biology and translational science, this review underscores how multi-omics is poised to drive the next generation of predictive, preventative, and personalized healthcare.

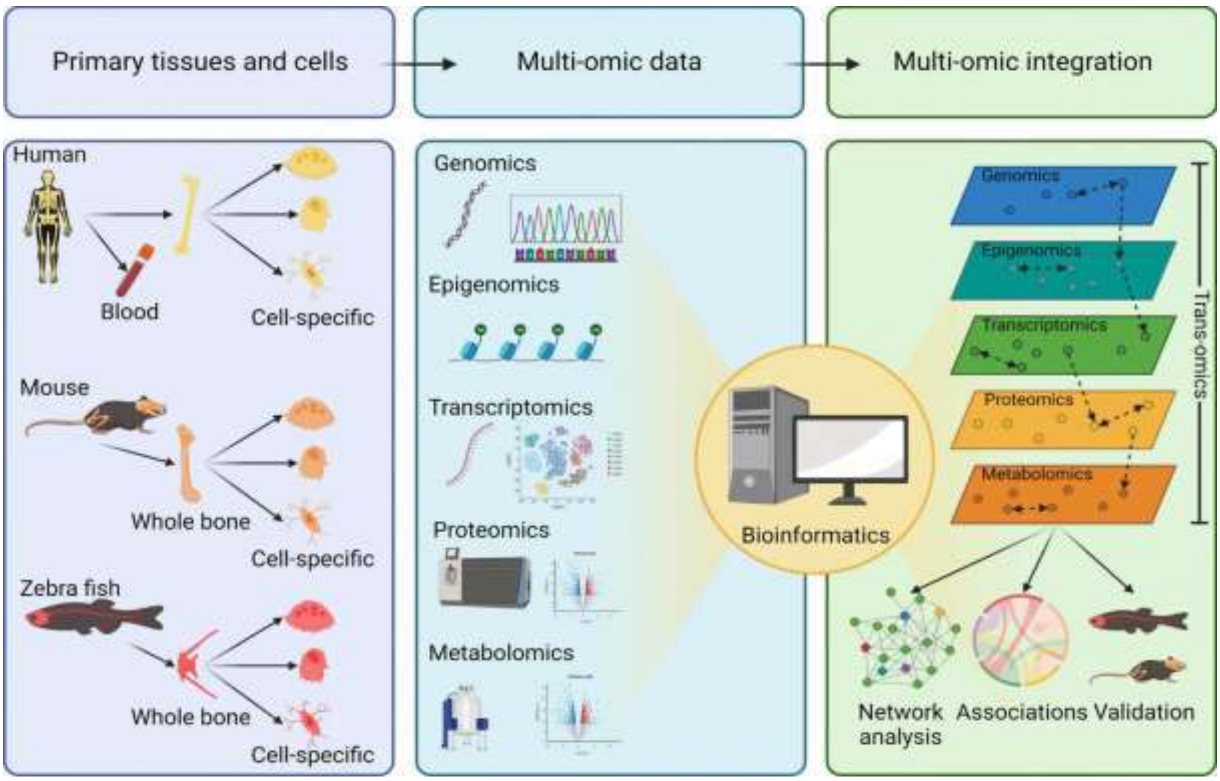

Figure 1. A comprehensive schematic illustrating the workflow of multi-omics research. Primary tissues and cells from humans and model organisms (mouse, zebrafish) are subjected to multi-omics profiling, including genomics, epigenomics, transcriptomics, proteomics, and metabolomics. These data are processed via bioinformatics pipelines and integrated through trans-omic models, leading to insights via network analysis, association studies, and biological validation. This integrative approach underpins precision medicine and systems-level biological discovery.

1. Individual Omics Layers in Drug Response and Disease Stratification

Understanding the individual contributions of genomics, epigenomics, transcriptomics, proteomics, and metabolomics is fundamental to appreciating their collective power in precision medicine. Each omics layer provides a distinct but interconnected perspective on biological function, disease development, and therapeutic response. When analysed in isolation, these layers offer critical mechanistic insights, identify key biomarkers, and inform drug development strategies. This section explores the mechanistic role, clinical utility, and inherent limitations of each omics domain, with examples drawn from large-scale datasets, including TCGA, METABRIC, CCLE, and CPTAC.

Genomics

Genomics represents the foundational layer of molecular biology, detailing the DNA sequence and its variations across individuals. Germline variants influence an individual's susceptibility to disease and their pharmacogenomic response to treatment. For example, polymorphisms in genes like *CYP2C19* and *TPMT* alter drug metabolism and toxicity profiles, influencing the efficacy of antiplatelet agents and thiopurines, respectively. Somatic mutations, on the other hand, are acquired alterations that drive tumour genesis and can predict therapeutic sensitivity or resistance. High-throughput whole-genome and whole-exome sequencing have facilitated the identification of actionable mutations such as *EGFR* in non-small cell lung cancer and *BRCA1/2* in breast and ovarian cancers. These discoveries have led to the development of targeted therapies (e.g., tyrosine kinase inhibitors for *EGFR* mutations, PARP inhibitors for *BRCA* mutations), now standard in clinical oncology. Genome-wide association studies (GWAS) further contribute by identifying loci associated with disease risk and treatment response across populations. However, the genomic layer alone often fails to capture regulatory and environmental influences that mediate the functional impact of genetic alterations. Not all mutations are biologically meaningful (i.e., passenger vs. driver mutations), and the penetrance of many germline variants is context-dependent. Thus, genomics provides necessary but insufficient information for a comprehensive understanding of complex phenotypes.[5]

Epigenomics

The epigenome encompasses heritable yet reversible modifications that regulate gene expression without altering the underlying DNA sequence. DNA methylation, histone modifications (e.g., acetylation and methylation), and chromatin remodeling collectively regulate transcriptional accessibility. Aberrant epigenetic regulation is a hallmark of cancer and other complex diseases, contributing to the silencing of tumour suppressors, the activation of oncogenes, and therapeutic resistance. DNA methylation profiling has identified hypermethylated promoters of genes such as *MGMT*, which predict response to alkylating agents in glioblastoma. Similarly, histone deacetylase inhibitors (HDACis) are being investigated as targeted therapies for epigenetically dysregulated tumours. Chromatin accessibility mapping using ATAC-seq reveals the dynamics of enhancers and transcription factor binding landscapes that influence gene expression programs during drug treatment. Despite these advances, epigenomic data are highly context-specific, varying across different cell types, developmental stages, and environmental exposures. Furthermore, distinguishing causal epigenetic alterations from secondary effects remains a challenge. The integration of epigenomics with transcriptomics and chromatin topology (e.g., Hi-C) is crucial to elucidate functional regulatory networks.[6]

Transcriptomics

Transcriptomics captures the functional output of the genome by measuring RNA expression levels, including mRNA, long non-coding RNAs (lncRNAs), and microRNAs (miRNAs). Differential gene expression profiling has been used for a long time to classify disease subtypes and identify predictive biomarkers. For instance, the PAM50 gene signature in breast cancer, derived from microarray data in the METABRIC cohort, stratifies patients into intrinsic subtypes (e.g., Luminal A, HER2-enriched) with distinct prognoses and treatment implications. RNA sequencing (RNA-seq) has largely supplanted microarrays, offering greater sensitivity and dynamic range. Transcriptomics also enables the discovery of alternatively spliced isoforms, fusion transcripts, and non-coding RNA elements involved in drug resistance and cellular reprogramming. Long non-coding RNAs (lncRNAs), such as HOTAIR, have been implicated in the metastatic progression and chemoresistance of cancer, while specific microRNAs (e.g., miR-21) regulate apoptosis pathways and influence drug response. Nevertheless, RNA abundance does not always correlate with protein levels due to post-transcriptional and translational regulation. Moreover, bulk transcriptomic analyses can obscure cell-type-specific expression patterns, particularly in heterogeneous tissues like tumours. These limitations are now being addressed through the use of single-cell RNA-seq and spatial transcriptomics.[7]

Proteomics

Proteomics investigates the proteome—the entire complement of proteins expressed by a cell or tissue at a given time. Since proteins are the primary effectors of cellular function and direct drug targets, proteomic data are uniquely positioned to link genotype to phenotype. Techniques such as tandem mass spectrometry (MS/MS), reverse-phase protein arrays (RPPA), and data-independent acquisition (DIA) enable high-resolution proteome profiling. CPTAC has demonstrated the power of proteomics in complementing genomic data. In ovarian cancer, for example, proteomic subtypes revealed biological distinctions not apparent from transcriptomic analysis alone. Quantitative proteomics can measure protein abundance, post-translational modifications (PTMs), and complex formation—critical factors in signal transduction and drug response. Phosphoproteomics, in particular, has been used to map kinase signalling networks and predict sensitivity to kinase inhibitors. However, proteomic analyses are technically demanding, with challenges in reproducibility, coverage, and sample preparation. PTMs are often labile, and low-abundance proteins may escape detection. Moreover, protein activity is influenced by localization, conformation, and interactions, which are challenging to capture comprehensively.[8]

