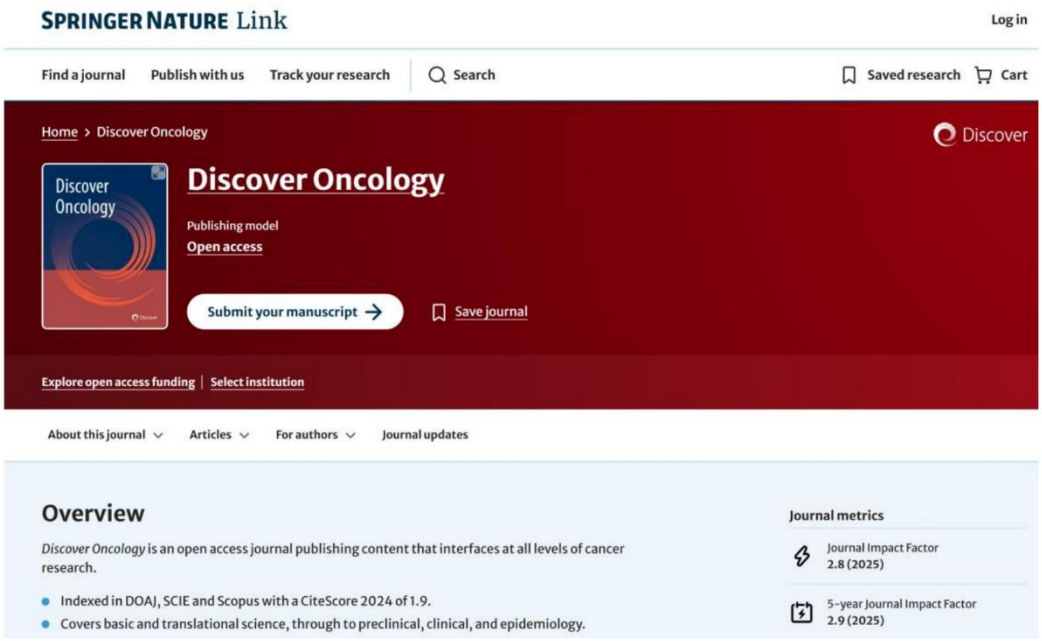
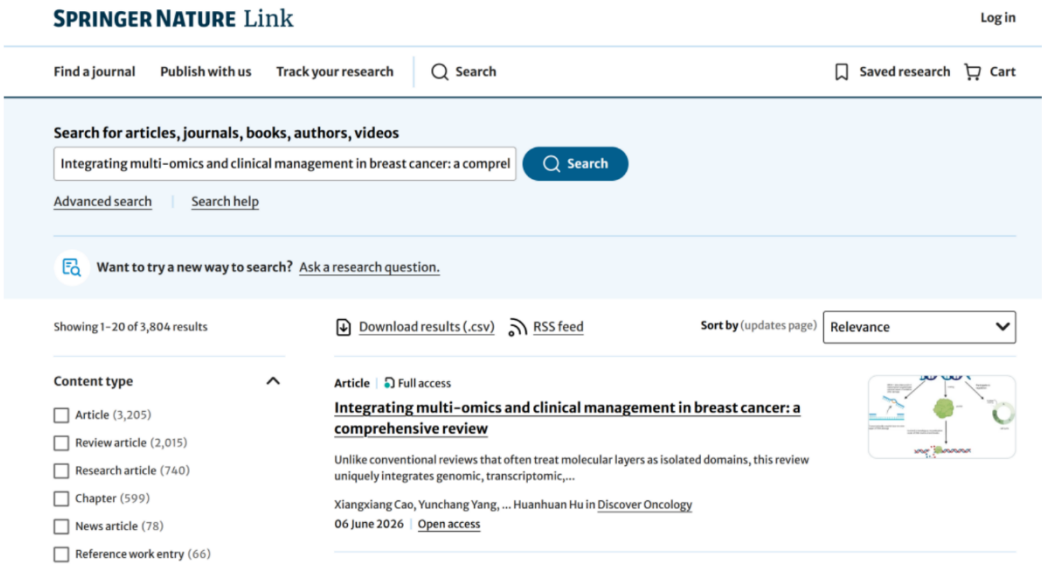
Integrating multi-omics and clinical management in breast cancer: a comprehensive Review、SCI（Discover Oncology，四区）2026 年 5 月 Xiangxiang Cao, Yunchang Yang, Pengbo Wang, Jinjin Wang, Yike Zhao, Zichun Zhang, Jiaqi Jiang, Hanwen Zhang, Xinyao Kang, Huigen Feng, Guojie Ji & Huanhuan Hu





Discover Oncology

https://doi.org/10.1007/s12672-026-05357-7

Article in Press

Integrating multi-omics and clinical management in breast cancer: a comprehensive review

Received: 22 January 2026

Accepted: 29 May 2026

Published online: 06 June 2026

Cite this article as: Cao X., Yang Y., Wang P. *et al.* Integrating multi-omics and clinical management in breast cancer: a comprehensive review. *Discov Onc* (2026). https://doi.org/10.1007/s12672-026-05357-7

Xiangxiang Cao, Yunchang Yang, Pengbo Wang, Jinjin Wang, Yike Zhao, Zichun Zhang, Jiaqi Jiang, Hanwen Zhang, Xinyao Kang, Huigen Feng, Guojie Ji & Huanhuan Hu

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

ARTICLE IN PRESS

© The Author(s) 2026. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

ARTICLE IN PRESS

Integrating Multi-Omics and Clinical Management in Breast Cancer: A Comprehensive Review

Xiangxiang Cao [a, 1], Yunchang Yang [a, 1], Pengbo Wang [a], Jinjin Wang [a], Yike Zhao [a], Zichun Zhang [a], Jiaqi Jiang [a], Hanwen Zhang [a], Xinyao Kang [b], Huigen Feng [a, *], Guojie Ji [a, *], Huanhuan Hu [a, *]

[a] Key Laboratory of Fertility Preservation, North Henan Medical University, Xinxiang 453003, Henan Province, P.R.China

[b] Henan University, Kaifeng, Henan Province, P.R.China

[1] These authors contributed equally to this work.

[*] Corresponding author: Huigen Feng. email address: huigenfeng1963@163.com. West Section of Changjiang Road, Pingyuan Demonstration Area, Xinxiang, Henan Province, P.R.China

[*] Corresponding author: Guojie Ji. email address: jiguojie87@163.com. West Section of Changjiang Road, Pingyuan Demonstration Area, Xinxiang, Henan Province, P.R.China

[*] Corresponding author: Huanhuan Hu. email address: huhuanhuan1987@163.com. West Section of Changjiang Road, Pingyuan Demonstration Area, Xinxiang, Henan Province, P.R.China

ARTICLE IN PRESS

Abstract

Unlike conventional reviews that often treat molecular layers as isolated domains, this review uniquely integrates genomic, transcriptomic, proteomic, and metabolomic data to bridge the gap between advanced tumor microenvironment (TME) profiling and actionable clinical management. Its objective is to provide a definitive translational roadmap that decodes TME reprogramming, surmounts therapeutic resistance, and optimizes personalized oncology. We dissect the multifaceted mechanisms driving therapeutic resistance and highlight the paradigm-shifting role of liquid biopsy (ctDNA, CTCs, and exosomes) in dynamically monitoring minimal residual disease (MRD).

Keywords: Breast cancer; Multi-Omics; Molecular mechanisms; Precision therapies; Tumor microenvironment

ARTICLE IN PRESS

1. **Background**

Breast cancer remains a formidable global health challenge, accounting for 11.6% of all cancer incidences and 6.9% of cancer-related mortality worldwide [1]. Its profound biological complexity is driven by molecular heterogeneity, traditionally categorized by receptor expression into Luminal, HER2-overexpressing, and triple-negative (TNBC) subtypes [2]. Malignant transformation and metastasis—the cause of over 90% of breast cancer fatalities—are primarily fueled by abnormal signaling cascades (e.g., hyperactive PI3K/AKT/mTOR and MAPK pathways) [3–5] and dynamic tumor microenvironment (TME) remodeling [6].

