

Multi-Omics Integration in Breast Cancer: From Molecular Mechanisms to Precision Therapeutics

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ABSTRACT

Breast cancer remains one of the most prevalent malignancies worldwide and continues to represent a major cause of cancer-related morbidity and mortality. In recent years, advances in high-throughput omics technologies, particularly genomics, transcriptomics, and proteomics, have substantially transformed our understanding of breast cancer biology. Transcriptomic analyses provide detailed insights into gene expression dynamics and regulatory mechanisms, whereas proteomic approaches elucidate protein abundance, post-translational modifications, and interaction networks, together enabling a systems-level characterization of disease processes. These integrative approaches have significantly contributed to the identification of robust biomarkers for early detection, prognosis, and therapeutic stratification. Furthermore, the convergence of multi-omics data has facilitated the development of composite biomarker signatures and precision-based therapeutic strategies, effectively bridging the gap between molecular insights and clinical translation. Despite these advances, several challenges remain, including the complexity of data integration, high operational costs, and limited accessibility to advanced analytical platforms, which collectively constrain their routine implementation in clinical settings. Nevertheless, the integration of omics technologies with advanced bioinformatics frameworks continues to accelerate the discovery of novel biomarkers and actionable therapeutic targets, thereby driving the evolution of personalized medicine. This review provides a comprehensive overview of genomic, transcriptomic, and proteomic approaches in breast cancer, with particular emphasis on their roles in biomarker discovery and therapeutic development, as well as the critical contribution of bioinformatics tools in enhancing data interpretation and clinical applicability.

Key words: Cancer omics, Multi-omics integration, Omics, Precision medicine, Precision therapeutics.

1. INTRODUCTION

Breast cancer is a highly heterogeneous disease characterized by extensive molecular and clinical diversity, and it remains a leading cause of cancer-related morbidity and mortality worldwide [1]. The disease encompasses multiple subtypes, including hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive, and triple-negative breast cancer (TNBC), each exhibiting distinct biological behaviors, molecular signatures, and therapeutic responses [2]. This intrinsic heterogeneity necessitates more precise and comprehensive diagnostic and therapeutic strategies. Conventional approaches, such as histopathological assessment and imaging modalities, have been instrumental in disease classification and clinical management [3]. However, these techniques primarily rely on morphological and phenotypic characteristics and often fail to fully capture the underlying molecular complexity that drives tumor initiation, progression, and treatment resistance [5].

Recent advances in multi-omics technologies have transformed our understanding of breast cancer by enabling the integrative analysis of genomic, transcriptomic, and proteomic landscapes [6]. While the genome encodes the complete set of genetic information, it does not directly dictate cellular function. Gene expression at the transcriptomic level is dynamically regulated by transcription factors, epigenetic modifications, and environmental cues, resulting in context-dependent variability [7,8]. Furthermore, transcriptomic data alone provide only a partial view of cellular processes, as protein function is governed by additional layers of regulation, including post-transcriptional and post-translational modifications such as phosphorylation, acetylation,

and glycosylation [8]. These modifications critically influence protein activity, stability, and interactions, underscoring the limitations of single-omics analyses [9]. In this context, multi-omics integration offers a systems-level perspective that enables a more comprehensive understanding of biological processes and disease mechanisms. The convergence of genomic alterations, transcriptomic expression patterns, and proteomic dynamics has significantly advanced the characterization of breast cancer heterogeneity [10-12]. Genomic analyses have identified key mutations, copy number variations, and structural alterations that define distinct subtypes shown in Figure 1 [12]. Complementarily, transcriptomic profiling has revealed differential gene expression patterns robustness, and well-established analytical frameworks as depicted in figure 2 [13], while proteomic studies have uncovered functional protein networks and post-translational modifications that drive tumor progression and metastasis [14,15].

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The integration of these multi-dimensional datasets has facilitated the discovery of novel biomarkers for early detection, prognostic assessment, and prediction of therapeutic response as shown in table 1 [16]. Moreover, it has laid the foundation for the development of precision medicine approaches, including targeted therapies and immunotherapeutic strategies, thereby improving clinical outcomes [17]. By synthesizing insights across multiple omics layers, multi-omics approaches bridge the gap between molecular biology and clinical application, enabling more accurate patient stratification and personalized treatment interventions [18-20]. This review aims to provide a comprehensive overview of the role of genomic, transcriptomic, and proteomic analyses in breast cancer, with a particular emphasis on their applications in biomarker discovery and therapeutic development [21]. In addition, it highlights the critical role of bioinformatics tools in integrating and interpreting complex datasets [24], discusses current challenges in clinical translation [22], and outlines future directions, including the incorporation of single-cell technologies and machine learning frameworks to further advance breast cancer research and patient care [23].

2. GENOMIC APPROACHES TO BREAST CANCER

Breast cancer is characterized by a broad spectrum of genomic alterations, including somatic mutations, copy number variations, and structural rearrangements, which collectively drive tumor initiation, progression, and therapeutic resistance [15,24]. Recurrent mutations in key oncogenes and tumor suppressor genes such as TP53, PIK3CA, AKT1, and RB1 are frequently observed and play critical roles in oncogenic signaling and disease progression [25]. Among these, amplification of the *HER2* gene, present in a significant subset of breast cancers, is strongly associated with aggressive tumor behavior and has become a cornerstone for targeted therapeutic interventions [26]. In addition, emerging genomic insights have identified alterations in genes such as estrogen receptor 1 (*ESR1*) in hormone receptor-positive breast cancer, which contribute to resistance against endocrine therapies and highlight the dynamic nature of tumor evolution [27-29].

Advances in genomic technologies have profoundly transformed breast cancer research and clinical management by enabling comprehensive characterization of tumor-specific genetic landscapes [30]. Key genomic aberrations, including mutations in *BRCA1/2*, *PIK3CA*, and amplification of *HER2*, have facilitated the development of targeted therapeutic strategies that exploit specific molecular vulnerabilities [9,31]. For instance, poly (ADP-ribose) polymerase (PARP) inhibitors such as olaparib are effective in tumors harboring defects in homologous recombination repair [32], while CDK4/6 inhibitors such as palbociclib have demonstrated efficacy in hormone receptor-positive breast cancer by targeting cell cycle dysregulation [33]. In parallel, genomic profiling has led to the development of clinically validated prognostic and predictive assays, such as Oncotype DX and Mamma Print, which inform treatment decisions by estimating recurrence risk and guiding the use of adjuvant chemotherapy [34,35]. Furthermore, the identification of biomarkers such as programmed death-ligand 1 (PD-L1) expression and tumor mutational burden has expanded the application of immunotherapeutic approaches, particularly in TNBC, where treatment options have historically been limited [36].

Despite these significant advances, several challenges remain in the clinical translation of genomic data, including high costs, limited accessibility, and the complexity of data interpretation [37]. Future directions in the field are focused on the integration of emerging technologies such as liquid biopsy for non-invasive disease monitoring, as well as the exploration of non-coding RNAs and the tumor-associated microbiome in cancer development [38]. In addition,

the incorporation of artificial intelligence (AI) and machine learning approaches is expected to enhance the analysis of complex genomic datasets, thereby accelerating biomarker discovery and therapeutic innovation [39]. Collectively, these developments hold considerable promise for advancing precision oncology and improving clinical outcomes in breast cancer management [40].