Metabolomics

Metabolomics provides a snapshot of metabolic activity by quantifying small-molecule metabolites in cells, tissues, or biofluids. As the downstream product of gene and protein function, the metabolome is a sensitive indicator of physiological and pathological states. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry are the principal platforms for metabolomics. Cancer cells often exhibit altered metabolism (e.g., the Warburg effect), and metabolomic profiling can reveal dependencies that are exploitable for therapeutic purposes. For example, glutamine addiction in certain cancers has led to the development of glutaminase inhibitors. Metabolomics also plays a role in pharmacokinetics, providing insight into drug absorption, distribution, metabolism, and excretion (ADME). Additionally, metabolite signatures can serve as biomarkers for early detection, prognosis, or treatment monitoring. However, metabolomics faces several hurdles, including sample variability, challenges in compound identification, and quantification difficulties. The dynamic and transient nature of the metabolome requires rigorous standardization and careful experimental design. Integration with upstream omics layers is crucial for interpreting metabolic phenotypes within a regulatory context. Each omics layer provides indispensable insights into the biological underpinnings of disease and therapeutic response. Genomics identifies the blueprint; epigenomics and transcriptomics define regulatory landscapes; proteomics captures functional execution; and metabolomics reflects phenotypic consequences. When examined individually, these modalities have advanced our understanding of complex diseases and informed the development of targeted therapies. However, their limitations underscore the necessity of integrative approaches. The subsequent sections of this review will explore how these omics layers converge in multi-dimensional models to reveal emergent biological phenomena, guide clinical decisions, and ultimately enhance the precision and personalization of medicine.[1]

2. Interconnection of Multi-Omics Layers: From Siloed to Systems Biology

The transition from isolated omics investigations to integrated, systems-level analyses marks a pivotal transformation in biomedical research. While individual omics layers—genomics, epigenomics, transcriptomics, proteomics, and metabolomics—offer valuable insights in isolation, it is their interconnection that reveals the full complexity of biological regulation and disease pathogenesis. Multi-omics integration not only captures molecular diversity across multiple biological scales but also unveils the causal and regulatory interplay among layers that shape phenotypic outcomes. This systems biology approach lies at the heart of precision medicine.

Regulatory Cascades Across Omics Layers

Molecular processes within cells operate as interconnected networks, where changes at one omic level ripple through other layers. For example, genomic mutations can reshape the epigenetic landscape by altering DNA-binding motifs for chromatin remodelers or transcription factors. This, in turn, can influence chromatin accessibility and histone modifications, ultimately modulating gene expression and downstream protein abundance. A canonical example is the effect of *TP53* mutations on cellular transcriptional programs. Mutations in this key tumour suppressor gene disrupt DNA-binding capacity and transcriptional regulation, leading to widespread epigenetic and transcriptomic dysregulation. Similarly, mutations in chromatin regulators, such as ARID1A or EZH2, alter histone methylation patterns, which in turn affect the expression of target genes involved in cell cycle regulation and apoptosis. Conversely, epigenetic modifications can themselves influence the transcriptome. DNA hypermethylation of promoter CpG islands typically silences gene expression, as observed in the suppression of the *MGMT* gene in glioblastoma, which predicts enhanced response to temozolomide chemotherapy. Histone deacetylation also compacts chromatin structure, restricting access to transcriptional machinery and reducing mRNA synthesis. These regulatory events translate into reduced protein levels, impacting signalling pathways and therapeutic sensitivity.[9] Proteomic outcomes are further modulated by transcript stability, translation efficiency, and post-translational modifications (PTMs) - for instance, phosphorylation and ubiquitination control protein activation, localization, and degradation. A decrease in mRNA levels may not result in reduced protein abundance if compensatory translational mechanisms are present. Thus, proteomic data can reveal discrepancies between gene expression and functional output, providing critical context for evaluating treatment responses. At the metabolic level, feedback from cellular metabolites influences both transcription and epigenetic regulation. Acetyl-CoA, a central metabolite in energy metabolism, serves as a substrate for histone acetyltransferases (HATs), linking metabolic flux to chromatin state. Fluctuations in acetyl-CoA concentrations under hypoxia or nutrient stress can alter histone acetylation and transcriptional activation of metabolic genes. Similarly, S-adenosylmethionine (SAM), the methyl donor for DNA and histone methylation, connects one-carbon metabolism to gene silencing.[10]

Trans-Omics Relationships: Illustrative Examples

Trans-omics refers to the vertical propagation of regulatory signals across molecular layers. One of the most striking examples involves mutations in *IDH1* and *IDH2* in gliomas. These mutations lead to the production of 2-hydroxyglutarate (2-HG), an oncometabolite that inhibits the activity of DNA and histone demethylases. The result is widespread epigenetic reprogramming, characterized by a CpG island methylator phenotype (G-CIMP), which silences tumour suppressor genes and alters transcriptional networks. This trans-omic cascade links a single genomic mutation to epigenomic, transcriptomic, and phenotypic alterations in tumour behaviour. Another case involves breast cancer subtyping. Integrative analysis from the METABRIC and TCGA cohorts has shown that distinct genomic alterations (e.g., *PIK3CA*, *TP53* mutations) correspond with epigenetic and transcriptomic signatures that define intrinsic subtypes (Luminal A/B, HER2-enriched, Basal-like). These subtypes exhibit differential protein expression patterns and metabolic dependencies, guiding subtype-specific therapeutic interventions.[11]

Data-Driven Approaches for Revealing Multi-Omic Structures

The complexity of cross-omic relationships necessitates robust computational frameworks that can capture latent structures and correlations across datasets. Several integrative models have been developed to address this need:

- **MOFA+ (Multi-Omics Factor Analysis Plus):** An unsupervised learning framework that decomposes multi-omics datasets into latent factors. These factors capture shared and modality-specific sources of variation, facilitating biological interpretation and downstream predictive modelling. MOFA+ has been successfully applied to cancer, immunology, and neurodegenerative diseases.[6,12]

- **iClusterPlus:** A probabilistic model that performs joint latent variable analysis for clustering and subtype discovery. It integrates diverse omics types and identifies molecular subtypes with coordinated alterations across layers.[13]
- **DIABLO (Data Integration Analysis for Biomarker discovery using Latent components):** Part of the mixOmics suite, DIABLO performs supervised integration to identify multi-omics signatures associated with outcomes such as treatment response or survival.[14]
- **SNF (Similarity Network Fusion):** Constructs similarity graphs for each omics type and fuses them into a consensus network, capturing patient similarities across modalities. SNF has been used to stratify tumours and predict drug sensitivity more accurately than single-omics methods.[15]

These models enable researchers to uncover trans-omic modules, pathway perturbations, and predictive signatures that are otherwise invisible to single-layer analyses. For example, multi-omics factor models have identified latent dimensions that correspond to immune infiltration, stromal activity, and metabolic states in tumours, all of which influence drug response.