While precision medicine has revolutionized clinical management, adaptive therapeutic resistance remains a critical bottleneck. For instance, although novel targeted agents (e.g., palbociclib, olaparib) and endocrine therapies have significantly expanded therapeutic options [10–12], up to 30% of early-stage patients ultimately progress to fatal bone or visceral metastases [13]. Furthermore, nearly 30% of HR+ patients develop acquired resistance driven by ESR1 mutations or compensatory pathway activation [5–9]. Overcoming these obstacles requires detecting minimal residual disease (MRD) prior to macroscopic relapse, an area where emerging diagnostic paradigms like liquid biopsy and AI-enhanced imaging show immense clinical promise [14,15].

ARTICLE IN PRESS

However, existing literature often treats molecular mechanisms and clinical diagnostics as isolated silos. To bridge this translational gap, this review uniquely integrates multi-omics data—encompassing genomics, transcriptomics, proteomics, and metabolomics. By synthesizing how proteomic validations of genomic alterations and real-time metabolomic profiling directly inform clinical decision-making, we provide a definitive, highly translational roadmap for decoding TME reprogramming, overcoming therapeutic resistance, and optimizing personalized oncology.We specifically focus on HR+/HER2− and triple-negative breast cancers, where multi-omics integration has yielded the most actionable clinical breakthroughs.

In particular, three aspects set this work apart. First, we emphasize proteomic

ARTICLE IN PRESS

validation of genomic alterations, demonstrating how static mutations translate into druggable protein activities. Second, we incorporate real-time metabolomic profiling as a functional readout for therapeutic response that precedes radiographic changes. Third, we provide an integrated analysis of liquid biopsy biomarkers (ctDNA, CTCs, exosomes), showing how each modality compensates for the blind spots of the others. Together, this cross-layer synthesis captures a translational perspective that is often lost when these domains are reviewed in isolation.

The clinical impact of such integration is already emerging. For instance, the I-PREDICT trial demonstrated that multi-omic-informed molecular tumor boards can match patients to individualized combination therapies, significantly improving progression-free survival. Similarly, the SAFIR02-BREAST trial used genomic and transcriptomic profiling to guide targeted therapy in metastatic breast cancer, illustrating real-world clinical utility[219,220]. These examples underscore the central premise of this review: that multi-omics integration is not merely a research aspiration but an increasingly actionable clinical tool.

2. Molecular Classification in the Multi-Omics Era

Traditionally, breast cancer classification relied heavily on morphological features, categorizing tumors into in situ lesions (e.g., ductal carcinoma in situ [DCIS]) and invasive carcinomas (e.g., invasive ductal and lobular carcinomas) [16-37]. Historically, pathologists also cataloged rare histological variants such as mucinous, medullary, and inflammatory breast cancers [38-50]. However, from a precision oncology perspective, morphological descriptions offer limited actionable insight.

Today, the paradigm has shifted toward molecular and multi-omic stratification. Breast cancer is dynamically classified by the multi-omic profiling of hormone receptors (HR) and human epidermal growth factor receptor 2 (HER2), alongside transcriptomic signatures (e.g., PAM50), into Luminal A, Luminal B, HER2-enriched, and Basal-like (frequently overlapping with TNBC) subtypes. This molecular framework, continually refined by integrating genomic mutations, transcriptomic reprogramming, and proteomic signaling networks, is the current

ARTICLE IN PRESS

cornerstone guiding targeted therapeutic interventions and predicting treatment resistance (**Table 1**).

Table 1: Molecular Classification in the Multi-Omics Era

Molecular Subtype	**Hormone Receptor (HR) Status**	**HER2 Status**	**Proliferation (Ki-67)**	**Prognosis & Characteristics**
Luminal A	ER+ and/or PR+	HER2-	Low	Good prognosis, high response to endocrine therapy
Luminal B	ER+ and/or PR+	HER2- (High Ki-67) or HER2+	High	Intermediate prognosis, higher risk of early relapse than Luminal A
HER2-enriched	ER- and PR-	HER2+	Variable	Aggressive but highly responsive to HER2-targeted therapies
Basal-like (TNBC)	ER- and PR-	HER2-	High	Highly aggressive, lacks traditional targeted receptors, high risk of early visceral metastasis

ARTICLE IN PRESS

3. Pathogenesis of Breast Cancer: Multidimensional Molecular Networks and Clinical Translation

ARTICLE IN PRESS

The pathogenesis of breast cancer involves complex dysregulation across multiple levels of molecular regulation, including genetic alterations, epigenetic aberrations, dysregulated signaling pathways, metabolic reprogramming, and interactions within the tumor microenvironment. These mechanisms intertwine to drive tumor initiation, progression, metastasis, and therapeutic resistance. The following section systematically elucidates the core pathogenic mechanisms of breast cancer, bridging molecular insights with clinical translation.

3.1 Multi-Omic Profiling of Oncogenic Signaling Pathways

DNA Damage Repair (DDR) Pathways and Genomic Instability

BRCA1/2 Mutations: BRCA1 and BRCA2 are critical components of the homologous recombination repair (HRR) pathway for DNA double-strand break repair [51]. Beyond HRR, BRCA1/2 are involved in cell cycle checkpoint regulation [52,53]. Mutational analyses reveal that BRCA1 also participates in transcription-coupled base excision repair of oxidative DNA damage [54]. Recent studies demonstrate that BRCA1 interacts with multiple proteins involved in DNA end-joining, mismatch repair, replication, and DNA damage signaling, underscoring its broad role in the DNA damage response network. Loss-of-function mutations in BRCA1/2 impair HRR, leading to genomic instability and a markedly elevated risk of breast cancer (**Figure 1**) [55].

ARTICLE IN PRESS

ARTICLE IN PRESS

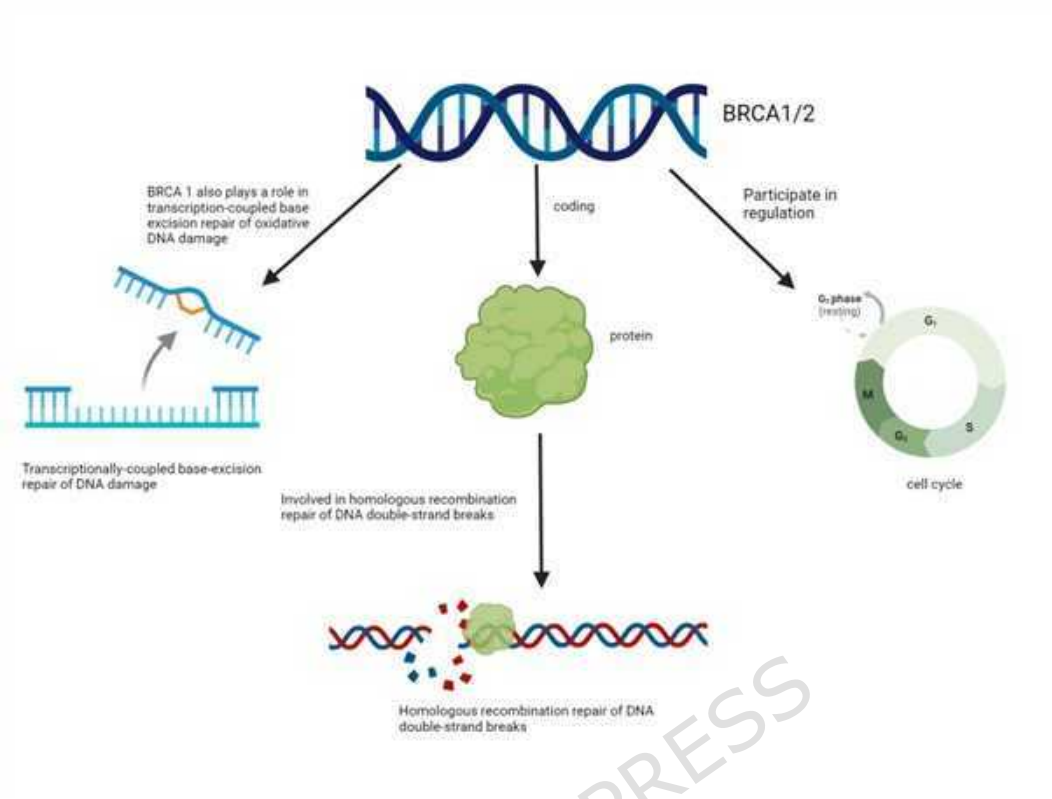


Figure 1. BRCA1/2 germline mutations and their role in the DNA damage response. Pathogenic variants in these pathways lead to homologous recombination deficiency (HRD), providing the critical clinical rationale for synthetic lethality via PARP inhibitors.