3. GENOMIC TECHNOLOGIES

Advancements in genomic technologies have substantially expanded our understanding of the genetic architecture of breast cancer, enabling high-resolution characterization of tumor heterogeneity and molecular alterations [14,31]. Whole-genome sequencing has emerged as a powerful approach for comprehensive analysis of the cancer genome, facilitating the identification of novel mutations, structural variants, and chromosomal rearrangements that may serve as potential therapeutic targets [41]. This unbiased, genome-wide strategy has provided critical insights into previously unrecognized genomic drivers of breast tumorigenesis. Next-generation sequencing has become a cornerstone technology in breast cancer genomics, enabling rapid and high-throughput identification of mutations in key cancer-associated genes such as *BRCA1/2* and *PIK3CA* [42]. Beyond mutation detection, next-generation sequencing allows for the detailed profiling of tumor heterogeneity, including the identification of subclonal populations that contribute to disease progression, therapeutic resistance, and recurrence [43]. The ability to resolve such intratumoral complexity has significant implications for precision oncology and treatment optimization [44].

In addition to sequencing technologies, genome editing tools such as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Cas9 have revolutionized functional genomics by enabling precise manipulation of specific genetic alterations. This technology has facilitated the systematic investigation of gene function in breast cancer and has provided a robust platform for validating candidate driver mutations and therapeutic targets [45]. For example, CRISPR-based approaches have been employed to model mutations in oncogenes such as *PIK3CA*, allowing the assessment of their functional impact and responsiveness to targeted therapies [40]. Collectively, these technological advancements have not only deepened our understanding of breast cancer biology but have also accelerated the identification of actionable targets and the development of novel therapeutic strategies, thereby reinforcing the foundation of precision medicine [46]. While genomic analyses provide the foundational blueprint of oncogenic alterations, a deeper understanding of breast cancer biology necessitates exploration of downstream transcriptional dynamics and functional proteomic landscapes [47,50].

4. TRANSCRIPTOMIC APPROACHES IN BREAST CANCER

Transcriptomic profiling has emerged as a fundamental approach for elucidating the molecular mechanisms underlying breast cancer, providing critical insights into gene expression dynamics and regulatory networks [48]. The identification of differentially expressed genes between normal and malignant tissues has enabled the characterization of key molecular drivers involved in tumorigenesis, metastasis, and therapeutic resistance [49]. These gene expression patterns are closely associated with distinct breast cancer subtypes, including hormone receptor-positive, *HER2*-positive, and TNBC, each defined by unique transcriptional signatures and biological behaviors [50]. For instance, overexpression of *HER2* in *HER2*-positive tumors is strongly linked to enhanced cellular proliferation and therapeutic resistance, whereas alterations in *ESR1* are characteristic of hormone receptor-positive breast cancers and contribute to endocrine resistance [51].



Transcriptomic analyses have also provided valuable insights into the role of immune-related pathways, particularly in TNBC, where immune signaling plays a pivotal role in disease progression and therapeutic response [52]. Large-scale gene expression profiling across patient cohorts has facilitated the development of robust molecular signatures that can predict clinical outcomes, treatment response, and potential therapeutic targets, thereby advancing personalized medicine [53]. Notably, early transcriptomic studies classified breast cancer into intrinsic molecular subtypes – luminal A, luminal B, HER2-enriched, and basal-like – based on distinct gene expression profiles, establishing a framework for subtype-specific therapeutic strategies [54]. The identification of molecular determinants of metastasis represents another critical application of transcriptomics. Gene expression analyses have revealed key mediators of tumor invasion and dissemination, including chemokines such as CXCL12 and matrix metalloproteinases, which contribute to extracellular matrix remodeling and metastatic colonization [55]. These findings underscore the importance of transcriptomic approaches in uncovering the biological pathways driving metastatic progression and in identifying potential therapeutic targets.

Moreover, transcriptomic studies have highlighted the heterogeneity of the tumor immune microenvironment across different breast cancer subtypes, emphasizing the necessity for tailored immunotherapeutic strategies [56]. Understanding the molecular basis of therapeutic resistance has also been significantly advanced through transcriptomic profiling. For example, upregulation of the FGFR signaling pathway has been implicated in resistance to endocrine therapy in hormone receptor-positive breast cancer, suggesting that targeting this pathway may enhance treatment efficacy [55]. These insights reinforce the importance of identifying subtype-specific resistance mechanisms to inform the development of targeted therapeutic interventions. In addition, transcriptomic analyses have provided a deeper understanding of tumor–microenvironment interactions. Activation of signaling pathways such as Wnt/ β -catenin within stromal components has been shown to promote tumor progression, immune evasion, and resistance to therapy [57], highlighting the complex interplay between cancer cells and their surrounding microenvironment. Emerging evidence also underscores the critical role of long non-coding RNAs in breast cancer biology. Specific long non-coding RNAs have been identified as regulators of tumor progression and metastasis, functioning either as tumor suppressors or oncogenic drivers [58]. These molecules represent promising candidates for novel therapeutic targeting and biomarker development. Furthermore, the advent of single-cell transcriptomics has provided unprecedented resolution in characterizing intratumoral heterogeneity and cellular diversity within the tumor microenvironment [59]. Single-cell RNA sequencing studies have revealed distinct cellular subpopulations, including immunosuppressive cell types and rare mutant clones that contribute to therapeutic resistance [60]. These findings highlight the potential of single-cell approaches to uncover previously unrecognized mechanisms of disease progression and resistance, thereby facilitating the development of more precise and personalized treatment strategies [52]. Collectively, transcriptomic approaches have significantly advanced our understanding of breast cancer biology by revealing complex regulatory networks, identifying clinically relevant biomarkers, and guiding the development of targeted and individualized therapeutic strategies [61]. Importantly, post-transcriptional and post-translational modifications introduce additional layers of regulation that can only be resolved through proteomic analysis [8,54].

5. TRANSCRIPTOMIC TECHNOLOGIES

RNA sequencing and microarray technologies represent the principal methodologies for transcriptomic profiling in breast cancer

research [62]. Among these, RNA sequencing has emerged as the gold standard due to its high sensitivity, broad dynamic range, and capacity to detect a wide spectrum of transcripts, including novel and low-abundance RNA species [63]. Furthermore, RNA sequencing enables the identification of alternative splicing events and post-transcriptional modifications, thereby providing a comprehensive and unbiased representation of the transcriptome. In contrast, microarray-based approaches rely on predefined probes, which limit their ability to detect novel transcripts; however, they remain widely utilized due to their cost-effectiveness, robustness, and well-established analytical frameworks [64].

Both platforms facilitate the identification of differentially expressed genes between normal and tumor tissues, contributing to the discovery of biomarkers that can distinguish breast cancer subtypes and predict clinical outcomes [65]. Notably, RNA sequencing has significantly expanded the scope of transcriptomic analysis by enabling the characterization of non-coding RNAs, including microRNAs and long non-coding RNAs, which are increasingly recognized as critical regulators of gene expression and tumor biology. Over the past two decades, the integration of transcriptomic data with advanced bioinformatics tools has enabled the identification of gene expression signatures that play pivotal roles in tumor classification, prognostic assessment, and the development of personalized therapeutic strategies, thereby reinforcing the importance of transcriptomics in precision oncology [66].