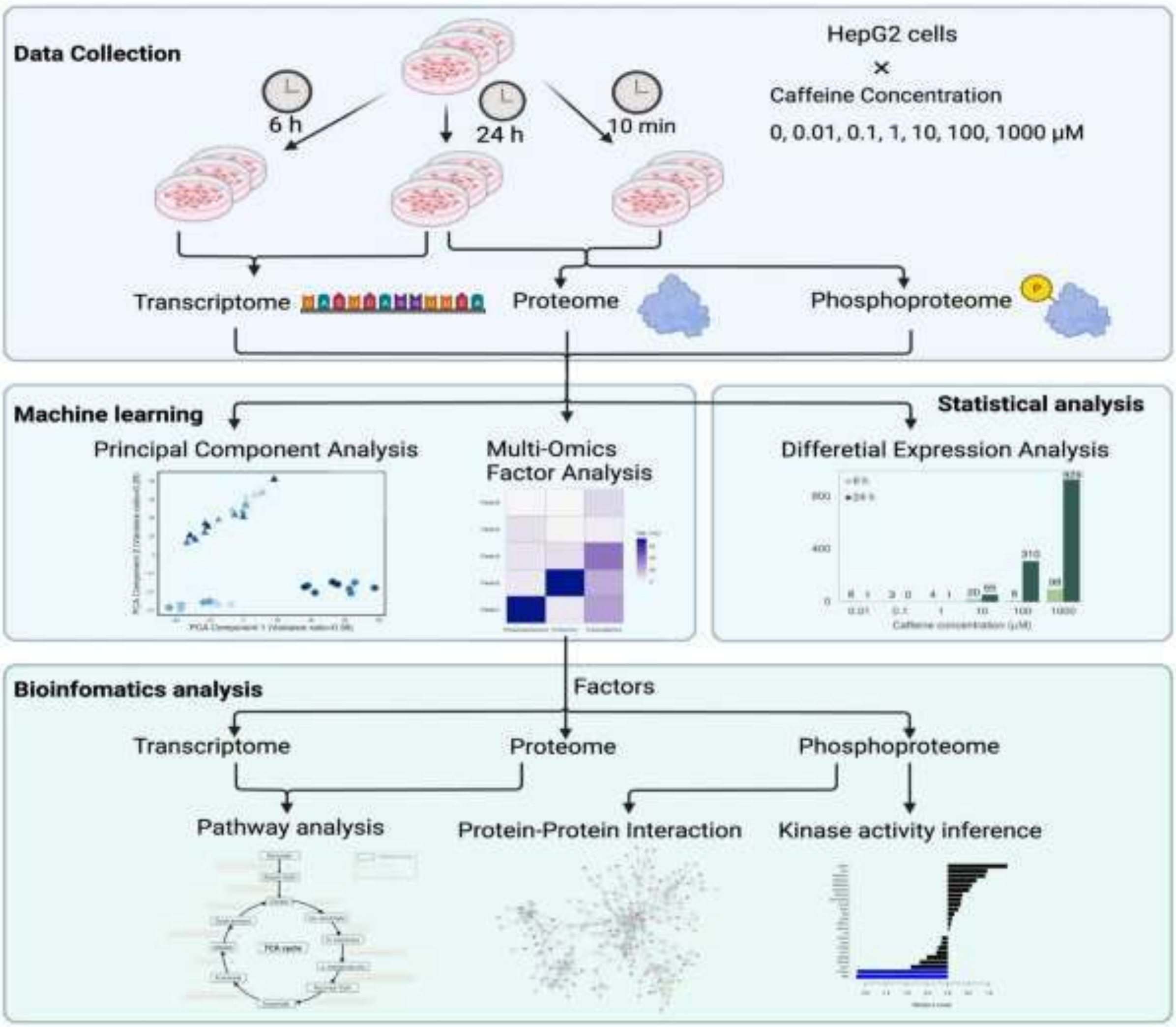

Figure 2. Practical Integration of Multi-Omics Layers Using Machine Learning and Bioinformatics. (Schematic representation of a time- and dose-dependent experimental setup using HepG2 cells exposed to varying caffeine concentrations. Transcriptomic, proteomic, and Phosphoproteomics

data are collected and processed using machine learning (PCA, MOFA), statistical analysis (differential expression), and bioinformatics pipelines (pathway analysis, protein-protein interactions, and kinase activity inference). This workflow demonstrates how multi-omics integration enables mechanistic interpretation and discovery of regulatory cascades across molecular layers in a trans-omic framework.)

Clinical and Biological Implications of Omics Interconnectivity

The interdependence of omics layers has profound implications for clinical diagnostics and therapeutic strategies. Single mutations or epigenetic events can have cascading effects across molecular networks, emphasizing the importance of comprehensive profiling. Multi-omics integration facilitates the identification of causal drivers rather than mere correlates, enhancing the precision of biomarker discovery. Additionally, it helps resolve discrepancies observed in clinical practice. For instance, patients with similar genomic profiles may exhibit vastly different responses to therapy due to downstream regulatory differences. By accounting for multi-layered variation, clinicians can refine treatment selection, monitor dynamic responses, and anticipate resistance mechanisms. Emerging applications in immunotherapy further illustrate the value of omics interconnectivity. Integrative analyses combining genomics, transcriptomics, and epigenomics have identified neoantigen landscapes, immune escape mechanisms, and response signatures to checkpoint inhibitors. These insights are now being translated into personalized immunotherapeutic regimens and adaptive trial designs. Multi-omics integration represents a fundamental advancement in our understanding of biological systems and disease mechanisms. The regulatory cascades and feedback loops spanning genomics, epigenomics, transcriptomics, proteomics, and metabolomics are essential for decoding cellular behaviour and therapeutic outcomes. Through data-driven models like MOFA+, iCluster, and DIABLO, researchers are unravelling these complex interdependencies and translating them into actionable insights. By embracing the interconnected nature of molecular biology, precision medicine can evolve beyond static biomarkers toward dynamic, systems-level predictors of health and disease.[1,2]

3. Single-Cell Multi-Omics and Cellular Heterogeneity

Cellular heterogeneity represents a significant challenge and opportunity in precision medicine. While bulk omics approaches average signals across populations of cells, masking rare and functionally important subpopulations, single-cell multi-omics technologies provide a high-resolution window into the diversity of cell states, lineages, and responses to therapy. This capability is particularly crucial in understanding cancer evolution, immune dynamics, and mechanisms of drug resistance. Recent advances have enabled the simultaneous measurement of multiple molecular modalities within individual cells, including gene expression, chromatin accessibility, protein abundance, and epigenetic modifications. By dissecting the interdependent layers of cellular regulation at single-cell resolution, researchers can capture emergent properties such as transcriptional noise, lineage plasticity, and microenvironmental adaptation that are pivotal to therapeutic response.[16]

Single-Cell Technologies and Modalities

Several landmark single-cell technologies now underpin this field:

- **scRNA-seq (Single-cell RNA sequencing):** Captures mRNA expression at single-cell resolution. Key to identifying cell types, differentiation trajectories, and transcriptional heterogeneity.
- **scATAC-seq (Single-cell Assay for Transposase-Accessible Chromatin):** Maps chromatin accessibility to identify regulatory elements, enhancers, and transcription factor binding sites.
- **CITE-seq (Cellular Indexing of Transcriptomes and Epitopes by sequencing):** Combines scRNA-seq with protein quantification using oligonucleotide-labelled antibodies, allowing joint measurement of transcriptome and surface proteome.

- **REAP-seq (RNA Expression and Protein sequencing):** Similar to CITE-seq, with variations in capture and barcode chemistry.
- **SHARE-seq (Simultaneous High-throughput ATAC and RNA Expression):** Enables parallel profiling of chromatin accessibility and gene expression in the same cell, linking cis-regulatory elements with transcriptional output.

These technologies are complemented by computational frameworks such as Seurat, Harmony, ArchR, and TotalVI, which perform dimensionality reduction, data integration, batch correction, and multimodal inference to extract biologically meaningful patterns.[17]

Capturing Rare Subclones and Drug Resistance

One of the most transformative applications of single-cell multi-omics is the detection of rare subclones that drive therapy resistance. In acute myeloid leukaemia (AML), for example, pre-treatment scRNA-seq profiling revealed minor subpopulations with transcriptional signatures associated with resistance, which expanded upon exposure to chemotherapy. These subclones expressed genes involved in quiescence, anti-apoptotic pathways, and drug efflux pumps—mechanisms not detectable in bulk transcriptomic data. Similarly, in breast and prostate cancers, rare stem-like or mesenchymal subpopulations identified by scRNA-seq exhibit intrinsic resistance to endocrine therapy or androgen deprivation, respectively. These cells often evade initial treatment but later seed relapse and metastasis.[18,19]

Cell Fate Plasticity and Adaptive Resistance

Single-cell studies have shown that drug exposure can induce plastic changes in cell state, allowing tumour cells to transition between epithelial and mesenchymal phenotypes, or between proliferative and dormant states. These transitions are accompanied by changes in gene regulatory networks and chromatin structure, as revealed by the integration of scRNA-seq and scATAC-seq. For instance, in melanoma treated with BRAF inhibitors, a subset of tumour cells enters a slow-cycling, dedifferentiated state characterized by elevated AXL expression and chromatin remodeling. These adaptive states are transient and reversible, challenging traditional notions of fixed genetic resistance.[20]

Immune Exhaustion and Immunotherapy Response

In immuno-oncology, single-cell technologies have been instrumental in dissecting the heterogeneity of tumour-infiltrating lymphocytes (TILs) and their role in response to immune checkpoint inhibitors. scRNA-seq of T cells from melanoma patients has identified distinct subsets, including exhausted CD8+ T cells expressing PD-1, TIM-3, and LAG-3, which exhibit reduced effector function. CITE-seq and TotalVI have further refined this characterization by integrating surface marker expression with transcriptomic states, revealing intermediate exhaustion phenotypes that correlate with clinical outcomes. These insights are now guiding the development of combination therapies that target co-inhibitory receptors or reinvigorate dysfunctional T cells.[21]

Single-Cell Profiling of CAR-T Therapy

CAR-T cell therapy has demonstrated remarkable efficacy in hematologic malignancies, yet responses in solid tumours remain limited. Single-cell multi-omics has helped uncover barriers to efficacy, such as T cell exhaustion, antigen loss, and suppressive tumour microenvironments. In a landmark study, single-cell profiling of CAR-T cells infused into patients with glioblastoma revealed heterogeneous activation states and clonal expansion patterns. Some CAR-T subsets exhibited high expression of exhaustion markers and cytokines, while others-maintained memory-like phenotypes. scATAC-seq of the same cells revealed regulatory elements associated with effector function and persistence, providing targets for the design of next-generation CARs.[22]

Integration and Trajectory Inference

Advanced computational tools enable the reconstruction of dynamic cell-state transitions over time. Tools like Monocle, Slingshot, and RNA velocity infer lineage trajectories and predict future states of individual cells based on RNA splicing dynamics. When coupled with chromatin data from