Women harboring BRCA1 mutations face a lifetime breast cancer risk of up to 72%, predominantly developing TNBC. HRR deficiency renders BRCA1/2-mutant tumors sensitive to DNA-damaging agents (e.g., anthracyclines, platinum compounds) and novel therapeutics targeting DNA repair, such as PARP inhibitors (PARPi). PARPi act by blocking single-strand break repair and trapping PARP at DNA damage sites, exploiting synthetic lethality to selectively kill BRCA-deficient tumor cells [56–59]. For instance, the OlympiAD trial reported a median progression-free survival (PFS) of 19.3 months with olaparib, significantly surpassing 17.1 months in the chemotherapy group [60].

TP53 Mutations: TP53 is the most frequently mutated tumor suppressor gene in breast cancer, with mutations detected in approximately 30% of cases and over 80% of basal-like subtypes [61]. TP53 mutations disrupt the transcriptional regulation of genes involved in DNA repair, cell cycle arrest, chromatin remodeling, and apoptosis. Mutant p53 proteins not only lose tumor-suppressive

ARTICLE IN PRESS

functions but may gain oncogenic properties, such as enhanced proliferation and migration [61,62]. TP53 inactivation fosters unchecked cell cycle re-entry, suppresses geroconversion (a senescence-like G1 arrest), and inhibits assembly of the DREAM complex (DP, RB-like, E2F, and MuvB), thereby evading cell cycle control. Notably, targeted therapies like APR-246 are under clinical evaluation for restoring wild-type p53 function and inducing apoptosis in p53-mutant tumors [63,64].

Moderate-Penetrance Genes

Pathogenic germline mutations in genes such as PALB2, CHEK2, and ATM confer a 2–4-fold increased risk of breast cancer. PALB2 mutations, in particular, disrupt HRR via defective BRCA2 interaction, and are significantly associated with TNBC and familial breast cancer [65].

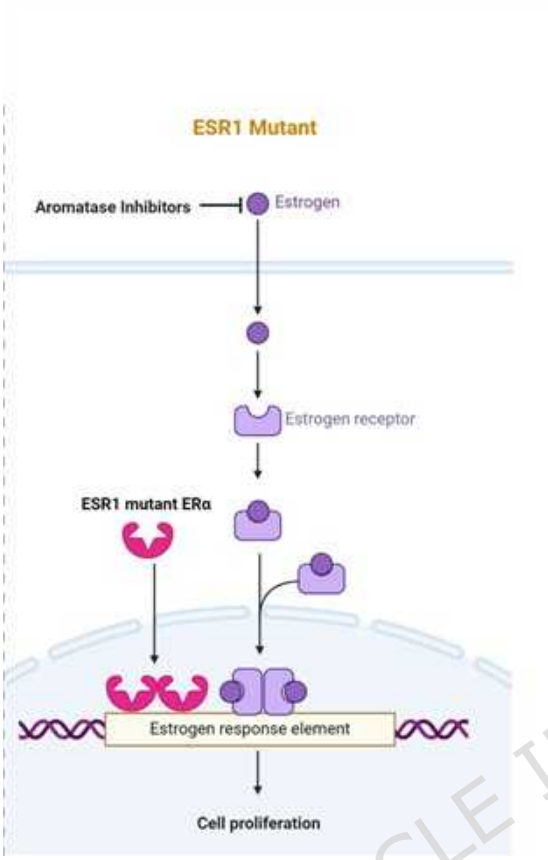
Somatic Driver Mutations

The PI3K/AKT/mTOR Signaling Axis: Beyond mere genomic sequencing, parallel phosphoproteomic profiling is crucial for validating the hyperactivation of downstream effectors in the PI3K/AKT/mTOR cascade. This multi-omic integration bridges the gap between static genetic alterations and dynamic, actionable protein targets in the clinic. PIK3CA mutations are present in 30%–40% of breast cancers, leading to constitutive activation of the PI3Kα isoform (p110α), which promotes cell growth, survival, metabolism, and migration via the PI3K/AKT/mTOR pathway. The most frequent mutations occur at three hotspots: p.E542K and p.E545K (helical domain) in exon 10, and p.H1047R (kinase domain) in exon 21. The SOLAR-1 trial demonstrated that alpelisib (a PI3K inhibitor) combined with fulvestrant significantly prolonged PFS in patients with PIK3CA mutations by 7.9 months [66–69].

ESR1 Mutations: First identified in 1997, ESR1 mutations gained clinical attention following genomic sequencing of metastatic breast cancer (MBC) in 2013 [70,71]. Given the prevalence of ER+ breast cancer, endocrine therapy (ET) targeting ER significantly reduces mortality. However, ET resistance remains a major clinical hurdle. ESR1 mutations contribute to resistance through ER downregulation, crosstalk with growth factor receptors, subclonal genomic alterations, and gain-of-function mutations [72,73]. ESR1 mutations are detected in 20%–40% of MBC patients previously treated with aromatase inhibitors (AIs), and

ARTICLE IN PRESS

mutation frequency varies by metastatic site, with higher rates in visceral compared to bone metastases (**Figure 2**) [74–76].



ARTICLE IN PRESS

Figure 2. ESR1 mutations confer resistance to aromatase inhibitors in breast cancer, highlighting the molecular rationale for utilizing selective estrogen receptor degraders (SERDs) to overcome ligand-independent receptor activation.

Wild-type ERα signaling: Estrogen binding activates ERα, which dimerizes and binds estrogen response elements (EREs) to drive transcription. **ESR1 mutant ERα:** Ligand-binding domain mutations (e.g., Y537S) enable estrogen-independent receptor activation. **Therapeutic bypass:** Mutant ERα recruits coactivators (e.g., SRC-3) without ligand binding, sustaining proliferation despite aromatase inhibition.

Abbreviations: ERα, estrogen receptor alpha; ERE, estrogen response element; SERD, selective estrogen receptor degrader.

ARTICLE IN PRESS

HER2 Heterogeneity and Proteomic Mapping:Recent multi-omic integration, particularly combining spatial transcriptomics with mass spectrometry-based proteomics, has revealed significant intratumoral HER2 heterogeneity [207]. This transcriptomic-proteomic discordance critically influences targeted therapy efficacy and drives clonal selection during treatment. Approximately 20% of breast cancers exhibit HER2 overexpression as determined by immunohistochemistry [77]. HER2, a member of the ERBB receptor family, promotes tumor cell proliferation and metastasis through aberrant signaling activation [78,79].

Recent advancements in mass spectrometry-based spatial proteomics have mapped the intricate protein-protein interaction networks driving targeted therapy resistance. For example, quantitative proteomic assessments have successfully stratified 'HER2-low' cohorts, revealing that even low levels of targetable receptor protein expression can yield significant clinical responses to next-generation ADCs, thereby expanding the therapeutic window for previously ineligible patients [207, 215, 216].

This proteomic refinement directly translates into clinical practice: patients with tumors reclassified as HER2-low can now receive trastuzumab deruxtecan, which demonstrated a 50% reduction in the risk of disease progression or death in the DESTINY-Breast04 trial[175].

3.2 Epigenetic Dysregulation

Aberrant DNA Methylation

DNA methylation is mediated by DNA methyltransferases (DNMT1, DNMT3A, DNMT3B), adding methyl groups to cytosine residues without altering DNA sequence [80]. Abnormal methylation patterns in breast cancer include global hypomethylation of repetitive elements, hypermethylation of CpG island promoters in tumor suppressor genes (TSGs), and gene-specific hypomethylation [81]. TSG hypermethylation facilitates unchecked proliferation and disease progression [82–84]. Notably, around 50% of breast cancers also exhibit hypomethylation, driven by either active demethylation of oncogenes or passive loss of methylation maintenance, resulting in oncogene activation [85,86] (**Figure 3**).