6. PROTEOMIC APPROACHES IN BREAST CANCER

Proteomics has emerged as a critical component in elucidating the molecular mechanisms underlying breast cancer, particularly through the identification of key proteins that regulate tumor progression, metastasis, and therapeutic resistance [67]. As the large-scale study of protein expression, function, and interactions, proteomics provides a functional perspective that complements genomic and transcriptomic analyses [54]. Proteins serve as the primary effectors of cellular processes, including signal transduction, metabolic regulation, and structural organization. Consequently, proteomic profiling enables the characterization of downstream molecular events resulting from genetic and transcriptional alterations, offering a comprehensive understanding of disease biology [16,68]. Proteomic analyses have been instrumental in the discovery of biomarkers for breast cancer diagnosis and prognosis. Mass spectrometry-based approaches have enabled the identification of plasma protein signatures associated with early-stage disease, including differential expression of apolipoproteins and inflammatory markers between patients and healthy individuals [54,70]. Similarly, high-throughput proteomic studies have uncovered novel biomarkers linked to metastatic progression, highlighting their potential utility in early detection and disease monitoring [69].

Comprehensive proteomic profiling of breast cancer specimens has further revealed substantial molecular heterogeneity across intrinsic subtypes [65]. Analyses of formalin-fixed paraffin-embedded samples have demonstrated distinct proteomic signatures among subtypes, with basal-like tumors exhibiting stratification into immune-active and immune-suppressed phenotypes, suggesting differential responsiveness to immunotherapy [69]. In HER2-enriched subtypes, variations in extracellular matrix composition, lipid metabolism, and immune signaling pathways have been observed, indicating opportunities for subtype-specific therapeutic interventions [70]. In TNBC, proteomic clustering has identified distinct subgroups with variable clinical outcomes, underscoring the necessity for personalized treatment strategies [71]. Given its aggressive nature and limited treatment options, TNBC has been a major focus of proteomic investigations. Advanced proteomic approaches, including label-free



quantitative analysis and immunoprecipitation mass spectrometry, have facilitated the identification of novel therapeutic targets [16]. Specific oncogenic proteins have been shown to be overexpressed in this subtype, promoting tumor proliferation and metastasis through activation of signaling pathways such as PI3K–AKT. In addition, protein–protein interaction analyses have revealed mechanisms by which these factors stabilize oncogenic proteins and contribute to tumor progression, thereby highlighting their potential as targets for therapeutic intervention [78].

In situ proteomic analyses using laser capture microdissection combined with quantitative shotgun proteomics have enabled precise characterization of protein expression within tumor epithelial compartments [72]. Comparative analyses between non-malignant and malignant epithelial cells have identified differentially expressed proteins associated with tumorigenesis. Functional enrichment analyses have further revealed alterations in ESR-dependent signaling pathways and cellular morphology-related processes, providing deeper insights into the molecular basis of breast cancer progression [73]. Proteomics has also significantly contributed to the identification of actionable therapeutic targets. Integration of proteomic and phosphoproteomic datasets has enabled the characterization of dysregulated signaling networks, particularly in HER2-positive breast cancer, where aberrant kinase activity and phosphorylation events have been identified as key drivers of tumor growth [74]. Advances in targeted proteomic techniques, such as parallel reaction monitoring, have further facilitated the clinical validation of candidate biomarkers and therapeutic targets, thereby enhancing the translational potential of proteomic findings [75]. Moreover, proteomic profiling has provided critical insights into tumor heterogeneity and the tumor microenvironment. Subtype-specific protein expression patterns, particularly in TNBC, have highlighted the involvement of immune-related pathways, suggesting potential responsiveness to immunotherapeutic strategies [59,76]. The integration of proteomic data with genomic information through proteogenomic approaches has further enabled a more comprehensive understanding of tumor biology and regulatory mechanisms.

The rapid advancement of proteomic technologies has been a major driver of these discoveries. Techniques such as liquid chromatography–tandem mass spectrometry and data-independent acquisition have significantly improved the depth, sensitivity, and reproducibility of proteomic analyses [77]. In parallel, the application of advanced bioinformatics and machine learning methodologies has enhanced the interpretation of complex proteomic datasets, facilitating the identification of clinically relevant molecular patterns [78]. Finally, proteins implicated in metastasis, including matrix metalloproteinases, vimentin, and E-cadherin, are frequently dysregulated in aggressive breast cancers and serve as important biomarkers of metastatic potential. Overall, proteomic profiling plays a pivotal role in the identification of novel biomarkers and therapeutic targets, particularly those involved in immune evasion and cell cycle regulation, thereby contributing to the advancement of precision medicine in breast cancer [79].

7. PROTEOMIC TECHNOLOGIES

A wide array of advanced proteomic technologies has been employed to comprehensively profile protein expression and characterize post-translational modifications in breast cancer. Among these, mass spectrometry represents a cornerstone technique due to its high sensitivity, broad dynamic range, and ability to identify diverse protein species along with critical post-translational modifications, including phosphorylation, glycosylation, and acetylation [77-80]. In particular, liquid chromatography–tandem mass spectrometry has proven highly effective for large-scale proteomic analyses, enabling deep coverage of the proteome and facilitating the detection of low-

abundance proteins that may play pivotal roles in tumorigenesis [81]. In addition to mass spectrometry-based approaches, antibody-based proteomic techniques such as immunohistochemistry and enzyme-linked immunosorbent assays remain widely utilized for the targeted detection and quantification of specific proteins in tissue specimens and biological fluids [80]. These methods provide valuable qualitative and quantitative insights into protein expression patterns within clinical samples [16,80].

Emerging technologies, including quantitative proteomics and single-cell proteomics, are further expanding the scope of proteomic investigations [81]. These approaches enable high-resolution analysis of protein expression at the level of individual cells or small cellular populations, thereby offering critical insights into intratumoral heterogeneity and cellular diversity. Collectively, these technological advancements are enhancing our ability to delineate complex protein networks and molecular mechanisms underlying breast cancer progression (Figure 3) [82]. While proteomic analyses provide critical insights into functional protein dynamics, a comprehensive understanding of disease biology requires the integration of multi-omics data across genomic, transcriptomic, and proteomic layers.

8. MULTI-OMICS INTEGRATION IN BREAST CANCER

The integration of multi-omics data, encompassing genomics, transcriptomics, and proteomics, has profoundly transformed our understanding of breast cancer by enabling a comprehensive characterization of its molecular landscape [78,83]. Multi-omics integration strategies are broadly categorized into early integration (data-level fusion), intermediate integration (feature-level), and late integration (model-level), each offering distinct advantages in capturing cross-omics relationships [96,99]. While each omics layer provides distinct and complementary insights, their combined analysis facilitates the identification of complex biological mechanisms and regulatory networks that cannot be fully elucidated through single-omics approaches [84]. Genomic data reveal underlying genetic alterations, transcriptomic profiling captures dynamic gene expression patterns, and proteomic analyses provide functional insights into protein activity and post-translational modifications [76]. The convergence of these datasets enables a more holistic understanding of tumor biology, bridging the gap between genetic variation and phenotypic manifestation [84]. Multi-omics integration enhances the identification of robust biomarkers, improves patient stratification, and supports the development of targeted and personalized therapeutic strategies [85].

By leveraging the interplay between genomic mutations, transcriptional regulation, and proteomic alterations, this integrative approach facilitates more precise disease classification and informs clinical decision-making, ultimately contributing to improved therapeutic outcomes in breast cancer management [86]. The effective integration of these heterogeneous datasets requires advanced computational and bioinformatics frameworks capable of harmonizing multi-layered data structures [61,106]. Techniques such as matrix factorization, network-based modeling, and machine learning algorithms are increasingly employed to extract biologically meaningful patterns and establish functional relationships across omics layers [87]. These integrative strategies enable the transition from descriptive analyses to predictive and systems-level modeling of breast cancer biology [42,72].