SHARE-seq or ArchR, these trajectories can be linked to the dynamics of regulatory elements, thereby enhancing mechanistic understanding. For example, in triple-negative breast cancer models, trajectory inference has shown how treatment-induced chromatin changes precede transcriptional reprogramming that culminates in resistant phenotypes. Such insights suggest that early chromatin remodeling events could serve as predictive biomarkers of resistance.[23]

Challenges and Future Directions

Despite their power, single-cell multi-omics technologies face several challenges. Technical noise, dropout events, and limited sensitivity can complicate the interpretation of data. High dimensionality necessitates sophisticated statistical models and large sample sizes to draw robust conclusions. Moreover, integrating modalities from the same cell (e.g., mRNA and chromatin) demands careful experimental and computational design. Recent innovations are addressing these barriers. Spatially-resolved single-cell methods are emerging, allowing researchers to map cellular interactions and niches within intact tissues. Lineage tracing and perturbation-based single-cell studies (e.g., CRISPR-Cas9 combined with single-cell RNA sequencing, scRNA-seq) are also expanding the functional interrogation of cellular heterogeneity.[24] Single-cell multi-omics represents a cornerstone of next-generation precision medicine. By resolving the cellular mosaic within tissues, these technologies reveal rare drug-resistant clones, dynamic cell state transitions, and immune phenotypes that dictate therapy outcomes. As analytical methods and multimodal assays continue to evolve, single-cell data will not only elucidate biological mechanisms but also inform clinical decisions in real time. Integrating these insights into multi-omics frameworks holds transformative potential for overcoming resistance, designing adaptive therapies, and advancing truly individualized care.[25]

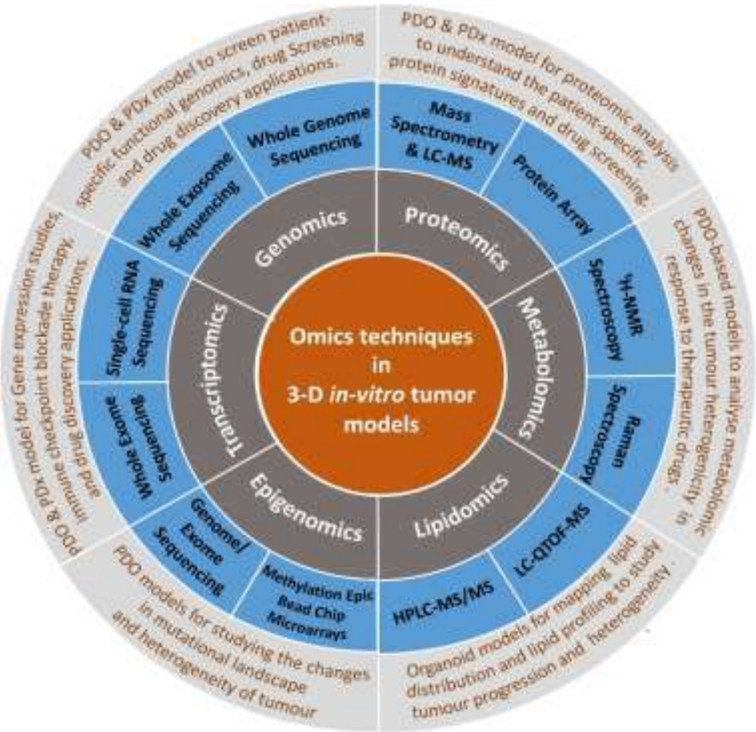

Figure 3. Circular representation of multi-omics platforms utilised in 3D in vitro tumour systems such as patient-derived organoids (PDOs) and xenografts (PDXs). The inner ring categorises major omics domains: genomics, transcriptomics, epigenomics, proteomics, metabolomics, and lipidomics. The middle ring lists specific technologies employed (e.g., scRNA-seq, mass spectrometry, HPLC-MS/MS), while the outer ring describes their functional applications—ranging from mutation analysis and immune checkpoint evaluation to therapeutic response and drug screening. This framework underpins precision oncology through physiologically relevant tumour modelling.

4. Spatial Omics: The Role of Microenvironment in Therapy Response

Spatial omics is redefining our understanding of tissue organization and its impact on therapeutic response. By preserving the spatial context of gene and protein expression within tissue architecture, spatial transcriptomics and proteomics allow researchers to study the tumour microenvironment (TME) with unprecedented resolution. These technologies are particularly valuable in heterogeneous diseases such as cancer, where the physical arrangement of malignant and non-malignant cells, along with factors like hypoxia, stromal interactions, and immune infiltration, profoundly impact treatment outcomes.[26]

Spatial Omics Technologies

Several cutting-edge platforms have emerged to measure spatially resolved molecular data:

- **10x Genomics Visium:** Captures whole-transcriptome spatial gene expression by embedding tissue sections on barcoded slides.
- **Nano String GeoMx Digital Spatial Profiler (DSP):** Quantifies transcripts and proteins in user-defined regions of interest (ROIs) using barcoded probes and oligo-tagged antibodies.
- **CODEX (CO-Detection by indexing):** Enables multiplexed spatial proteomics via iterative rounds of antibody staining and imaging, revealing the spatial distribution of dozens to hundreds of proteins.

These platforms provide high-dimensional molecular maps that reveal not only the composition of the TME but also the spatial relationships that govern cell-cell communication and response to therapy.

Spatial Context and Drug Response

Spatial omics has uncovered critical microenvironmental features that influence drug efficacy:

- **Hypoxic Tumour Zones:** Hypoxia, a common feature of poorly vascularized tumour regions, drives resistance to chemotherapy, radiotherapy, and immunotherapy. Spatial transcriptomics has identified hypoxia-inducible gene signatures that cluster in specific tumour regions and correlate with aggressive phenotypes and immune exclusion.
- **Immune Desert vs. Inflamed Phenotypes:** Tumours exhibit a spectrum of immune microenvironments. "Inflamed" tumours contain abundant T cell infiltration and often respond to immune checkpoint inhibitors (ICIs), whereas "immune deserts" lack effector immune cells, indicating a non-permissive or actively suppressive TME. Spatial profiling can distinguish these states, revealing that even within a single tumour, inflamed and non-inflamed regions may coexist, affecting treatment response heterogeneity.
- **Stromal Barriers:** Cancer-associated fibroblasts (CAFs) and extracellular matrix components can spatially restrict the penetration of drugs and immune cells. Spatial omics has shown that high-density stromal regions correlate with poor infiltration of cytotoxic T cells and reduced efficacy of ICIs and adoptive cell therapies.[27,28]

Case Study: Spatial Omics in Melanoma Immunotherapy

A landmark 2021 study by Ji et al. applied spatial transcriptomics and single-cell RNA-seq to tumour biopsies from melanoma patients treated with anti-PD-1 therapy. The study revealed distinct spatial niches characterized by immune activation, suppression, or exclusion. In responders, tumour regions showed colocalization of cytotoxic CD8+ T cells with tumour cells and expression of IFN-γ-related genes, forming "immune hubs." In contrast, non-responders exhibited spatial segregation between tumour and immune cells, with high expression of immune checkpoint molecules (e.g., PD-L1, LAG3) in stromal compartments. These findings demonstrated that spatial proximity between T cells and tumour cells—not just overall T cell presence—was critical for therapeutic efficacy.[29]

Integration with Single-Cell Omics

Spatial omics achieves its full potential when integrated with single-cell technologies. For instance, clustering results from scRNA-seq can be spatially mapped back to tissue sections, allowing for the high-resolution identification of cell types and states within their anatomical context. This integration allows researchers to:

- Track **cell-cell interactions** such as ligand-receptor signalling (e.g., CXCL9-CXCR3) between tumour and immune cells.
- Reconstruct **tumour-immune dynamics** under therapy pressure, including changes in spatial organization of Tregs, macrophages, and effector T cells.
- Visualize **clonal expansion** and migration patterns of immune cells following checkpoint blockade.