ARTICLE IN PRESS

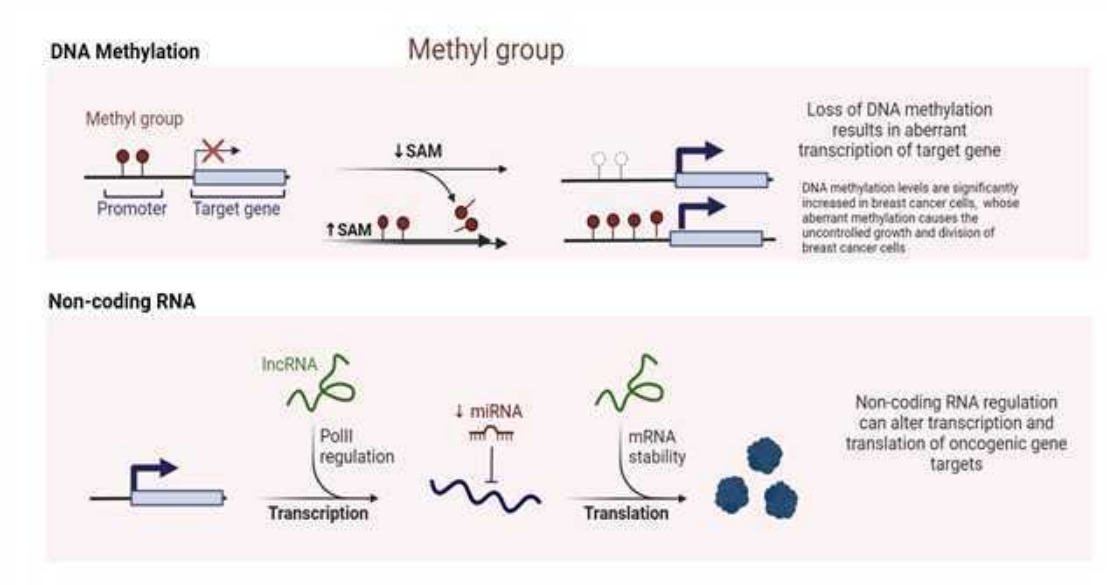


Figure 3. DNA methylation dynamics and non-coding RNA regulation in breast cancer. These epigenetic alterations serve not only as drivers of oncogenesis but also as highly specific, emerging biomarkers for liquid biopsy panels.

Methylation process: SAM (S-adenosylmethionine) donates methyl groups to CpG islands in gene promoters, silencing tumor suppressors (e.g., BRCA1). **Hypermethylation in breast cancer:** Elevated DNA methylation at oncogenic loci (e.g., ESR1) drives uncontrolled proliferation. **Non-coding RNA interplay:** lncRNAs modulate RNA polymerase II (Pol II) activity, influencing mRNA stability and translation.

Abbreviations: SAM, S-adenosylmethionine; lncRNA, long non-coding RNA; Pol II, RNA polymerase II.

Histone Modification Dysregulation

Post-translational histone modifications—methylation, acetylation, ubiquitination, sumoylation, and phosphorylation—regulate chromatin structure and gene expression [87]. Loss of H3K27me3, for example, is linked to EZH2 overexpression, which silences differentiation genes (e.g., CDH1) via the Polycomb repressive complex 2 (PRC2), maintaining cancer stem cell phenotypes [88,89].

Non-Coding RNA Regulation

MicroRNAs (miRNAs) are short (18–26 nucleotides), evolutionarily conserved non-coding RNAs that regulate gene expression post-transcriptionally. They act as

ARTICLE IN PRESS

oncogenes or tumor suppressors in cancer development. miR-21, one of the most commonly dysregulated miRNAs in breast cancer, promotes tumorigenesis by targeting genes involved in proliferation, angiogenesis, and invasion [90–95].Beyond miRNAs, the complex regulatory frameworks of breast cancer are deeply modulated by other non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs). Recent comprehensive analyses highlight that specific lncRNAs, such as HOTAIR, MALAT1, and NEAT1, play pivotal roles in regulating cell proliferation, apoptosis, and therapeutic resistance. Furthermore, dysregulation of these ncRNAs is intrinsically linked to the epithelial-mesenchymal transition (EMT). By managing the intricate molecular pathways of EMT at various levels, EMT-associated ncRNAs not only drive the metastasis of initial tumors to remote organs but also hold significant promise as early-stage diagnostic biomarkers. Despite their undeniable vast functions in cancer progression, translating these ncRNAs into clinical therapy remains challenging, partly due to the absence of sufficient validations in advanced in vivo mouse models[96,97].

3.3 Dysregulation of Signaling Pathways

Hormone Receptor Signaling Reprogramming

ER signaling is a primary driver in most breast cancers and serves as a key target for endocrine therapy [98]. ER, a ligand-dependent transcription factor, modulates the expression of factors such as GRHL2 and DCL1, influencing tumorigenesis [99]. Aberrant activation of FOXA1, a pioneer factor in ER-positive cancers, also contributes to cell proliferation and differentiation, although its downstream mediators remain poorly defined [100].

Growth Factor Receptor Pathway Alterations

Fibroblast growth factor receptor (FGFR) signaling plays essential roles in mammary gland development, tissue homeostasis, tumorigenesis, and metastasis. Dysregulation of FGFRs, their ligands, and co-factors is associated with therapy resistance. As a subclass of receptor tyrosine kinases (RTKs), FGFRs—along with IGFR and VEGFR—activate downstream signaling cascades (e.g., RAS-MAPK) upon ligand binding, contributing to resistance to CDK4/6 inhibitors [101–104] (**Figure 4**).

ARTICLE IN PRESS

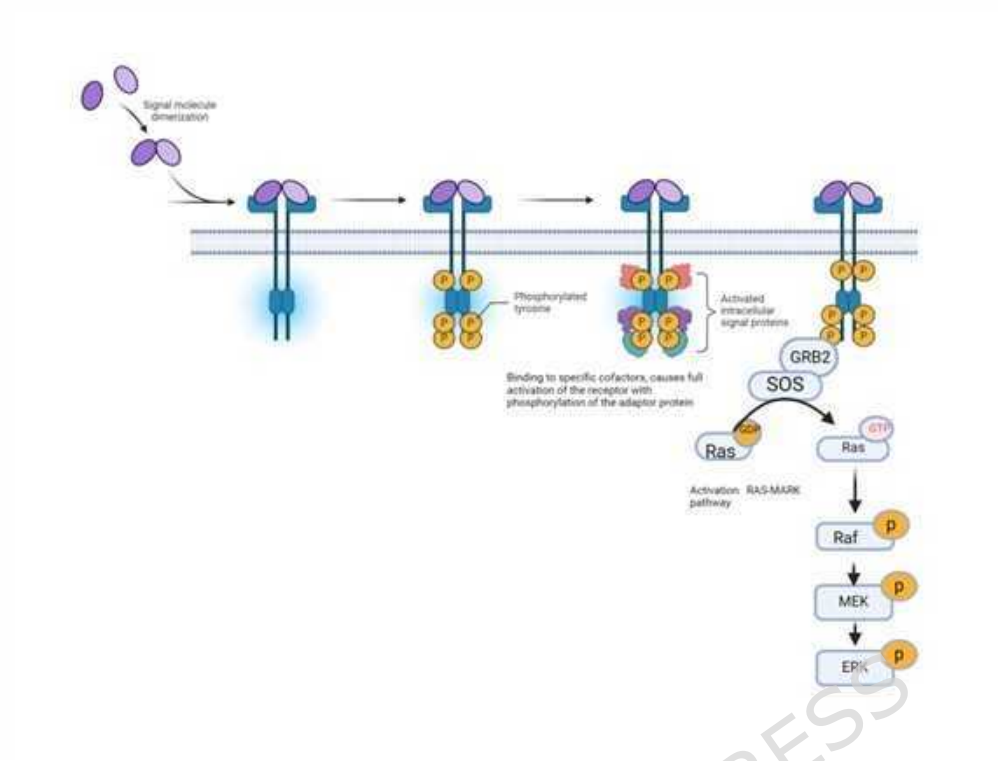


Figure 4. Growth factor receptor signaling and RAS-MAPK pathway activation. Hyperactivation of these cascades often serves as a compensatory bypass mechanism, driving acquired resistance to targeted therapies such as CDK4/6 inhibitors.

Receptor dimerization: Ligand binding induces tyrosine kinase receptor (e.g., EGFR) dimerization and autophosphorylation. **Adaptor recruitment:** Phosphorylated tyrosines recruit GRB2-SOS complexes, activating RAS via GTP exchange. **MAPK cascade:** Sequential phosphorylation of RAF, MEK, and ERK regulates cell proliferation and survival.