9. BIOINFORMATICS AND MULTI-OMICS DATA INTEGRATION STRATEGIES

The successful integration of multi-omics data in breast cancer research relies heavily on advanced bioinformatics methodologies



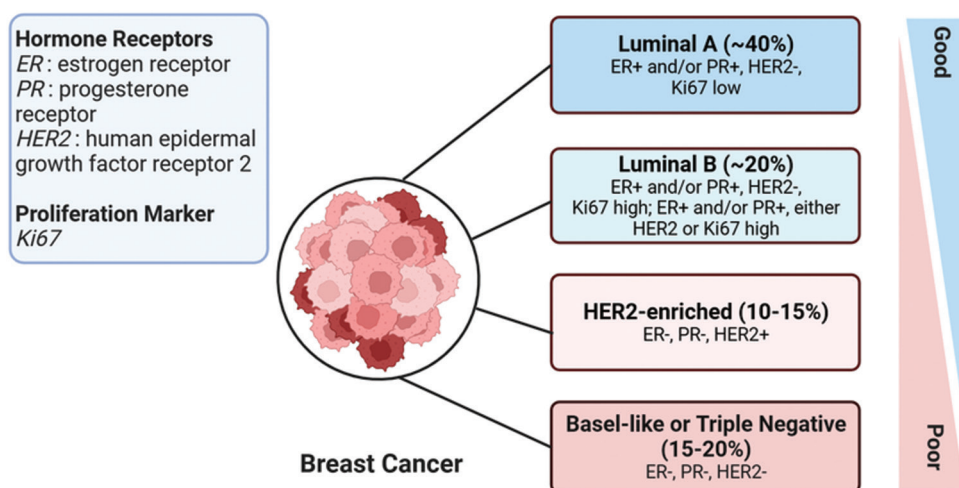


Figure 1: Molecular subtypes of breast cancer including luminal a, luminal b, human epidermal growth factor receptor 2-enriched and triple-negative breast cancer, along with their key biomarkers (Adapted from Wang *et.al.* 2024).

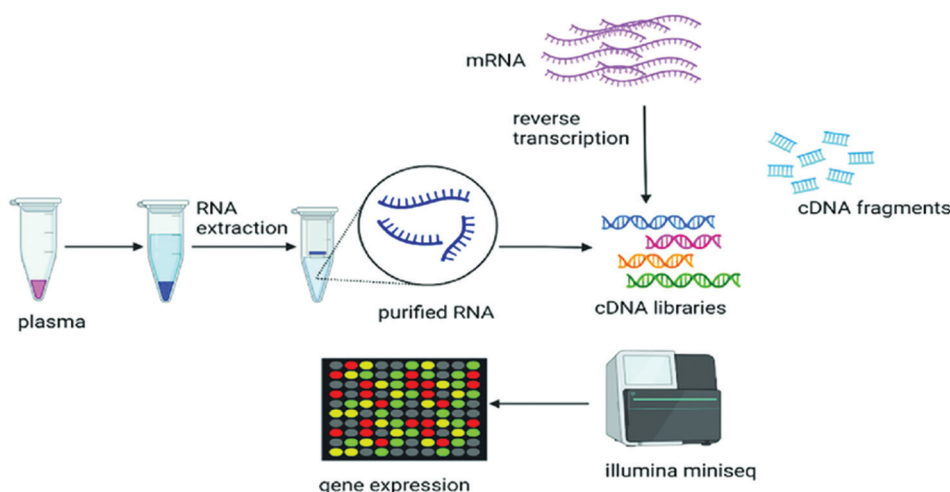


Figure 2: Workflow of transcriptomic analysis including RNA extraction, sequencing, data pre-processing, differential expression analysis, and pathway enrichment (Adapted from Eric Adua *et al.* 2022).

capable of handling high-dimensional, heterogeneous datasets [88]. Genomic, transcriptomic, and proteomic data differ significantly in scale, structure, and variability, necessitating robust computational frameworks to harmonize and interpret these complex datasets as shown in table 2 [96,106]. Effective integration not only enhances biological insight but also improves the identification of clinically relevant biomarkers and therapeutic targets [89]. A variety of statistical and computational approaches have been developed to facilitate multi-omics data integration. Among these, matrix factorization-based methods, such as multi-omics factor analysis (MOFA), have gained prominence for their ability to decompose heterogeneous datasets into shared and modality-specific latent factors [85,97]. These approaches enable the identification of underlying biological signals that drive disease heterogeneity while reducing noise and dimensionality [90]. Similarly, integrative clustering methods, such as iCluster, combine multiple data types to classify tumors into molecular subgroups, thereby improving patient stratification and prognostic accuracy. Network-based approaches also play a critical role in multi-omics integration. By constructing gene-protein interaction networks and pathway maps, these methods enable the identification of key regulatory hubs and signaling cascades that are dysregulated in breast cancer [74,90]. Integration of omics layers within biological networks facilitates the

discovery of functional relationships between genomic alterations, transcriptional changes, and protein-level effects, thereby providing a systems-level understanding of tumor biology [91]. In recent years, machine learning and AI-driven approaches have emerged as powerful tools for multi-omics data analysis. Supervised learning models, including support vector machines and random forests, are widely used for biomarker discovery and classification tasks. Meanwhile, deep learning architectures, such as autoencoders and neural networks, can capture complex, non-linear relationships across omics layers, enabling improved prediction of clinical outcomes, treatment response, and disease progression. These approaches are particularly valuable in handling large-scale datasets and uncovering hidden patterns that may not be apparent through traditional statistical methods.

Despite these advancements, several challenges remain in multi-omics data integration. Data heterogeneity, batch effects, and differences in data normalization across platforms can introduce biases and affect reproducibility [96]. In addition, missing data and uneven sample representation across omics layers complicate integrative analyses. To address these issues, pre-processing steps such as normalization, imputation, and batch effect correction are essential for ensuring data consistency and reliability [92]. Furthermore, the development

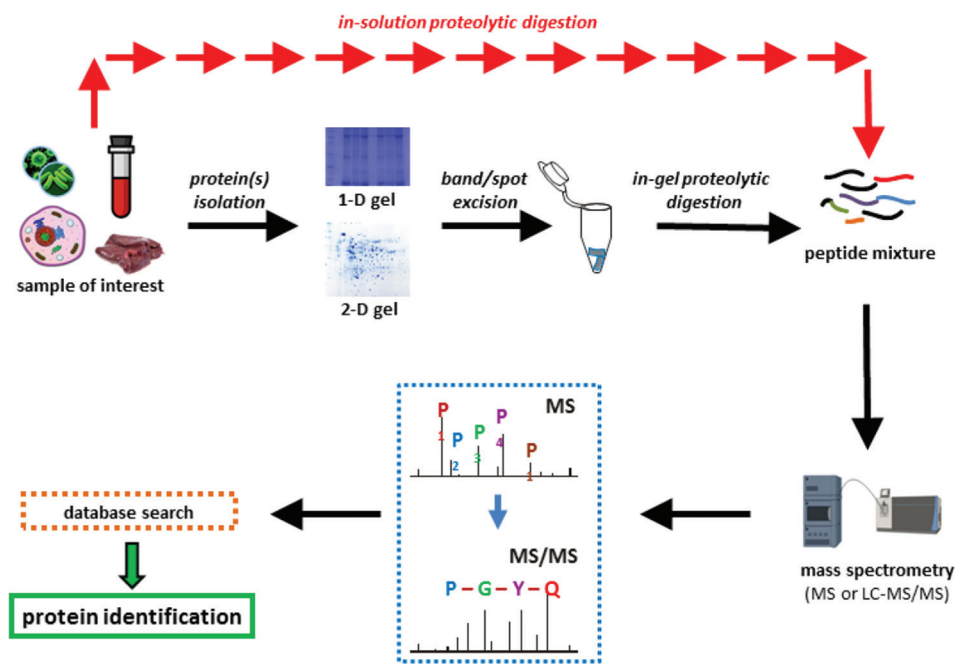


Figure 3: Proteomics workflow showing sample preparation, protein digestion, liquid chromatography-tandem mass spectrometry analysis, and protein identification (Adapted from Dupree *et.al.* 2020).