Tools like **Seurat v4**, **SpaOTsc**, and **STUtility** facilitate this cross-modal mapping, combining gene expression signatures from single cells with spatial coordinates from tissue slices.[30,31]

Clinical Implications and Future Directions

The ability to dissect the spatial architecture of tissues is transforming how we evaluate therapeutic response and resistance. Spatial biomarkers—such as immune cell proximity scores, stromal exclusion indices, or hypoxia gradients—are being developed to guide patient stratification and therapy selection. Clinical trials are increasingly incorporating spatial omics to refine inclusion criteria and identify predictive markers of response to treatment. Looking ahead, next-generation platforms aim to achieve subcellular resolution, integrate multi-omics layers (e.g., epigenome, metabolome), and enable real-time spatial analysis in clinical workflows. As spatial omics becomes more accessible, it is poised to become a cornerstone of personalized oncology and a critical component of systems-level precision medicine.[32]

5. Computational and AI Tools for Multi-Omics Integration

The integration of multi-omics data poses a formidable computational challenge due to the heterogeneity, dimensionality, and noise inherent in these diverse biological layers. To extract actionable insights from multi-omics datasets, researchers have developed a range of computational strategies, spanning statistical frameworks to artificial intelligence (AI) and deep learning models. These methods aim to capture shared and unique patterns across omics types, improve phenotype prediction, and enhance biological interpretability. This section provides a comprehensive overview of computational paradigms and AI-driven tools for multi-omics integration.[33,34]

Integration Paradigms: Early, Intermediate, and Late Fusion

Three major paradigms underpin the computational integration of multi-omics data:

- **Early Integration (Concatenation-Based):** Omics features from different modalities are merged into a single matrix before analysis. This approach is straightforward but suffers from data imbalance, scale disparity, and potential overfitting due to increased dimensionality. It often requires rigorous preprocessing and normalization.
- **Intermediate Integration (Joint Modelling):** Separate omics layers are analysed concurrently through shared latent representations or joint factor models. This method captures cross-modal correlations while preserving modality-specific variance. Tools like MOFA and iCluster exemplify this approach.
- **Late Integration (Decision-Level Fusion):** Independent models are trained for each omics type, and their outputs (e.g., predictions or latent features) are combined in a second-stage model. This modular design allows flexibility but may overlook complex inter-layer interactions.[35]

The choice of paradigm depends on the biological question, data type compatibility, and interpretability requirements.

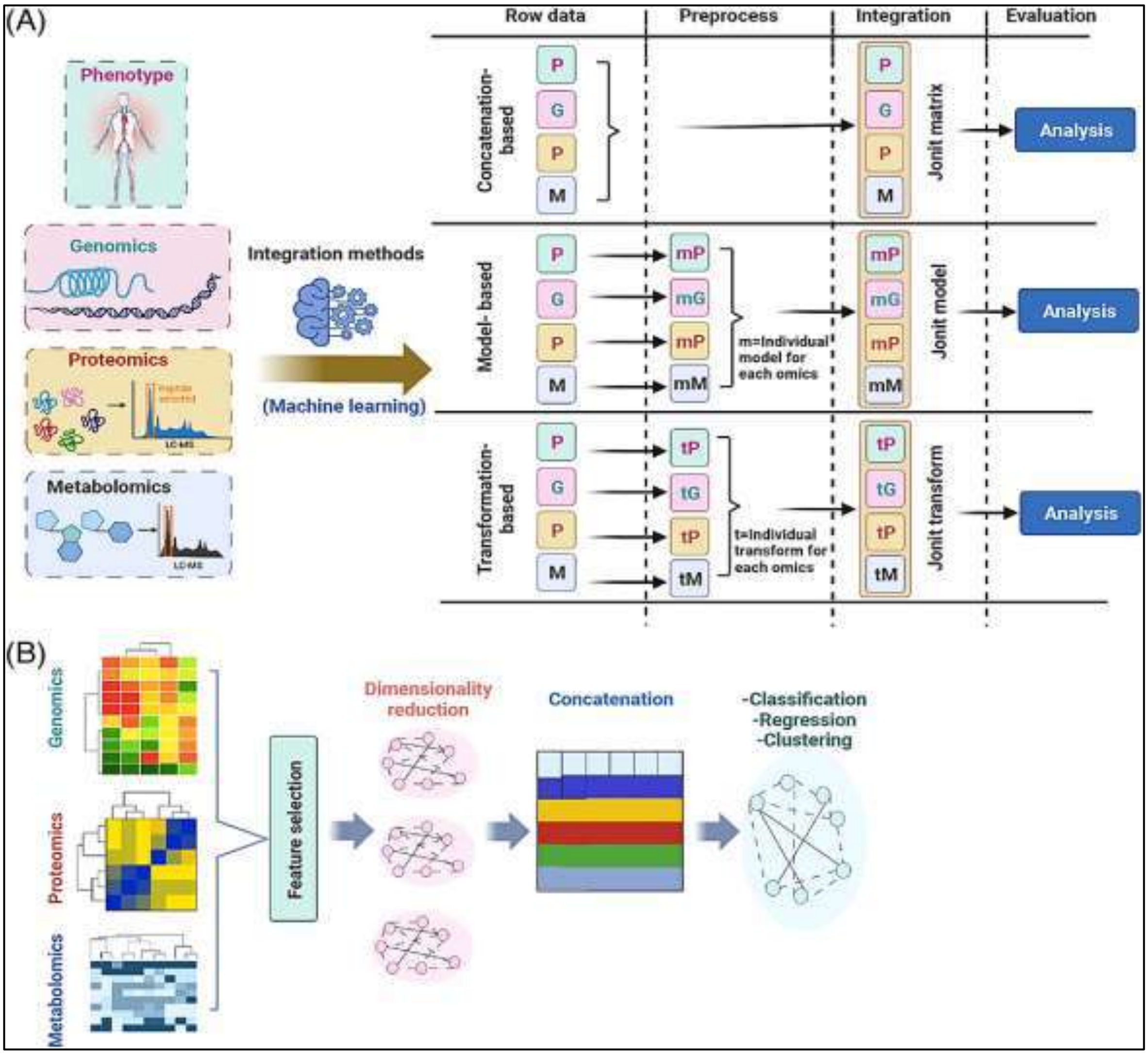

Figure 4. The brief process of integrating multi-omics data with machine learning and deep learning. (A) The process of data integration by machine learning. The concatenation-based integrated approach pipeline includes raw data from individual omics with corresponding phenotypic information, the data from the individual omics are then concatenated to form a single large matrix of multi-omics data, and finally, supervised or unsupervised methods are used for joint matrix analysis. The model-based integration method flow contains the establishment of the original data of various omics and the corresponding phenotypic information, develop individual models for each omics and then integrate them into a joint model, and finally, to analyse the joint model. And transformation-based method starts with raw data of individual omics and corresponding phenotypic information, followed by developing individual transformations (in the form of graphs or kernel relations) for each omics, and then integrating it into joint transformations, and finally, analyzing it. The letters of PGPM are represented as phenotypic data (P), genomic data (G), proteomic data (P), and metabolomic data (M) in sequence. (B) The brief concept of data integration is achieved by deep learning. First, preprocess and clean the multi-omics data, and then use conventional feature selection techniques or feature reduction methods for feature selection or dimensionality reduction to reduce the number of multi-omics variables. Next, multiple omics variables are concatenated into one large data set for data integration. Finally, further feature selection or reduction techniques are applied to reduce the variables, and the integrated data are analysed using classification, regression, and clustering.

Dimensionality Reduction and Latent Factor Models

Given the high dimensionality of omics data, dimensionality reduction is crucial for mitigating overfitting, enhancing computational efficiency, and uncovering latent biological structures.

- **MOFA (Multi-Omics Factor Analysis):** An unsupervised method that decomposes multi-omics datasets into a set of latent factors capturing shared and modality-specific variation. MOFA+ extends this approach to handle missing data and time-series data, enabling dynamic modelling of disease progression and treatment response.
- **DIABLO (Data Integration Analysis for Biomarker discovery using Latent components):** Part of the mixOmics R package, DIABLO performs supervised integration using latent components to identify multi-omics biomarkers predictive of phenotypes (e.g., treatment outcomes). It excels in classification tasks and supports sparse feature selection.
- **mixOmics:** A suite of multivariate methods for exploring relationships between omics datasets. It supports various integration methods, including PLS, CCA, and sPLS-DA for dimension reduction and classification.

These tools are widely used in multi-omics studies of cancer, metabolic diseases, and neurodegeneration, revealing clinically relevant molecular signatures.[14,36]

Network-Based Integration Methods

Network-based approaches leverage biological interactions to contextualize omics features and improve interpretability.

- **Similarity Network Fusion (SNF):** Constructs similarity graphs for each omics dataset and fuses them into a unified network that preserves both shared and unique sample similarities. SNF has been applied to patient stratification, revealing subtypes with distinct prognosis and drug responses.
- **NetDx:** A network-based patient classification tool that builds similarity networks from individual omics layers and integrates them using machine learning. It enables explainable predictions by identifying which features (e.g., gene pathways or clinical variables) drive classification.

These methods are especially powerful when paired with prior knowledge such as protein-protein interaction maps, signalling networks, and pathway databases, grounding computational predictions in biological context.[37,38]

Deep Learning for Multi-Omics Integration

Deep learning models can automatically learn complex, hierarchical representations from multi-modal data, offering scalability and high predictive power.