Abbreviations: GRB2, growth factor receptor-bound protein 2; SOS, Son of Sevenless; RAS, rat sarcoma viral oncogene; MAPK, mitogen-activated protein kinase.

3.4 Metabolic Reprogramming and Tumor Microenvironment (TME) Interactions

Aberrant Glycolysis (Warburg Effect)

ARTICLE IN PRESS

The Warburg effect describes a metabolic hallmark of cancer, wherein proliferating cells convert glucose to lactate even under aerobic conditions [105,106]. This process involves glucose uptake via GLUT transporters, glycolytic conversion to pyruvate, and subsequent lactate formation by lactate dehydrogenase (LDH), with export via monocarboxylate transporters (MCTs) [107]. Hexokinase (HK), especially HK2, is a key glycolytic enzyme highly expressed in tumor cells, promoting lactate accumulation and acidification of the microenvironment, thereby suppressing antitumor immunity [108,109] (**Figure 5**).

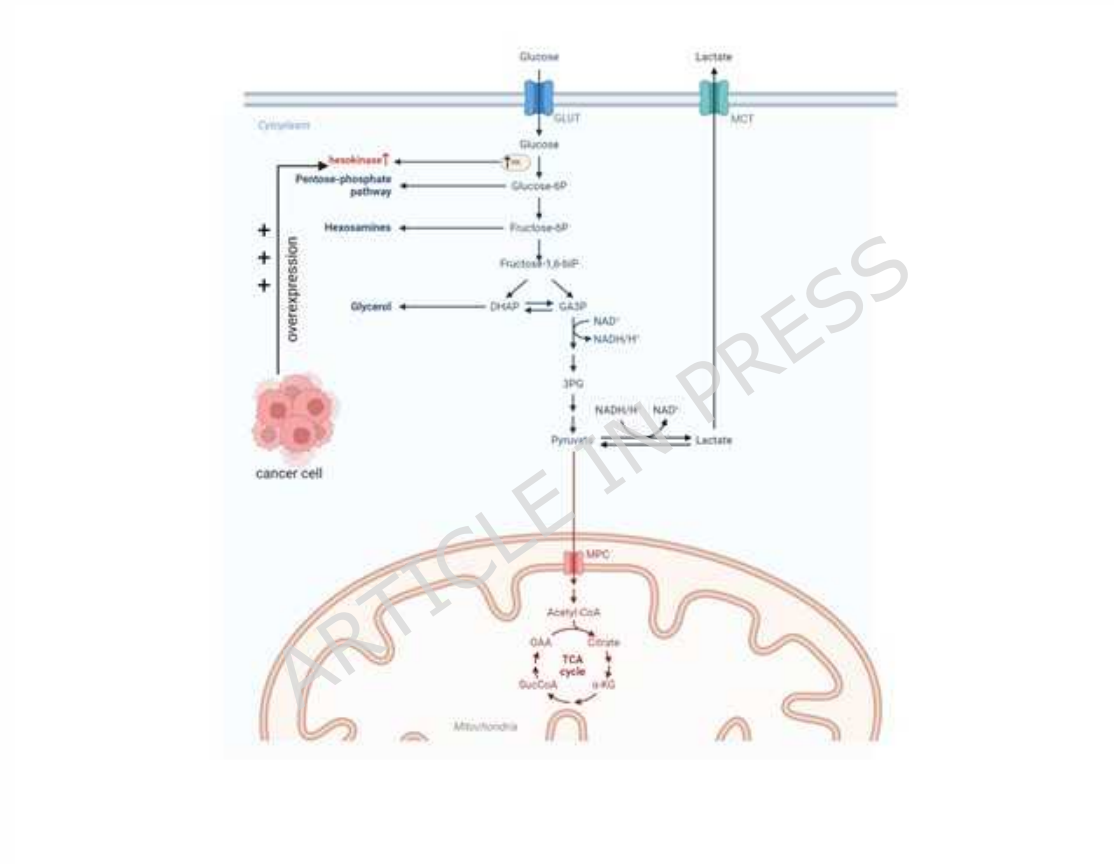


Figure 5. Aberrant glycolysis and mitochondrial metabolism in cancer cells. The resulting lactate accumulation and microenvironmental acidification actively suppress antitumor immunity, presenting novel targets for precision metabolic interventions.

Warburg effect: Enhanced glucose uptake via GLUT transporters and flux through hexokinase (HK)-mediated glycolysis, yielding lactate even under aerobic conditions. **Mitochondrial coupling:** Citrate from the TCA cycle fuels lipid

ARTICLE IN PRESS

synthesis via acetyl-CoA carboxylase (ACC). **Metabolic symbiosis:** Lactate export via MCT4 acidifies the microenvironment, promoting invasion and immune evasion.

Abbreviations: GLUT, glucose transporter; HK, hexokinase; TCA, tricarboxylic acid; MCT4, monocarboxylate transporter 4.

Lipid Metabolism Rewiring

Recent research has linked dysregulated lipid metabolism—including fatty acid synthesis, elongation, desaturation, and oxidation—to cancer progression. Key enzymes such as ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), carnitine palmitoyltransferase (CPT), and various acyl-CoA dehydrogenases (e.g., ACADS, ACADM, ACADL, ACADVL) are upregulated in tumors. Notably, CPT1B, the rate-limiting enzyme of fatty acid β-oxidation (FAO), contributes to chemoresistance via the STAT3–CPT1B–FAO axis, making lipid metabolism enzymes potential therapeutic targets [110-114].

Tumor Microenvironment (TME) Regulation

The TME comprises cancer cells, immune cells, fibroblasts, endothelial cells, and extracellular matrix components. c-MYC serves as a central regulator by modulating angiogenesis and cell proliferation through TME interactions [115]. Cancer-associated fibroblasts (CAFs) promote immune suppression by secreting TGF-β to recruit regulatory T cells (Tregs) and upregulate PD-L1, thereby enhancing tumor progression [116,117].Notably, immune cell heterogeneity plays a pivotal role in dictating therapeutic responses. Tumor-associated macrophages (TAMs) frequently polarize towards an immunosuppressive M2-like phenotype, secreting IL-10 and TGF-β to orchestrate an immuno-cold niche[210]. Concurrent single-cell analyses reveal diverse subpopulations of cancer-associated fibroblasts (CAFs), particularly inflammatory CAFs (iCAFs), which structurally deposit dense collagen matrices that impede drug penetration and immune cell infiltration[211]. Advancements in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have profoundly decoded this TME complexity. These high-resolution tools reveal how cancer-associated fibroblasts (CAFs) and macrophages physically remodel the matrix and secrete cytokines, actively exhausting CD8+ T cells and building formidable barriers against emerging immunotherapies [206].

ARTICLE IN PRESS

These high-resolution insights are directly translatable to clinical decisions. For example, the presence of tertiary lymphoid structures (TLS) within the TME has been correlated with improved responses to immunotherapy in TNBC, guiding patient stratification. Furthermore, therapeutic strategies targeting FAP+ immunosuppressive CAFs are now entering clinical settings, and the polarization status of TAMs is being used to select candidates for CSF1R inhibitor combinations. [221,222]These examples illustrate how TME profiling is moving from descriptive biology to actionable oncology.

Furthermore, dynamic lipidomic profiling has demonstrated that overactivation of fatty acid oxidation (FAO) heavily correlates with immune-cold phenotypes. Real-time metabolomic tracking of circulating oncometabolites in patient serum can now predict resistance to immune checkpoint inhibitors weeks before radiological progression, offering a highly actionable therapeutic window [217,218].

3.5 Bridging Molecular Pathogenesis and Diagnostics

Understanding these intricate multi-omic networks—from genomic instability to metabolic reprogramming—lays the crucial foundation for modern clinical management. To effectively target these specific molecular aberrations, oncologists require highly sensitive, real-time diagnostic modalities. The following section explores how traditional imaging is evolving into multi-omic molecular diagnostics to capture this complex tumor biology.