Table 1: Summary of multi-omics approaches in breast cancer

Omics layer	Key features	Major findings in breast cancer	Technologies used	Clinical applications
Genomics	Analysis of DNA mutations, copy number variations, structural alterations	Identification of driver mutations (TP53, PIK3CA, BRCA1/2), HER2 amplification, tumor heterogeneity	WGS, NGS, CRISPR-Cas9	Targeted therapies (PARP inhibitors, HER2-targeted drugs), risk prediction, prognostic assays
Transcriptomics	Gene expression profiling, RNA regulation, non-coding RNAs	Identification of differentially expressed genes, molecular subtypes (luminal A/B, HER2-enriched, basal-like), immune-related pathways	RNA-Seq, Microarrays, Single-cell RNA-Seq	Biomarker discovery, subtype classification, prediction of therapy response, immunotherapy targets
Proteomics	Protein expression, post-translational modifications, protein interactions	Identification of signaling pathways, biomarkers (MMPs, vimentin), drug resistance proteins, tumor microenvironment interactions	LC-MS/MS, Mass Spectrometry, IHC, ELISA	Diagnostic biomarkers, therapeutic target identification, monitoring disease progression
Multi-omics integration	Integration of genomic, transcriptomic, and proteomic data	Identification of complex regulatory networks, pathway dysregulation (PI3K/AKT/mTOR), immune evasion, metastasis drivers	MOFA, I Cluster, Machine Learning, AI-based models	Precision medicine, patient stratification, prediction of treatment response, personalized therapies
Clinical translation	Application of omics data in patient care	Development of gene signatures (Oncotype DX), immune profiling, detection of minimal residual disease	Liquid biopsy, ctDNA analysis, multi-gene panels	Personalized treatment decisions, early detection, monitoring therapy response
Emerging approaches	Advanced technologies for deeper resolution	Identification of tumor heterogeneity, spatial interactions, rare cell populations	Single-cell omics, Spatial transcriptomics, AI-driven analytics	Improved diagnosis, targeted therapies, real-time disease monitoring

WGS: Whole genome sequencing, NGS: Next-generation sequencing, HER2: Human epidermal growth factor receptor 2, RNA-Seq: RNA sequencing, IHC: Immunohistochemistry, ELISA: Enzyme-linked immunosorbent assay, MMPs: Matrix metalloproteinases, ctDNA: Circulating tumor DNA, PARP: Poly (ADP-ribose) polymerase, AI: Artificial intelligence, CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats, LC-MS/MS: Liquid chromatography-tandem mass spectrometry, MOFA: Multi-omics factor analysis

of standardized pipelines and reproducible workflows is critical for translating multi-omics findings into clinical applications [106]. The integration of multi-omics data also necessitates the use of comprehensive bioinformatics resources and databases, including The Cancer Genome Atlas, Clinical Proteomic Tumor Analysis

Consortium, and Gene Expression Omnibus, which provide large-scale, publicly available datasets for integrative analysis [93]. These repositories have been instrumental in advancing breast cancer research by enabling cross-study comparisons and validation of findings. Collectively, bioinformatics-driven multi-omics integration

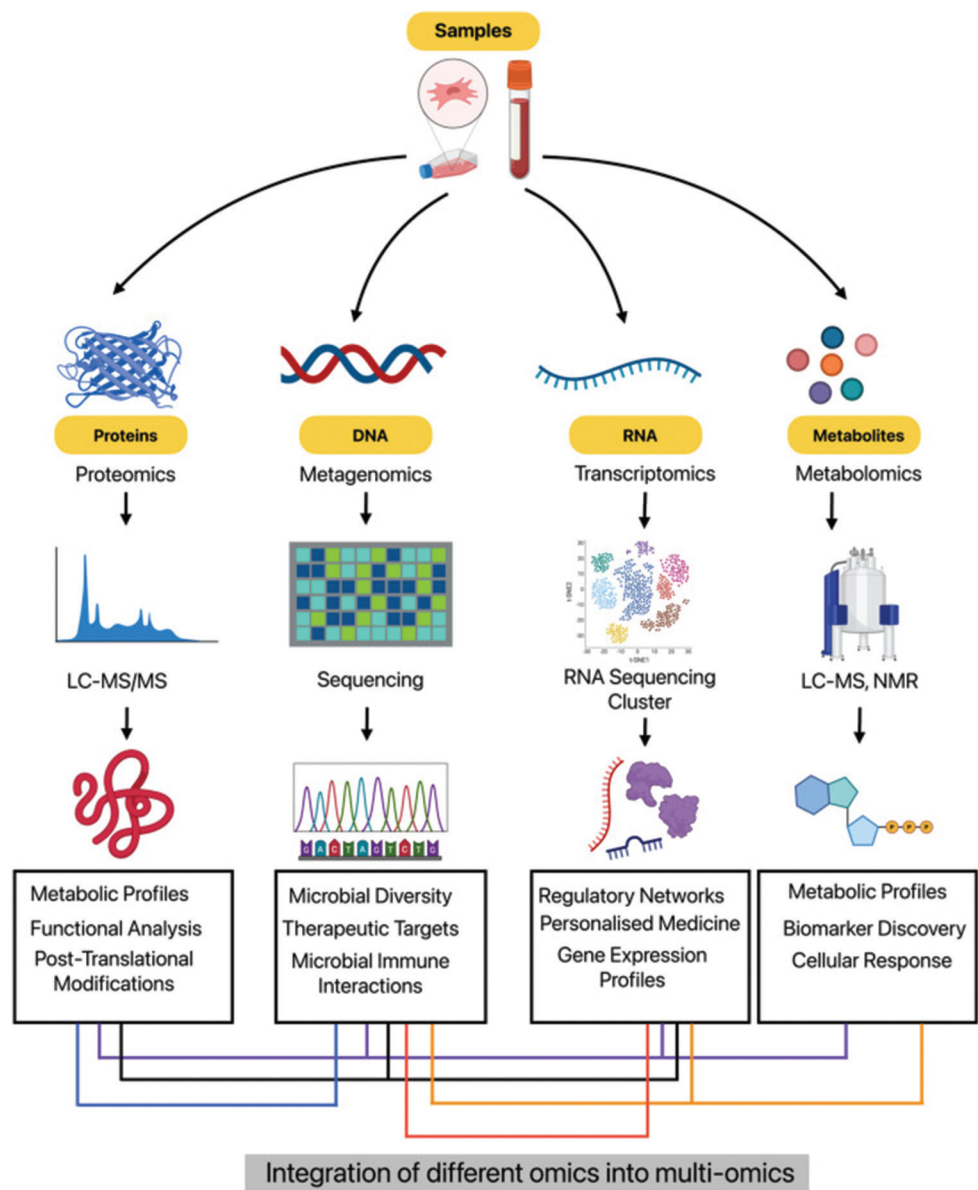


Figure 4: How individual omics such as proteomics, genomics, transcriptomics, and metabolomics could be integrated into multi-omics with a better understanding and outcome. (Adapted from Jiamei Lu *et al.* 2025).