- **Autoencoders:** Neural network models that compress high-dimensional input into a latent space and reconstruct it. Variational autoencoders (VAEs) and multi-modal autoencoders are commonly used for integrating omics data. They enable unsupervised learning of latent features and data denoising.
- **Graph Neural Networks (GNNs):** Encode structured biological knowledge by modelling omics data as graphs (e.g., gene-gene or cell-cell interactions). GNNs can capture dependencies between features and have been applied to predict gene function, drug-target interactions, and disease subtypes.
- **Transformers:** Initially developed for natural language processing, transformer architectures (e.g., BERT-like models) are being adapted for multi-omics tasks. Their self-attention mechanism enables the model to focus on relevant feature relationships across data types.[39,40]

Interpretable Deep Learning Models: Drug Cell and Deep MO

Interpretability remains a significant concern in applying deep learning to clinical decision-making. Recent efforts focus on embedding biological knowledge into model architecture or generating feature importance scores.

- **Drug Cell:** A biologically interpretable deep learning model that maps genomic alterations to drug responses by embedding a hierarchical structure of cellular subsystems. Each subsystem corresponds to a biological process or pathway, allowing users to trace predictions to specific molecular mechanisms. DrugCell demonstrated high accuracy in predicting the sensitivity of cancer cell lines and provided mechanistic insights into the action of drugs.

- **DeepMO:** A deep neural network model designed for late-fusion integration of multi-omics data. It trains separate encoders for each omics type and combines the outputs in a shared latent layer. DeepMO has been used for drug synergy prediction and cancer subtype classification. Unlike early fusion methods, it allows flexibility in handling missing modalities.

These interpretable frameworks bridge the gap between predictive performance and clinical trust, making them suitable for translational applications.[39,41]

Challenges and Considerations

Despite their promise, computational models for multi-omics face several challenges:

- **Data heterogeneity:** Varying scales, distributions, and missingness complicate integration.
- **Sample size limitations:** High dimensionality often exceeds the number of available samples, necessitating regularization and careful validation.
- **Biological validation:** Computational predictions require experimental corroboration, which can be time-consuming and resource-intensive.
- **Generalizability:** Models trained on specific cohorts may not transfer across populations due to demographic or technical variability.

Continued development of benchmarking frameworks, interpretability tools, and biologically informed architectures will be essential to overcoming these barriers. Computational and AI tools are foundational to realizing the potential of multi-omics in precision medicine. From statistical factor models like MOFA and DIABLO to deep learning architectures such as DrugCell and DeepMO, these approaches enable integrative analysis that uncovers hidden structures, predicts treatment responses, and informs clinical decision-making. As algorithms become more interpretable and scalable, their adoption in clinical workflows is expected to accelerate, ushering in an era of data-driven, individualized healthcare.[42]

6. Case Studies and Clinical Applications

Real-world implementation of multi-omics in clinical settings has begun to reshape therapeutic decision-making, biomarker development, and patient stratification across various cancers and complex diseases. Between 2021 and 2024, several influential studies and clinical trials have demonstrated how multi-omics integration improves the prediction of treatment outcomes and enables personalized therapeutic strategies. The following case studies exemplify the transformative potential of multi-omics in practice.

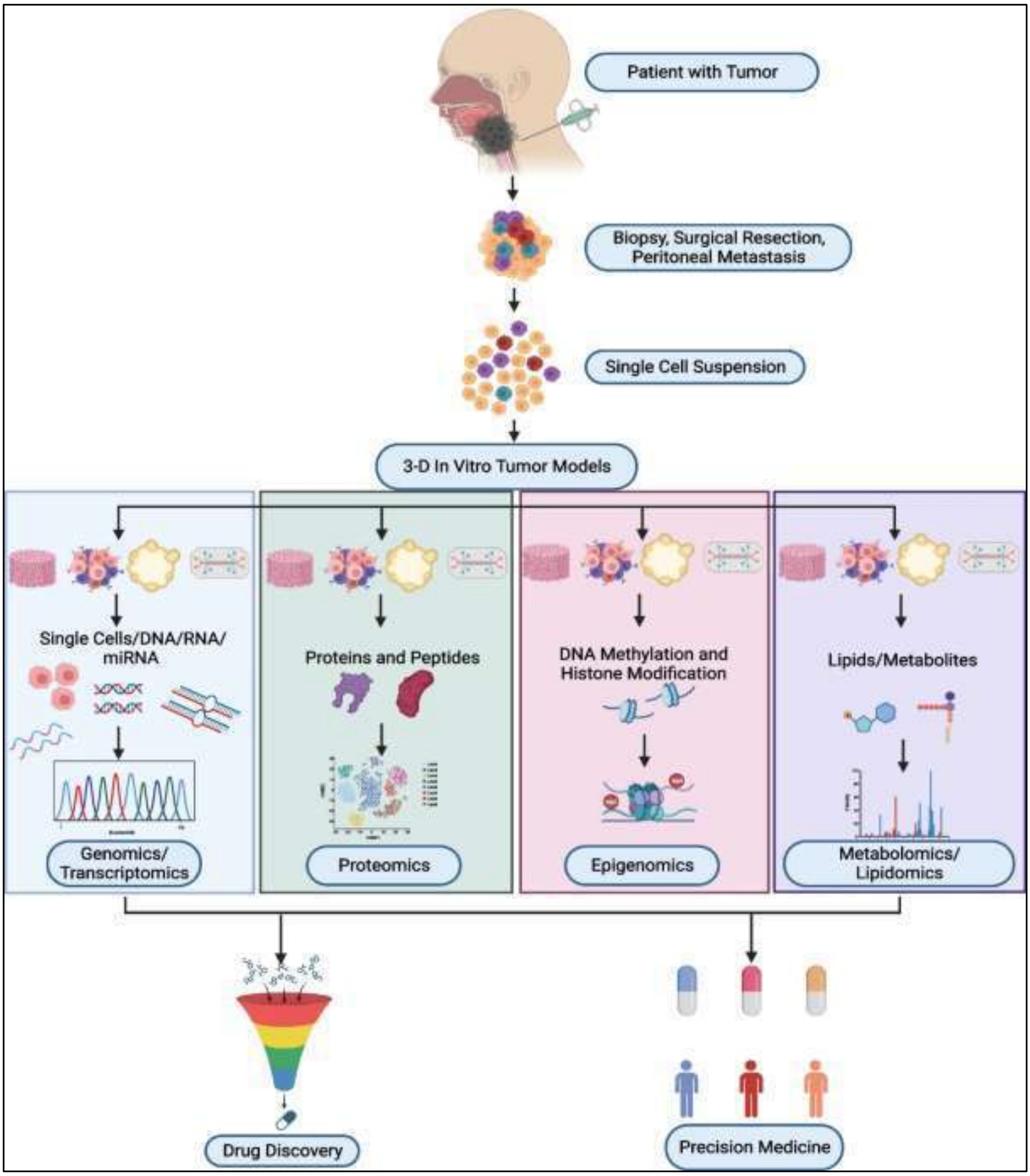

Figure 5. Diagram showing the process beginning with tumour biopsy and surgical resection, leading to single-cell suspensions and the generation of 3D in vitro tumour models. Multi-omics profiling—including genomics, transcriptomics, proteomics, epigenomics, and metabolomics—is then applied to these models. The integration of these data facilitates drug discovery pipelines and supports the development of tailored therapeutic strategies in precision oncology.

1) TCGA Pan-Cancer Atlas: Multi-Omics Integration for Survival Prediction

The TCGA Pan-Cancer Atlas project represents one of the most comprehensive efforts to integrate multi-omics data across diverse tumour types. In a 2022 extension of the initiative, researchers combined genomic, transcriptomic, epigenomic, and proteomic profiles across over 10,000 tumour samples to identify multi-modal molecular subtypes linked to clinical outcomes. Latent factor analysis (e.g., using MOFA and iCluster) revealed trans-omic features that stratified patients more effectively than single-omics approaches. For instance, a pan-cancer immune infiltration signature combining mRNA expression

(CD8A, GZMB), methylation (PD-L1 promoter), and proteomic markers (interferon-stimulated proteins) was predictive of survival across multiple cancer types. This integrative approach not only enhanced prognostic accuracy but also highlighted tissue-agnostic therapeutic targets, supporting a shift toward biomarker-driven oncology.[43]

2) WINTHER Trial: Transcriptome-Guided Therapy in Metastatic Cancer

The WINTHER trial (Lancet Oncology, 2022) was among the first clinical trials to use transcriptomic profiling to guide therapy in advanced solid tumours beyond genomic alterations alone. Patients underwent both DNA and RNA sequencing, and those without actionable genomic mutations were matched to therapies based on RNA expression signatures. By integrating transcriptomic data into the treatment algorithm, the trial achieved a 35% clinical benefit rate in the transcriptome-matched group compared to 20% in the genome-only group. Importantly, RNA-based therapy recommendations were feasible in 98% of patients, compared to only 40% based on genomic profiling. These findings underscore the clinical relevance of transcriptomics, especially when genomic alterations are insufficient to guide therapy.[44]