4. Diagnostic Approaches for Breast Cancer

4.1 Multimodal Imaging in Breast Cancer Diagnostics

While imaging is pivotal for morphological evaluation and lesion localization, optimizing modality selection requires balancing diagnostic yield against risks like radiation-induced DNA damage, a notable concern even with the low-dose X-rays of conventional mammography (MG) [120]. To enhance accessibility and mitigate costs without sacrificing image detail, synthesized mammography (SM) has emerged as a robust alternative to digital mammography (DM) [119] , though MG accuracy remains inherently limited by individual breast density [118]. To overcome such anatomical limitations, the clinical focus has decisively shifted toward multimodal integration. In ultrasonography (US), combining conventional assessments with contrast-enhanced US (CEUS) significantly clarifies intralesional vascularity [121,122]. Furthermore, quantitative perfusion analysis via CEUS

ARTICLE IN PRESS

effectively characterizes solid cystic lesions [123] , and its multimodal integration drastically reduces diagnostic uncertainty for complex, non-mass abnormalities [124].Beyond localized morphological assessments, computed tomography (CT) remains indispensable for comprehensive staging and metastasis detection [125]. Specifically, abdominal CT demonstrates high diagnostic accuracy for monitoring visceral spread in stage III or HER2-positive breast cancers [126]. When coupled with modalities like color Doppler US, multimodal CT strategies significantly enhance the detection of regional and distant lymph node metastases [127-129]. Functional imaging via single-photon emission computed tomography (SPECT) further complements this by characterizing pathophysiological tumor metabolism. Recent breakthroughs in peptide-based, breast cancer-targeted radiopharmaceuticals have markedly elevated SPECT's sensitivity and specificity [130]. By fusing this functional data with anatomical CT, and incorporating emerging tools like artificial intelligence and hardware optimization, SPECT/CT hybrid platforms now provide the high-dimensional precision required for personalized oncology [131,132].

4.2 Molecular Biotechnology-Based Examinations

Breakthroughs in molecular biotechnology have revolutionized the traditional diagnostic and therapeutic paradigms for breast cancer by enabling multi-dimensional analysis of tumor biology—including genetic alterations, epigenetic regulation, and protein–protein interactions—thus laying a robust foundation for precision medicine (Table 2).

Genomic Sequencing technologies have mapped comprehensive mutational landscapes of breast cancer, identifying critical driver mutations such as PIK3CA and ESR1, including rare but actionable variants. This facilitates personalized therapeutic strategies, especially in advanced-stage disease [133]. Moreover, transcriptome-based molecular classification systems—such as those tailored to TNBC—have enhanced the development of individualized chemotherapy regimens [134].

Epigenetics, particularly studies on DNA methylation and chromatin remodeling, have uncovered silencing mechanisms involving genes such as BRCA1/2. These findings have not only supported early detection strategies but also fueled the development of epigenetic-targeted therapeutics [135].

ARTICLE IN PRESS

Single-cell technologies have provided a microscopic lens into tumor heterogeneity by elucidating dynamic interactions between immune and stromal components within the tumor microenvironment. These insights are reshaping prognostic assessment models and guiding the design of combinatorial therapies [136].

Nanotechnology-based drug delivery systems, such as functionalized exosomes and biomimetic liposomes, have improved tumor-targeted drug accumulation, thereby enhancing chemotherapeutic efficacy while minimizing systemic toxicity [137].

Aptamer-based smart probes, exemplified by HER2-specific recognition elements, offer integrated diagnostic and therapeutic (theranostic) functionalities, expanding the toolkit for precision intervention [138,139].

Emerging molecular diagnostics, including CRISPR-Cas12a–based detection systems, have overcome the sensitivity limitations of conventional methods. These platforms allow ultra-early detection of low-abundance mutations in circulating tumor DNA (ctDNA), thereby accelerating the clinical translation of liquid biopsy techniques [140].

Collectively, these technological advancements have constructed a full-spectrum clinical management framework that spans molecular subtyping, real-time monitoring, and precision targeting. This paradigm marks the transition of breast cancer care into a multi-omics–driven era of precision oncology.

ARTICLE IN PRESS

4.3 Liquid Biopsy and Minimal Residual Disease (MRD) Monitoring

To overcome the spatial and temporal limitations of traditional tissue biopsies, liquid biopsies have emerged as a cornerstone of precision oncology. This approach primarily analyzes circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and tumor-derived exosomes, offering a non-invasive, multi-omic snapshot of the tumor's dynamic evolution.

Circulating Tumor DNA (ctDNA) and CTCs: ctDNA profiling is highly effective for detecting minimal residual disease (MRD) and monitoring therapeutic response. Clinical validations of tumor-informed ctDNA assays (such as those targeting patient-specific clonal mutations) have demonstrated exceptional performance. In

ARTICLE IN PRESS

early-stage breast cancer, serial ctDNA monitoring has achieved analytical sensitivities exceeding 89% for predicting clinical relapse, often detecting MRD with a median lead time of 8 to 10 months prior to radiographic progression [141,142]Complementary to ctDNA, CTCs provide critical cellular and transcriptomic information. The FDA-approved CellSearch system has established that the presence of ≥5 CTCs per 7.5 mL of blood is robustly associated with decreased progression-free and overall survival in metastatic breast cancer, acting as an independent prognostic biomarker [143]

Exosomes: In addition to ctDNA and CTCs, tumor-derived exosomes play a critical role in intercellular communication and pre-metastatic niche formation. These nanoscale extracellular vesicles encapsulate a highly stable, multi-omic payload of proteins, lipids, and ncRNAs (including miRNAs and lncRNAs). Because exosomal lipid bilayers protect their genomic and proteomic cargo from enzymatic degradation in the bloodstream, they offer significantly higher stability than free-floating ctDNA. Emerging diagnostic platforms leveraging exosomal multi-omic signatures show high sensitivity (often >90%) in distinguishing breast cancer patients from healthy cohorts, positioning them as highly promising biomarkers for ultra-early diagnosis and real-time mapping of the tumor microenvironment [144].

Comparative Efficacy of Liquid Biopsy Biomarkers: Comparatively, ctDNA assays demonstrate remarkable analytical sensitivity (exceeding 89%) and high specificity (up to 99%) for MRD detection, often anticipating clinical relapse with a lead time of 8 to 10 months [212]. CTCs, while offering lower numerical sensitivity (typically 50-60% in early stages) compared to ctDNA, provide invaluable transcriptomic and proteomic cellular information that ctDNA cannot capture [143]. Conversely, exosomes offer a unique advantage in molecular stability due to their protective lipid bilayers, routinely achieving over 90% diagnostic sensitivity, though their clinical specificity remains challenged by the lack of standardized isolation protocols [213]. Integrating these three modalities uniquely compensates for individual assay limitations.

ARTICLE IN PRESS

Translational Relevance and Clinical Implementation: Despite their immense translational relevance, the routine clinical implementation of liquid biopsies faces several formidable barriers. High sequencing costs and the lack of robust assay standardization across different multi-omic platforms currently limit their widespread accessibility. Furthermore, stringent regulatory considerations—such as the need for large-scale, prospective clinical utility trials to secure FDA approval and standardized reimbursement frameworks—must be addressed before liquid biopsy can seamlessly transition from a specialized research tool to an integrated standard of care in routine oncology practice[214].

However, a balanced assessment must acknowledge key limitations. First, ctDNA assays may yield false-negative MRD results in patients with low tumor burden or non-shedding tumors, and clonal hematopoiesis of indeterminate potential (CHIP) can cause false positives. Second, CTC enumeration in early-stage disease lacks sensitivity, limiting its MRD role. Third, exosome-based diagnostics still lack standardized isolation protocols and clinical-grade validation. Additionally, high costs and the absence of large-scale prospective utility trials prevent regulatory approval and insurance coverage. Overcoming these hurdles requires multicenter harmonization efforts and consensus guidelines to integrate liquid biopsy reliably into routine care.