Table 2: Bioinformatics tools for multi-omics integration in breast cancer

Tool	Type	Function	Application
MOFO	Factor analysis	Data integration	Biomarker discovery
iCluster	Clustering	Patient stratification	Subtyping
DESeq2	Statistical	DEG analysis	Transcriptomics
Cytoscape	Network	Pathway analysis	Interaction mapping
Random forest	ML	Classification	Prognosis
Deep learning	AI	Pattern detection	Prediction

MOFO: Multi-omics factor analysis, AI: Artificial intelligence, ML: Machine learning, DEG: Differential gene expression

represents a cornerstone of modern cancer research. By enabling the systematic analysis of complex biological systems, these approaches

facilitate the identification of novel biomarkers, elucidation of disease mechanisms, and development of precision medicine strategies [90]. As computational tools continue to evolve, their integration with experimental and clinical data will further enhance the translational potential of multi-omics research in breast cancer [94].

10. REVEALING PATHWAY DYSREGULATION

Multi-omics approaches have been instrumental in elucidating the dysregulation of key signaling pathways that drive breast cancer progression and contribute to therapeutic resistance [61,72,74]. Integrative analyses combining genomic, transcriptomic, and proteomic data provide a comprehensive framework for understanding how molecular alterations converge to activate oncogenic pathways [95]. Among these, mutations in the PIK3CA gene are frequently observed, particularly in HER2-enriched breast cancer subtypes, and are closely associated with aberrant activation of the PI3K-AKT signaling pathway [96]. The PI3K-AKT pathway plays a central role in regulating cellular processes such as proliferation, survival, and metabolism, making it a critical target for therapeutic intervention [92].

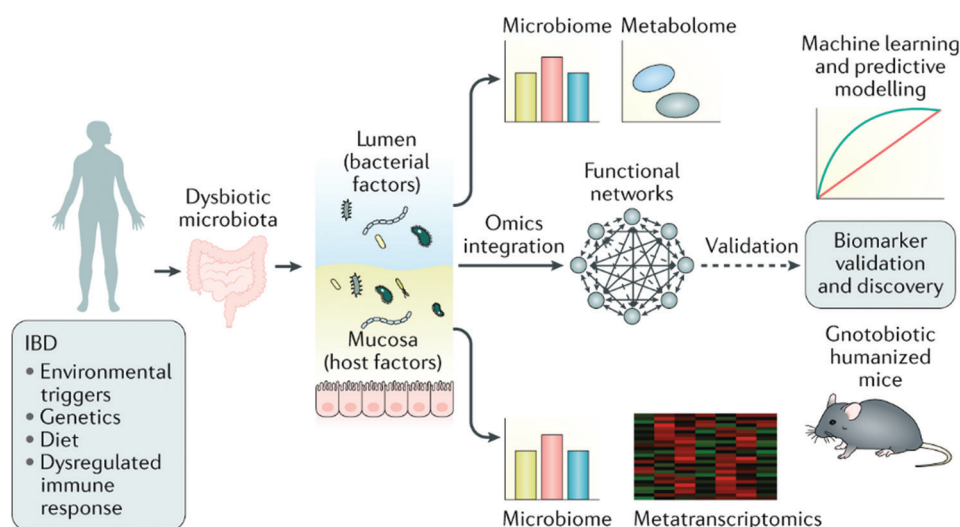


Figure 5: Conceptual model for multi-omics integration towards mechanistic biomarker discovery. (Adapted from Haller *et al.* 2019).

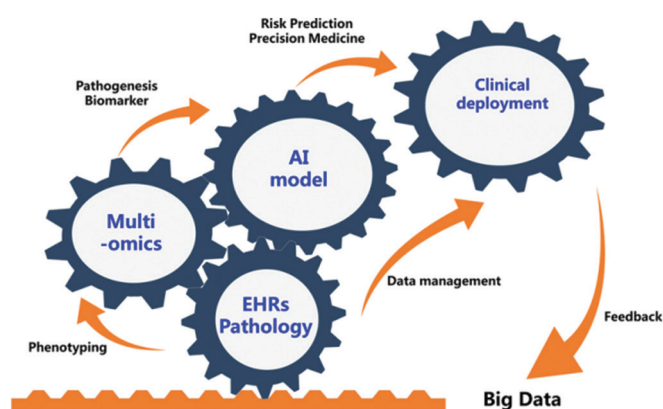


Figure 6: Future Integration of artificial intelligence and multi-omics will benefit precision medicine for immune-mediated disorders. EHRs: Electronic health records. (Adapted from Zhou *et al.* 2022).

Table 3: Key biomarkers and their clinical relevance in breast cancer

Biomarker	Omics level	Function	Clinical use
HER2	Genomic/Protein	Growth signaling	Target therapy
BRCA1/2	Genomic	DNA repair	PARP inhibitors
PD-L1	Protein	Immune evasion	Immunotherapy
ESR1	Transcriptomic	Hormone signaling	Endocrine therapy

HER2: Human epidermal growth factor receptor 2, BRCA1/2: BRCA1 and 2, PD-L1: Programmed death-ligand 1, ESR1: Estrogen receptor 1, PARP: Poly (ADP-ribose) polymerase

Transcriptomic analyses have demonstrated upregulation of genes involved in this pathway, while proteomic studies have confirmed increased phosphorylation of AKT, a key event required for downstream signaling activation [67]. These findings highlight the importance of integrating multiple omics layers to validate pathway activation at both the transcriptional and functional protein levels [61,72].

Furthermore, integrative studies have shown that hyperactivation of the PI3K–AKT pathway, driven by PIK3CA alterations, is associated with

poor clinical outcomes and resistance to targeted therapies [40,53]. This activation has been consistently observed not only in tumor samples but also in patient-derived xenograft models, reinforcing its biological and clinical relevance [73]. Importantly, these insights have led to the proposal of combinatorial therapeutic strategies targeting both the PI3K–AKT pathway and HER2 signaling, with the aim of overcoming resistance and improving treatment efficacy [36,53]. These findings underscore the value of multi-omics integration in identifying dysregulated signaling networks and actionable therapeutic targets, thereby advancing precision oncology in breast cancer [52,91].

11. IDENTIFYING BIOMARKERS FOR IMMUNE EVASION

Multi-omics integration has significantly enhanced our understanding of the immune landscape in breast cancer, particularly in the context of immune evasion, a key hallmark of tumor progression as shown in table 3 by analyzing the key biomarkers and their clinical relevance in breast cancer [61,77]. By combining genomic, transcriptomic, and proteomic data, researchers can comprehensively characterize the mechanisms through which tumors evade immune surveillance [72,100]. Transcriptomic analyses frequently reveal the upregulation of immune checkpoint molecules, such as PD-L1, which suppress anti-tumor immune responses and facilitate tumor immune escape [48,69]. In parallel, genomic alterations in immune regulatory pathways, including the JAK–STAT signaling axis, further contribute to immune modulation and tumor progression [74,90]. Integrative multi-omics studies have enabled the stratification of tumors based on their immune profiles. For instance, analyses of TNBC have identified distinct immune subgroups, commonly referred to as “immune-hot” and “immune-cold” phenotypes, which are associated with differential immune infiltration and clinical outcomes [57,71].