3) EGFR-Mutant Lung Cancer: Multi-Omics Modelling for Osimertinib Resistance

A 2023 study (Nature Medicine) investigated mechanisms of acquired resistance to Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, using an integrative multi-omics framework. Researchers profiled pre- and post-resistance biopsies using whole-exome sequencing, Phosphoproteomics, and single-cell RNA sequencing. The study identified multiple resistance mechanisms, including MET amplification (genomics), activation of bypass pathways (proteomics), and phenotypic transformation to a mesenchymal state (single-cell RNA sequencing, scRNA-seq). Importantly, proteogenomic analysis revealed persistent activation of the PI3K-AKT signalling pathway, even in the absence of genomic alterations, highlighting hidden vulnerabilities for combination therapy with PI3K inhibitors. This integrative approach has informed the design of ongoing basket trials combining EGFR and PI3K/AKT inhibitors in patients with resistant NSCLC, demonstrating the value of linking multimodal data to therapeutic strategy.[13,45]

4) PARP Inhibitors in BRCA-Wild-Type Tumour s: Multi-Omics-Derived HRD Scores

While BRCA1/2 mutations are established biomarkers for PARP inhibitor response, many BRCA-wild-type tumours exhibit homologous recombination deficiency (HRD) through alternative mechanisms. A 2021 multi-centre study employed genomic, methylation, and transcriptomic data to develop an integrative HRD score across ovarian and breast cancer cohorts. The model incorporated promoter methylation of *BRCA1*, mutational signatures (Signature 3), gene expression of HR pathway genes (e.g., *RAD51*, *ATM*), and large-scale state transitions (LSTs) to classify HRD-positive tumours. Patients with high composite HRD scores derived significant benefit from PARP inhibition, despite lacking BRCA mutations. This approach has been validated in the NOVA and ARIEL3 trials, prompting efforts to adopt pan-omics HRD profiling as a standard for patient selection and treatment.[46]

5) Single-Cell and Spatial Omics in Melanoma Immunotherapy (Cell, 2022)

A pivotal study published in *Cell* (2022) integrated single-cell RNA-seq, TCR sequencing, and spatial transcriptomics to examine tumour-immune interactions in melanoma patients receiving immune checkpoint inhibitors (ICIs). The analysis revealed that responders had spatially organized "immune hubs," where clonally expanded CD8+ T cells expressing cytotoxic and memory markers co-localized with tumour cells and antigen-presenting cells. Non-responders, in contrast, showed spatial segregation of immune cells and tumour cells, along with elevated expression of exhaustion markers (e.g., TOX, LAG3) in T cells. These findings demonstrate how spatial and single-cell resolution can reveal functional heterogeneity that is invisible to bulk profiling. The study provided a blueprint for spatial biomarkers and informed strategies for enhancing immune infiltration and response to ICIs. These recent case studies illustrate the clinical impact of multi-omics integration across various cancer types and treatment modalities. Whether by improving survival prediction (TCGA), guiding therapy beyond DNA mutations (WINTHER), resolving resistance mechanisms (EGFR/Osimertinib), refining biomarker definitions (HRD), or mapping immunotherapy responses (melanoma), multi-omics approaches are enabling a new level of precision in medical decision-making. As omics technologies become more accessible and interoperable, their incorporation into clinical workflows is poised to accelerate. The future of personalized medicine will be increasingly shaped by integrative, context-aware models that align molecular complexity with therapeutic intent.[1]

7. Microbiome-Host Omics Integration

The human microbiome, particularly the gut microbiota, plays a crucial role in modulating drug response through direct metabolic interactions, immune modulation, and systemic signalling. As the interface between host physiology and environmental exposures, the microbiome acts as both a driver and a sensor of therapeutic outcomes. Integrating microbiome profiling with host omics—such as transcriptomics and metabolomics—offers a powerful approach to uncovering the complex and bidirectional influences of microbial communities on precision medicine.

Microbiota-Driven Drug Metabolism

Microbial enzymes can alter the bioavailability and toxicity of drugs by chemically modifying active compounds. For instance, bacterial β-glucuronidases reactivate the chemotherapy drug irinotecan in the colon, resulting in gastrointestinal toxicity. Inhibiting these microbial enzymes has been shown to reduce side effects without compromising anticancer efficacy. Similarly, *Eggerthella lenta* metabolizes the cardiac drug digoxin into inactive forms, modulating its therapeutic window based on the abundance of specific bacterial strains. Methotrexate, an immunosuppressant used in the treatment of cancer and autoimmune diseases, is also subject to microbial transformation, which can either amplify or attenuate its effects. Understanding these drug-microbe interactions requires comprehensive profiling of microbial gene function. Tools like PICRUSt, QIIME2, and HUMAnN2 enable functional annotation of metagenomic data, linking microbial composition to metabolic capacity and predicting how microbial enzymes impact host drug metabolism.[47]

Integration with Host Transcriptomics and Metabolomics

Multi-omic integration facilitates a systems-level view of host-microbiome interactions. For example, combining microbiome profiles with host transcriptomics can help identify microbe-induced changes in gene expression in epithelial or immune cells. In one study, microbiota-mediated changes in tryptophan metabolism altered the expression of AHR-dependent genes in intestinal tissue, impacting mucosal immunity and barrier function. Metabolomic integration further reveals microbially derived metabolites such as short-chain fatty acids (SCFAs), bile acids, and polyamines that regulate immune tone and inflammation. These metabolites can shape transcriptional responses, modulate histone acetylation, and influence T cell differentiation—thereby linking microbiome status to systemic immunity and drug efficacy.[48]

Impact on Immunotherapy and FMT

The gut microbiome has emerged as a significant determinant of response to immune checkpoint inhibitors (ICIs). Responders to PD-1 blockade often harbour distinct microbial signatures enriched in taxa such as *Akkermansia muciniphila* and *Faecal bacterium prausnitzii*, which are associated with increased antigen presentation and T-cell priming. Conversely, antibiotic exposure that disrupts microbiome diversity has been correlated with reduced ICI efficacy. Mechanistic studies have shown that transferring microbiota from responders into germ-free or antibiotic-treated mice enhances anti-tumour immunity, validating causality. Faecal microbiota transplantation (FMT) is being investigated as a therapeutic strategy to restore responsiveness in individuals who do not respond to conventional treatments. Clinical trials in melanoma patients have shown that FMT from ICI responders can reprogram the tumour microenvironment and reinvigorate exhausted T cells. Ongoing efforts aim to identify the specific microbial functions and metabolites that mediate these effects. As microbiome profiling becomes more routine, integrating microbial and host omics will be essential to refining therapeutic strategies, predicting toxicity, and engineering the microbiome for clinical benefit.[49]

8. Temporal Omics and Dynamic Response

Biological systems are inherently dynamic, and static snapshots provided by conventional omics often fail to capture the temporal evolution of disease and treatment response. Temporal omics—based on longitudinal sampling and time-series analysis-provides critical insights into how molecular profiles change over time, enabling the development of adaptive strategies in precision medicine.

Time-Series Omics Platforms

Technologies such as longitudinal RNA-seq, phospho-proteomics, and metabolomics allow repeated sampling from the same patient or model system across treatment timelines. For example, tracking Phosphoproteomics changes during kinase inhibitor therapy can reveal early rewiring of signalling pathways that precede phenotypic resistance. Serial metabolomic profiling during immunotherapy has been used to monitor shifts in metabolic signatures, such as amino acid depletion or lipid remodeling, that correlate with immune activation or suppression. Similarly, repeated transcriptomic analysis can detect immune-related gene expression dynamics in blood or tumour biopsies.[50]

Modelling Approaches for Temporal Data

Several computational methods have been developed to analyse time-series omics:

- **Dynamic Bayesian Networks (DBNs):** Infer probabilistic temporal dependencies between molecular entities. DBNs have been used to reconstruct gene regulatory networks that evolve during drug response.
- **Gaussian Process Models:** Provide a flexible framework for modelling non-linear temporal patterns and estimating confidence intervals. These models are well-suited for small-sample longitudinal data with irregular time points.
- **Trajectory Inference Tools (e.g., Monocle, Slingshot):** While initially designed for single-cell pseudo time analysis, these tools can be adapted to bulk omics data to reconstruct differentiation or resistance trajectories over time.

By combining these models with prior biological knowledge, researchers can identify transient regulators, bifurcation points, and feedback loops that drive therapeutic adaptation.[51]

Applications in Immunotherapy and Resistance Tracking

In cancer immunotherapy, temporal transcriptomics has revealed how interferon response genes and checkpoint molecules fluctuate throughout treatment. Early elevation of IFN-γ-responsive genes has been associated with long-term benefit, whereas persistent expression of exhaustion markers predicts relapse. Time-series omics also aids in tracking the emergence of resistance. In chronic myeloid leukaemia, sequential transcriptomic profiling during tyrosine kinase inhibitor therapy uncovered activation of compensatory signalling pathways that herald treatment escape. By capturing molecular dynamics, temporal omics enables real-time monitoring, early warning systems for resistance, and optimization of treatment schedules. Temporal and microbiome-host omics integration offer powerful extensions to traditional multi-omics frameworks. While temporal omics decodes the kinetics of molecular adaptation, microbiome integration contextualizes systemic influences on therapy response. Together, these dynamic and ecological perspectives will be instrumental in designing truly adaptive, personalized, and resilient therapeutic strategies.[52,53]

9. Ethical, Legal, and Social Implications

The integration of multi-omics into precision medicine raises a complex array of ethical, legal, and social implications (ELSI) that must be addressed to ensure responsible and equitable implementation. As omics technologies advance in sensitivity and scale, so too do the risks associated with privacy, consent, and access.