ARTICLE IN PRESS

Table 2: Advanced Diagnostic and Multi-Omic Monitoring Modalities

Diagnostic Modality	Technology / Marker Focus	Clinical Application	Key Advantages
Liquid Biopsy (ctDNA)	Next-Generation Sequencing (NGS) of circulating tumor DNA	Minimal Residual Disease (MRD) monitoring, early relapse prediction	High sensitivity (>89%), detects tumor evolution and resistance mutations months ahead of clinical progression

ARTICLE IN PRESS

Diagnostic Modality	Technology / Marker Focus	Clinical Application	Key Advantages
Liquid Biopsy (CTCs)	CellSearch system / Multi-omic cellular profiling	Prognostic evaluation and progression monitoring in metastatic disease	Captures intact cellular and transcriptomic information; independent prognostic biomarker
Liquid Biopsy (Exosomes)	Nanoscale extracellular vesicles (proteins, lipids, ncRNAs)	Ultra-early diagnosis, mapping of tumor microenvironment (TME) crosstalk	High stability in bloodstream; lipid bilayer protects cargo from enzymatic degradation
Advanced Imaging (MRI, PET-CT)	Dynamic functional imaging / Soft-tissue resolution	High-risk screening, evaluation of neoadjuvant therapy response	Superior soft-tissue resolution; non-invasive assessment of tumor vascular permeability

ARTICLE IN PRESS

4.4 Genetic Testing

The widespread application of multi-gene panel testing has markedly improved the precision of early-stage breast cancer management. By integrating risk stratification with adjuvant treatment planning, these genetic assays enhance the

ARTICLE IN PRESS

clinical utility of traditional pathological parameters; however, their translational application still requires further standardization [145].

BRCA1 and BRCA2 are the most critical pathogenic genes associated with hereditary breast cancer. The presence of deleterious mutations in these genes significantly influences treatment decisions. Tumors harboring such mutations show marked sensitivity to DNA-damaging agents, particularly PARP inhibitors. Nevertheless, poor adherence to testing recommendations results in up to 30% of carriers remaining undiagnosed and untreated [146].

Advancements in molecular diagnostics have promoted the clinical adoption of expanded gene panels beyond BRCA1/2, encompassing genes such as PALB2 and ATM. Despite this progress, the interpretation of variants of uncertain significance (VUS) remains a major clinical challenge, as their pathogenic potential is not yet fully understood [147].

Genetic analysis has become deeply integrated into the entire breast cancer care continuum. Firstly, it facilitates intensified screening and prophylactic interventions in high-risk populations. Secondly, it serves as a predictive biomarker for targeted therapies such as PARP inhibitors, with objective response rates reaching up to 65% in patients harboring pathogenic mutations [148].

Epidemiological studies have revealed that among breast cancer survivors meeting NCCN criteria for genetic testing, only 38% undergo formal genetic counseling. While 92% of those tested report discussing genetic risk with family members, the overall clinical uptake of direct-to-consumer genetic testing remains below 5% [149].

4.5 Transitioning from Molecular Diagnostics to Precision Intervention

The aforementioned diagnostic and multi-omic monitoring modalities provide a high-resolution map of the tumor's vulnerabilities. However, the ultimate goal of precision oncology is translating these sophisticated molecular and imaging insights into actionable clinical strategies. In the following section, we detail how these diagnostic breakthroughs are directly shaping the evolution of breast cancer treatments, moving from broad cytotoxic regimens to highly tailored targeted therapies and novel immunomodulators.Table 3 provides a synthesis of how each

ARTICLE IN PRESS

omics layer informs specific clinical decisions, with real-world examples that are elaborated in subsequent treatment sections.

Table 3: Multi-Omics Data Integration in Clinical Decision-Making

Omics Layer	Representative Technology	Clinical Decision/Use	Real-World Example
Genomics	NGS panels, ctDNA sequencing	Select PARP inhibitors, track ESR1 mutations	OlympiAD (olaparib), ctDNA-guided SERD switch
Transcriptomics	RNA-seq, PAM50	Subtype classification, TMB & immune signature for immunotherapy	Transcriptome-based subtyping for chemotherapy selection in TNBC; immune gene signatures to guide pembrolizumab eligibility (KEYNOTE-522)
Proteomics	Mass spectrometry, quantitative IHC	Determine HER2-low status, activate ADC therapy	DESTINY-Breast04 (T-DXd)
Metabolomics	NMR/MS serum profiling	Early pharmacodynamic response assessment, immune-cold detection	Real-time lactate/kynurenine monitoring to predict ICI resistance
Multi-omics Integration	Molecular tumor board	Combinatorial targeted + immunotherapy regimen	I-PREDICT trial, SAFIR02-BREAST

ARTICLE IN PRESS

5. Treatment

5.1 Chemotherapy

Chemotherapy remains a primary treatment for certain cancers, despite its strong side effects, which often raise patient concerns. Recent advancements in combination therapies, such as chemotherapy combined with targeted therapies

ARTICLE IN PRESS

and immunotherapies, have both improved efficacy and reduced side effects [150]. Neoadjuvant chemotherapy (NACT) plays a significant role in treating HER2-positive and TNBC, as it can shrink tumor size, reduce the risks associated with breast-conserving surgery, and help guide subsequent treatment strategies [151]. In early-stage breast cancer, adjuvant chemotherapy effectively reduces the risk of recurrence and death, though its applicability should be assessed based on the patient's overall health status and other factors [152]. For metastatic breast cancer, chemotherapy does not offer a cure but remains valuable in alleviating symptoms and extending survival [153]. However, the long-term side effects of chemotherapy, such as cardiac toxicity, cognitive dysfunction, and neurotoxicity, warrant careful attention [154]. Additionally, chemotherapy resistance has become a major challenge in breast cancer treatment. Research indicates that specific molecular markers may be linked to resistance, providing a new direction for personalized treatments [155]. For instance, the combination of platinum-based drugs and PARP inhibitors in TNBC has shown promising preclinical results, reflecting the trend towards diversified and more precise chemotherapy regimens [156].

5.2 Endocrine Therapy

Endocrine therapy is the cornerstone of treatment for hormone receptor-positive (HR+) breast cancer. It primarily targets the ER signaling pathway to significantly suppress cancer cell proliferation and progression, effectively reducing recurrence rates and improving survival outcomes, making it a standard treatment for both early and late-stage breast cancer [157,158]. Clinically, endocrine therapy for early-stage breast cancer typically lasts for five years, with treatment duration extended for high-risk patients, particularly postmenopausal women, where aromatase inhibitors have shown superior efficacy compared to tamoxifen [159,160].

In late-stage breast cancer, endocrine therapy is often combined with targeted therapies to overcome resistance and enhance efficacy. The introduction of CDK4/6 inhibitors (such as palbociclib, ribociclib, and abemaciclib) has significantly enhanced the anti-tumor effects of endocrine therapy by blocking the cell cycle [161,162]. Furthermore, the combination of mTOR inhibitors and PI3K

ARTICLE IN PRESS

inhibitors with endocrine therapy holds great promise, offering new directions for improving patient prognosis [163,164].

However, endocrine therapy still faces the major challenge of resistance. Research shows that specific ESR1 gene mutations and compensatory signaling pathway activations are primary drivers of aromatase inhibitor resistance. Clinically, identifying these mutational profiles via serial ctDNA monitoring directly informs the decision to switch patients to oral Selective Estrogen Receptor Degraders (SERDs, such as elacestrant) or novel targeted combinations, ensuring that therapeutic regimens adapt in real-time to the tumor's clonal evolution [165-168].Ongoing studies are actively exploring new endocrine drugs and combination therapies to improve the durability and efficacy of treatment [167,168].

5.3 Heavy Ion Therapy

Heavy ion therapy, particularly carbon ion therapy, demonstrates significant advantages in breast cancer treatment due to its high linear energy transfer (LET) characteristics. It provides stronger tumor cell-killing effects while reducing damage to surrounding healthy tissues, ensuring more thorough eradication of localized cancer cells [169]. The Heavy Ion Therapy Center (HITC) at Yonsei Cancer Center in Korea, the first carbon ion therapy center equipped with fixed beams and superconducting rotational machines, has confirmed the significant clinical effectiveness and utility of carbon ion therapy for tumor treatment [170]. Clinical trials show that carbon ion therapy in partial breast irradiation for early-stage breast cancer yields good therapeutic outcomes with minimal adverse reactions. Although it requires a longer treatment duration, its persistence and safety provide a foundation for future studies [171]. Despite its high costs and technological complexity limiting global application, carbon ion therapy is expected to play an increasingly important role in breast cancer treatment as technology advances [172].