Tumors classified as immune-hot exhibit higher levels of immune cell infiltration and are generally associated with improved prognosis, whereas immune-cold tumors display limited immune engagement and poorer clinical outcomes [57,71]. Importantly, this molecular stratification has significant therapeutic implications. Patients with immune-hot tumors are more likely to respond to immune checkpoint blockade therapies, such as programmed cell death protein 1 or PD-L1 inhibitors, including pembrolizumab [48,69]. These findings highlight the potential of multi-omics approaches to inform patient-

specific immunotherapeutic strategies and improve treatment efficacy [77,100]. Overall, the integration of multi-omics data provides a powerful framework for identifying biomarkers of immune evasion and tailoring immunotherapy, thereby advancing precision medicine in breast cancer [61,91].

12. UNDERSTANDING THE MOLECULAR DRIVERS OF METASTASIS

Metastasis remains the primary cause of breast cancer-related mortality, and the integration of multi-omics data has provided critical insights into the molecular mechanisms that drive metastatic progression [62,80]. By combining genomic, transcriptomic, and proteomic datasets, researchers can systematically dissect the complex regulatory networks underlying tumor cell invasion, migration, and colonization of distant organs [61,72]. Genomic analyses frequently reveal amplifications or mutations in oncogenes such as MYC, which play a central role in promoting cellular proliferation, invasion, and metastatic potential [62,73]. Complementary transcriptomic profiling has identified the upregulation of genes associated with epithelial-to-mesenchymal transition, a key biological process that facilitates tumor cell dissemination [74]. Proteomic studies further validate these findings by demonstrating increased expression of proteins involved in cytoskeletal remodeling and cell motility, including vimentin and N-cadherin, which are hallmarks of invasive tumor phenotypes [22,98]. The integration of these multi-layered datasets enables the identification of key molecular drivers of metastasis and provides a more comprehensive understanding of the biological processes involved [61,72]. Importantly, such integrative analyses have highlighted the role of MYC-driven signaling networks in promoting metastatic progression, particularly in aggressive breast cancer subtypes such as luminal B [62]. These findings suggest that targeting MYC-associated pathways may represent a promising therapeutic strategy to inhibit metastatic spread and improve clinical outcomes [91]; multi-omics integration offers a powerful framework for elucidating the molecular determinants of metastasis and for identifying novel targets for therapeutic intervention in breast cancer [52,61].

13. ENHANCING PATIENT STRATIFICATION THROUGH MULTI-OMICS INTEGRATION

The integration of multi-omics data has significantly improved patient stratification in breast cancer by enabling the identification of individuals who are more likely to benefit from specific therapeutic interventions [52,91]. By combining genomic, transcriptomic, and proteomic information, this approach provides a comprehensive molecular profile that facilitates more accurate prediction of treatment response [61,72]. For instance, genomic analyses frequently identify mutations in genes such as BRCA1, which are associated with defects in homologous recombination-mediated DNA repair [86,94]. These alterations are further reflected at the transcriptomic and proteomic levels, where dysregulation of DNA repair pathways and changes in protein expression patterns can be observed [24,25]. Such multi-layered insights enable clinicians to predict sensitivity to targeted therapies, particularly those that exploit DNA repair deficiencies, such as PARP inhibitors [47]. Integrative multi-omics studies have demonstrated that tumors harboring BRCA1 mutations exhibit increased markers of DNA damage, including elevated levels of γ H2AX, indicative of genomic instability [86]. These findings suggest that patients with BRCA1-deficient tumors are more likely to respond favorably to PARP inhibition [47]. Importantly, the incorporation of multi-omics data enhances the precision of patient stratification, improving the selection of candidates for targeted therapies and enabling more accurate prediction of therapeutic outcomes [52,61].

Overall, multi-omics integration represents a powerful strategy for advancing precision oncology by aligning molecular characteristics with individualized treatment approaches in breast cancer [91].

14. DECIPHERING MECHANISMS OF THERAPY RESISTANCE THROUGH MULTI-OMICS INTEGRATION

Therapy resistance remains a major obstacle in the effective management of breast cancer, and multi-omics approaches have emerged as essential tools for elucidating the underlying molecular mechanisms [39,72,77]. The integration of genomic, transcriptomic, and proteomic data enables a comprehensive assessment of how genetic alterations influence gene expression patterns and protein function, thereby driving resistance to therapeutic interventions [24,61]. Genomic analyses can identify mutations in drug targets and resistance-associated genes, while transcriptomic and proteomic profiling reveal the downstream functional consequences of these alterations [73,41]. For example, the overexpression of ATP-binding cassette transporters, which actively efflux chemotherapeutic agents from cancer cells, represents a well-established mechanism of drug resistance [82]. Integrative multi-omics analyses have demonstrated that elevated expression of these transporters contributes significantly to chemotherapy resistance, particularly in aggressive subtypes such as TNBC [56,82]. These insights have facilitated the development of combinatorial therapeutic strategies that target drug efflux mechanisms alongside conventional chemotherapy, thereby improving treatment efficacy [77]. Beyond drug transport mechanisms, multi-omics integration has also enabled the identification of novel therapeutic targets associated with resistance. Comprehensive analyses of breast cancer cell lines and patient-derived samples have revealed consistent upregulation of kinases such as Protein Kinase C delta (PRKCD) across genomic, transcriptomic, and proteomic levels [17,41]. Given its role in regulating cell survival and metastatic signaling, PRKCD has emerged as a promising candidate for targeted intervention, particularly in TNBC, which lacks well-defined therapeutic targets [98].

Furthermore, multi-omics approaches have provided critical insights into the role of the tumor immune microenvironment in therapy resistance [76]. Integrative analyses combining transcriptomic and proteomic data from tumor-infiltrating immune cells have uncovered complex interactions between immune and tumor cells, including the activation of immune-related pathways that contribute to immune evasion [87]. These findings have led to the identification of novel immune checkpoint targets and have highlighted the potential of immunotherapeutic strategies, particularly in patients with high tumor mutational burden [69,48]. Collectively, these studies underscore the value of multi-omics integration in uncovering the multifactorial mechanisms of therapy resistance, identifying actionable biomarkers, and guiding the development of more effective, personalized treatment strategies in breast cancer [52,91]. Integrated multi-omics approaches have significantly transformed both biomarker discovery and therapeutic development in breast cancer by enabling a comprehensive characterization of the disease at multiple molecular levels [61,72]. The convergence of genomic, transcriptomic, and proteomic data allows for the identification of key molecular alterations that reflect the underlying biological complexity of breast cancer, thereby improving diagnostic precision, prognostic assessment, and prediction of therapeutic response [31,41]. One of the major outcomes of multi-omics integration is the identification of robust biomarker signatures that surpass the limitations of single-omics analyses [52]. Gene expression-based signatures have been widely utilized to predict disease recurrence and treatment outcomes, particularly in ESR-positive breast cancer [33,34]. These multigene panels enable accurate risk stratification and guide clinical decision-making, facilitating the implementation of

personalized therapeutic strategies [34,66]. In addition to tissue-based biomarkers, multi-omics approaches have also advanced the discovery of circulating biomarkers, including protein markers and circulating tumor DNA or RNA, which provide dynamic insights into tumor evolution, heterogeneity, and resistance mechanisms [49,68]. Such biomarkers have been instrumental in the development of liquid biopsy technologies, offering a minimally invasive approach for monitoring disease progression and therapeutic response [68].