Risks of Data Re-Identification

Multi-omics datasets, especially when linked to clinical and demographic metadata, create highly identifiable molecular fingerprints. Even when anonymized, the depth of information in genomic, transcriptomic, and epigenomic profiles enables re-identification through triangulation with public databases or environmental metadata. This raises critical concerns about individual privacy, potential discrimination, and unauthorized use of sensitive health data.[54]

Cross-Jurisdictional Data Governance

Global research collaborations must navigate differing legal frameworks governing data protection and sharing. The European Union's General Data Protection Regulation (GDPR) and the U.S. The Health Insurance Portability and Accountability Act (HIPAA) imposes strict conditions on the use of data, de-identification, and obtaining participant consent. Compliance challenges arise when datasets are shared across borders or integrated into multinational studies, necessitating robust data governance structures, including data access committees and ethical oversight.[55]

Dynamic Consent and FAIR Principles

Traditional static consent models are inadequate for multi-omics research, which often involves longitudinal studies, the use of secondary data, and evolving research objectives. Dynamic consent frameworks enable participants to update their preferences over time, enhancing transparency and autonomy. Additionally, adherence to FAIR (Findable, Accessible, Interoperable, Reusable) principles promotes responsible data stewardship while maximizing scientific value. FAIR-compliant infrastructures also facilitate reproducibility and trust in AI-driven models trained on omics data.[56]

Equity and Inclusion in Omics and AI

A major ethical challenge lies in the underrepresentation of non-European ancestries in omics datasets, which biases biomarker discovery, risk prediction, and the performance of AI models. This disparity risks exacerbating health inequalities by producing clinical tools that are less effective or even harmful for marginalized populations. Equitable precision medicine requires deliberate inclusion of diverse populations in biobanks, sequencing efforts, and clinical trials. Additionally, AI models must be audited for fairness, explainability, and generalizability across populations. Ethical frameworks should also account for systemic factors influencing access to omics-based care, including socioeconomic status, digital literacy, and healthcare infrastructure. Addressing these ELSI dimensions is essential not only for public trust but also for ensuring that the benefits of multi-omics in precision medicine are distributed fairly and sustainably.[57]

10. Challenges and Unmet Needs

While multi-omics technologies hold transformative potential, their clinical translation is impeded by numerous technical, infrastructural, and social challenges. Addressing these unmet needs is essential for realizing the full promise of omics-driven precision medicine.

Data Harmonization and Standardization

Multi-omics integration is hindered by data heterogeneity, which encompasses differences in sample processing, sequencing platforms, normalization protocols, and annotation standards. The lack of harmonized pipelines leads to irreproducibility and limits the potential for meta-analysis. Standardized workflows for data preprocessing, quality control, and integration are urgently needed. Community-driven efforts, such as the Global Alliance for Genomics and Health (GA4GH) and the Human Cell Atlas, are developing interoperable standards; however, adoption remains inconsistent across institutions.[58]

Clinical Reporting and Regulatory Alignment

Translating omics insights into clinical action requires transparent, standardized reporting of findings. Currently, there is no universal format for integrating multi-omics results into electronic health records (EHRs) or for conveying actionable results to clinicians. Guidelines akin to those for genomics (e.g., ACMG variant classification) are needed for other omics layers, including transcriptomics, proteomics, and metabolomics. Regulatory frameworks must also evolve to assess the validity and clinical utility of multi-omics tests.[59]

Interoperability with Electronic Health Systems

Integrating omics data into EHRs presents a significant logistical hurdle. Most health IT systems are not designed to accommodate high-dimensional, longitudinal, or unstructured omics data. Efforts like SMART on FHIR are beginning to bridge this gap, but scalable, secure, and interoperable solutions remain limited. Bidirectional integration, where clinical context informs omics interpretation, and omics data inform decision support, is crucial for real-time, adaptive precision medicine.[60]

Cost, Accessibility, and Infrastructure

High costs associated with sequencing, data storage, and bioinformatics analysis pose barriers to widespread adoption. In low- and middle-income countries, limited infrastructure exacerbates disparities in access to omics technologies and expertise. Strategies to reduce costs include pooled sequencing, federated data analysis, and cloud-based platforms. Investments in capacity building and international data sharing are also necessary to democratize multi-omics research and its applications.

Inclusion and Representation

A persistent gap in current omics studies is the underrepresentation of individuals from non-European ancestries, rural populations, and socioeconomically disadvantaged groups. This limits the generalizability of findings and perpetuates biases in predictive models. Programs like All of Us and H3Africa are attempting to address this imbalance, but broader efforts are necessary. Representation should also extend to disease types, environmental exposures, and gender identities to capture the full diversity of human biology.[61] Overcoming these challenges will require coordinated efforts among researchers, clinicians, policymakers, and communities. By building equitable, interoperable, and standards-based systems, the field can ensure that multi-omics fulfils its promise as a cornerstone of 21st-century medicine.

11. Future Outlook: Real-Time and Predictive Precision Medicine

The next frontier of precision medicine is being shaped by real-time, predictive, and mechanistic insights derived from integrated multi-omics. Rapid advances in technology, computation, and healthcare infrastructure are converging to enable continuous, adaptive, and decentralized models of care.

Real-Time Omics via Liquid Biopsies

Traditional tissue biopsies provide static, invasive snapshots of disease. In contrast, liquid biopsies, analyzing circulating cell-free DNA (cfDNA), RNA, and extracellular vesicles, such as exosomes, offer minimally invasive access to dynamic molecular information. These biospecimens enable the longitudinal monitoring of tumour burden, clonal evolution, and resistance mutations without the need for repeated invasive procedures. Recent developments in ultra-sensitive sequencing have improved detection of low-frequency variants in cfDNA, making it feasible to track molecular relapse before clinical progression. Integration with proteomic and metabolomic data from exosomes and plasma extends this approach to functional monitoring of disease.[62]

Digital Health Integration

Combining multi-omics with digital health data, such as wearable sensors, patient-reported outcomes, and EHR-derived clinical variables, enhances contextualization of molecular signals. For example, linking glucose monitoring, physical activity, and metabolomics can refine precision nutrition or diabetes management. Similarly, wearable-based heart rate variability and immune profiling could inform the timing of immunotherapy.[63]

Federated Learning and Edge Computing

To overcome barriers in data centralization, federated learning enables decentralized model training across multiple institutions without requiring the transfer of raw data. This preserves patient privacy while harnessing population-scale omics datasets. Coupled with edge computing, real-time analysis of omics data at the site of collection (e.g., hospitals, biobanks, mobile devices) becomes viable, supporting time-sensitive clinical decisions.[64]

Rise of Clinical Decision Support Tools (CDSTs)

AI-driven CDSTs are being developed to integrate multi-omics profiles with clinical data, offering evidence-based treatment recommendations. Tools like DeepMO and NetDx are being adapted for clinical environments, with a focus on prioritizing interpretability, robustness, and user trust. These systems can assist clinicians in identifying therapeutic matches, flagging adverse events, or tailoring monitoring strategies.[65]

Toward Mechanistic and Trans-Omics Models

Future predictive frameworks will not only identify correlations but also uncover causal relationships using trans-omics models that link genetic variants to phenotypes through layered regulatory networks. Causal inference algorithms and perturbation-based data (e.g., CRISPR screens, drug perturbations) will be vital for translating omics into actionable mechanisms.[66] Ultimately, the goal is a real-time, learning health system where mechanistic omics insights drive personalized, proactive, and equitable healthcare.

CONCLUSION

Multi-omics has redefined the landscape of biomedical science, propelling precision medicine from descriptive stratification to mechanistic, individualized interventions. By integrating genomics, epigenomics, transcriptomics, proteomics, and metabolomics, researchers and clinicians can decode the complexity of human biology with unprecedented depth and precision. The transition from siloed analyses to interconnected, systems-level approaches has been accelerated by technological advances and computational innovation. Notably, single-cell, spatial, and temporal multi-omics have exposed critical dimensions of heterogeneity, dynamic adaptation, and tissue microarchitecture that directly inform therapy response. This review has explored how integrative multi-omics is being deployed across domains—from clinical trials to routine care through AI-driven models, real-time liquid biopsies, and microbiome-host interactions. While challenges in standardization, ethics, and accessibility remain, the roadmap to implementation is increasingly evident. The future of omics-powered medicine demands multidisciplinary collaboration, inclusivity in data representation, and a commitment to responsible innovation. By embracing these principles, we can ensure that the full potential of multi-omics is realized, leading to improved health outcomes for all individuals, regardless of their background, geography, or disease type.

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