Beyond biomarker identification, multi-omics integration has played a pivotal role in uncovering novel therapeutic targets and advancing precision oncology [61,91]. By linking genomic alterations to downstream transcriptional and proteomic changes, this approach enables the identification of actionable molecular drivers of tumor progression [24,25]. A prominent example is the identification of HER2 as a critical oncogenic driver, which led to the development of targeted therapies that have substantially improved patient outcomes [44,36]. Similarly, key signaling pathways such as PI3K, AKT, and mTOR, frequently dysregulated in breast cancer, have emerged as important therapeutic targets, with inhibitors demonstrating promising efficacy in clinical settings [53,92]. Furthermore, multi-omics approaches have provided critical insights into the tumor microenvironment, particularly in the context of immune regulation and evasion [69]. The identification of immune checkpoint molecules, such as PD-L1, has facilitated the development of immunotherapeutic strategies aimed at enhancing anti-tumor immune responses [48]. In addition, the characterization of tumor-infiltrating immune cells and immune-related gene signatures has enabled the prediction of patient responsiveness to immunotherapy, especially in aggressive subtypes such as TNBC [57,71]. Collectively, the integration of multi-omics data has not only enhanced the discovery of clinically relevant biomarkers but has also accelerated the identification of novel therapeutic targets, thereby bridging the gap between molecular research and clinical application [61,52]. These advancements are central to the progression of precision medicine, enabling more accurate patient stratification and the development of individualized treatment strategies that improve clinical outcomes in breast cancer [91].

15. CLINICAL APPLICATIONS

The clinical translation of multi-omics-driven biomarkers and therapeutic strategies has led to several notable advancements in breast cancer management, with ongoing efforts aimed at validating these approaches through large-scale clinical trials [61,91]. One of the most prominent examples is the implementation of multigene expression assays, such as the Oncotype DX test, which utilizes integrated genomic and transcriptomic data to predict the risk of recurrence in ESR-positive breast cancer [34,66]. This assay has become an integral component of clinical decision-making, guiding the use of adjuvant chemotherapy and enabling more personalized treatment strategies [34]. In the context of targeted therapies, HER2-directed treatments represent a major success of multi-omics integration in clinical practice [36,44]. The identification of HER2 amplification and overexpression in specific breast cancer subtypes facilitated the development of monoclonal antibodies and targeted agents, including trastuzumab, pertuzumab, and lapatinib, which have significantly improved outcomes in patients with HER2-positive disease [44,81]. Building on these advances, ongoing clinical trials are investigating combination therapeutic strategies, such as the integration of HER2-targeted agents with immune checkpoint inhibitors, as well as the combined use of PI3K inhibitors with endocrine therapies in hormone receptor-positive breast cancer [48,53]. In addition, the application of liquid biopsy technologies is emerging as a promising tool for non-invasive disease monitoring [68]. These approaches enable the detection of circulating tumor-derived biomarkers, facilitating the

assessment of minimal residual disease and the early identification of metastatic progression [49,68]. Clinical studies are actively evaluating the utility of these techniques in real-world settings to enhance disease surveillance and treatment adaptation. Another rapidly evolving application of multi-omics is the use of integrated molecular signatures to predict patient response to neoadjuvant therapies, including chemotherapy and immunotherapy, before surgical intervention [52,91]. This strategy enables the tailoring of treatment regimens based on individual tumor biology, thereby improving therapeutic efficacy and patient outcomes [91].

16. CHALLENGES AND FUTURE DIRECTIONS

In addition, the integration and interpretation of multi-omics datasets pose substantial computational challenges [39,96]. The high dimensionality and complexity of these data require advanced bioinformatics frameworks, standardized analytical pipelines, and robust computational infrastructure [99]. Although significant progress has been made in developing integrative algorithms and machine learning approaches, further efforts are needed to enhance data harmonization, reproducibility, and clinical interpretability [42,102]. Another critical barrier is the time-intensive and costly nature of clinical validation. The translation of multi-omics-based biomarkers and therapeutic strategies into clinical practice requires extensive validation through large-scale, multi-center clinical trials, which can delay implementation and limit accessibility [91]. Furthermore, issues related to standardization, regulatory approval, and data sharing continue to hinder widespread adoption [96]. Nevertheless, ongoing technological advancements and the gradual reduction in the cost of high-throughput omics platforms are expected to address many of these limitations [100]. Emerging approaches, including single-cell multi-omics, spatial transcriptomics, and artificial intelligence-driven analytics, hold considerable promise for refining disease characterization and improving predictive accuracy [19,75,102].

Looking forward, the integration of multi-omics data into clinical workflows is anticipated to drive the evolution of precision oncology, enabling more accurate prediction of disease outcomes, improved patient stratification, and the development of personalized therapeutic strategies [91,101]. As these technologies continue to mature, they are expected to play a central role in optimizing breast cancer diagnosis, treatment, and long-term disease management [52,72]. In addition, issues related to data standardization and reproducibility remain significant barriers to the clinical translation of multi-omics approaches [102]. Variability in sample preparation, sequencing platforms, and data processing pipelines can lead to inconsistencies across studies, thereby limiting cross-cohort comparisons and validation of findings [96]. The lack of universally accepted standards for data normalization and integration further complicates reproducibility. Ethical considerations, including patient data privacy, secure data sharing, and regulatory compliance, also present challenges in large-scale multi-omics studies [106]. Addressing these issues through standardized protocols, robust validation frameworks, and secure data-sharing infrastructures will be essential for the successful implementation of multi-omics in clinical practice [93].

17. CONCLUSION

The integration of transcriptomic and proteomic approaches has substantially advanced our understanding of breast cancer biology by providing comprehensive insights into the molecular mechanisms underlying tumor development, progression, and therapeutic response [54,61,72]. These complementary technologies enable the identification of clinically relevant biomarkers and actionable therapeutic targets, while also addressing the inherent heterogeneity



and complexity of breast cancer [41,52]. Despite these significant advancements, several challenges persist, including the complexity of multi-omics data integration, high costs, and limited accessibility to advanced analytical platforms [39,96]. However, continuous progress in computational methodologies, bioinformatics frameworks, and high-throughput technologies is steadily overcoming these limitations [102,106]. Future research efforts should prioritize the incorporation of emerging approaches such as spatial omics, single-cell analyses, and machine learning-driven models to enhance the resolution and clinical applicability of multi-omics data [19,75,102]. The integration of these technologies is expected to refine disease characterization, improve predictive accuracy, and facilitate more effective therapeutic interventions [61,91]. Ultimately, by bridging the gap between molecular research and clinical application, integrative omics strategies will play a central role in advancing precision oncology, enabling personalized treatment approaches, and improving clinical outcomes for patients with breast cancer [52,91]. While this review places particular emphasis on transcriptomic and proteomic analyses, the integration of genomic data remains fundamental to achieving a comprehensive multi-omics framework [61,72].

18. AUTHORS' CONTRIBUTIONS

B.K. conceived the study and prepared the drafting of the manuscript and performed literature studies. M.A. also assisted in data collection and drafting. A.K. assisted with the drafting of the manuscript. All authors reviewed the manuscript and agreed to the published version.

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20. CONSENT FOR PUBLICATION

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The authors declare that they have no competing interests or conflicts of interest related to this study.

24. AVAILABILITY OF DATA AND MATERIALS

Not Applicable

25. STANDARDS OF REPORTING

The author followed standard scientific reporting practices and ethical academic guidelines during the preparation of this computational and imaging-based research study.

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