5.4 Targeted Therapy

Targeted therapy has become a crucial treatment approach in recent years for breast cancer. With the continuous development of targeted drugs, the treatment of breast cancer with targeted therapies has become more refined and comprehensive. Targeted drugs inhibit specific growth pathways in tumor cells, effectively suppressing tumor development. For HER2-positive breast cancer, the

ARTICLE IN PRESS

use of monoclonal antibodies such as trastuzumab and pertuzumab has significantly improved patient survival and overall survival rates [173]. For tumors harboring germline BRCA1/2 mutations (predominantly TNBC), multi-omic profiling of homologous recombination deficiency (HRD) has successfully guided the clinical application of PARP inhibitors. Landmark trials, such as OlympiA and OlympiAD [9,60], have cemented the role of PARP inhibitors (e.g., olaparib and talazoparib) in significantly prolonging both progression-free and overall survival by exploiting synthetic lethality in DNA repair-deficient cancer cells.[174]

Furthermore, antibody-drug conjugates (ADCs) have revolutionized the targeted therapy landscape by integrating highly specific monoclonal antibodies with potent cytotoxic payloads to deliver precision strikes against tumor cells. Currently, several FDA-approved ADCs have reshaped clinical paradigms, whereas others remain under active clinical investigation. Most notably, quantitative proteomic reassessments of HER2 expression have birthed the 'HER2-low' clinical category. The FDA-approved trastuzumab deruxtecan (T-DXd) demonstrated unprecedented survival benefits in this cohort during the landmark Phase III DESTINY-Breast04 trial, reducing the risk of disease progression or death by 50% (Hazard Ratio 0.50) and significantly extending median progression-free survival (9.9 months vs. 5.1 months for chemotherapy), representing a massive paradigm shift[175].However, critical evaluation of this trial highlights that while survival is significantly prolonged, the emergence of acquired resistance and severe toxicities—particularly interstitial lung disease (ILD)—necessitate stringent clinical monitoring. Similarly, the FDA-approved Trop-2-targeted ADC sacituzumab govitecan (SG) showed marked efficacy in the ASCENT trial by efficiently bypassing traditional chemoresistance mechanisms in heavily pretreated TNBC [175–177]. Yet, its clinical tolerability is frequently limited by high rates of neutropenia and diarrhea. Concurrently, investigational ADCs such as datopotamab deruxtecan (Dato-DXd) are undergoing rigorous Phase III evaluations (e.g., TROPION-Breast01), offering promising preliminary efficacy with differentiated toxicity profiles [208]. Current research is also actively exploring novel targets (such as HER3, LIV-1) and bispecific ADCs to overcome existing treatment barriers [178].In HR+/HER2- advanced breast cancer, transcriptomic and genomic profiling of cell cycle dysregulation has established the combination of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib)

ARTICLE IN PRESS

with endocrine therapy as the gold-standard first-line treatment. Extensive clinical data reveal that this blockade comprehensively halts the G1-to-S phase transition, effectively doubling progression-free survival compared to endocrine therapy alone [179]. Similarly, PI3K/AKT/mTOR pathway inhibitors have shown promising applications in this subtype [180].

However, targeted therapy still faces the challenge of resistance. Research indicates that mutations in the PI3K/AKT pathway may lead to resistance to HER2-targeted therapy [181]. Therefore, a deeper understanding of resistance mechanisms is critical for developing more effective treatment strategies.

5.5 Immunotherapy

Immunotherapy has shown significant efficacy in breast cancer, especially in cases where conventional treatments have limited success. In TNBC, the landmark Phase III KEYNOTE-522 trial established pembrolizumab with neoadjuvant chemotherapy as the standard of care, significantly improving pathological complete response (pCR) rates to 64.8% (compared to 51.2% with placebo) [203]. Nevertheless, a critical limitation remains the identification of precise predictive biomarkers. Multi-omic analyses demonstrate that relying solely on PD-L1 immunohistochemistry is clinically insufficient to predict immune-related adverse events or long-term therapeutic durability. Therefore, comprehensive transcriptomic immune signatures (such as tumor mutational burden and specific T-cell inflamed gene expression profiles) offer far superior predictive value for immunotherapy response [204]. This predictive mechanism is closely linked to CXCL13+ T cell-mediated immune activation and the enrichment of pro-inflammatory macrophages (CXCL9/CXCL10 overexpression) [182,183]. For HER2-positive subtypes, research has shifted toward multi-modal immunomodulation, including the synergistic application of immune checkpoint inhibitors, HER2-targeted ADCs, CAR-T therapies, and bispecific antibodies (such as PD-1/HER2) [184,185].As detailed in Section 3.4, the immunosuppressive TME severely limits therapeutic efficacy. Consequently, modern immunomodulatory strategies are now targeting the M2 phenotype of tumor-associated macrophages (TAMs) and blocking fibroblast-derived TGF-β to therapeutically reverse this 'immune-cold' state, significantly enhancing cytotoxic T cell infiltration [186]. Finally, genomic-driven screening of public neoantigens (such as TP53/PIK3CA

ARTICLE IN PRESS

mutation-derived epitopes) lays the foundation for developing universal TCR-T therapies, overcoming technical bottlenecks in personalized treatment [187].

5.6 Traditional Chinese Medicine (TCM) Therapy

Traditional Chinese Medicine (TCM) has gained increasing attention in clinical practice and is playing an increasingly important role in breast cancer treatment. Studies have shown that certain active components in Chinese herbs can significantly interfere with intracellular signaling cascades in cancer cells. For instance, the active compound in Huangqin has been found to block the Wnt/β-catenin pathway, which is crucial for tumor cell growth. Inhibition of this pathway can effectively suppress the spread of breast cancer cells [188,189]. Furthermore, combining Chinese medicine with chemotherapy yields enhanced therapeutic effects. For patients undergoing surgery, a combination of Western and Chinese medicine not only leads to more noticeable tumor shrinkage but also reduces the severe anemia and thrombocytopenia often induced by chemotherapy [190,191]. For TNBC, Chinese medicine improves the patient's immune status, alters the tumor microenvironment by modifying immune-suppressive macrophages, and facilitates the infiltration of cytotoxic T cells into the tumor area, resulting in a fourfold improvement in therapeutic outcomes [192]. Notably, Huangqi (Astragalus) has demonstrated potential in enhancing the efficacy of radiotherapy by effectively eliminating drug-resistant cancer cells, doubling the therapeutic effect of radiation. It has also been shown to reverse drug resistance in tumors, restoring their sensitivity to chemotherapy in experimental settings [193].

5.7 Combination Therapy

As mentioned earlier, the combination of different treatment modalities has shown significant therapeutic benefits, particularly in cases where conventional single treatments are less effective, such as TNBC. In addition, the combination of RET inhibitors with CDK4/6 inhibitors and endocrine therapy in ER+ breast cancer, as well as the use of inetetamab with pyrotinib and chemotherapy, and apatinib combined with trastuzumab and albumin-bound paclitaxel in HER2-positive breast cancer patients with brain metastases, have all demonstrated significant therapeutic effects and notable suppression of resistant tumor cell growth [194-196]. It is well-known that radiotherapy can cause neurotoxicity; however, when combined with novel targeted drugs, it can enhance efficacy while

ARTICLE IN PRESS

controlling toxicity [197]. The integration of various treatment approaches allows for better management of breast cancer metastasis, recurrence, drug resistance, and heterogeneity, while also minimizing the side effects of treatments, providing patients with better therapeutic options and prognoses **(Table 4)**[198].

Table 4: Paradigm-Shifting Combination Therapies & Clinical Outcomes

Therapeutic Strategy	**Applicable Subtypes**	**Key Mechanism of Action**	**Landmark Trials & Clinical Outcomes**
CDK4/6 Inhibitors + Endocrine Therapy	HR+/HER2- Advanced Breast Cancer	Comprehensive blockade of G1-to-S cell cycle transition, overcoming primary endocrine resistance	Significantly doubles progression-free survival (PFS) compared to endocrine therapy alone.
Immune Checkpoint Inhibitors + Chemotherapy	TNBC (PD-L1+ or high neoantigen burden)	Overcomes immune evasion by blocking PD-1/PD-L1; reactivates cytotoxic T-cell responses	KEYNOTE-522: Standard of care for early TNBC, significantly improving pathological complete response.
Next-Generation ADCs (e.g., T-DXd)	HER2-positive & HER2-low Metastatic Breast Cancer	Integrates specific monoclonal antibodies with highly potent cytotoxic	DESTINY-Breast04: Significant survival benefit in HER2-low cohort (mPFS 9.9 vs. 5.1 months).

ARTICLE IN PRESS

ARTICLE IN PRESS

Therapeutic Strategy	Applicable Subtypes	Key Mechanism of Action	Landmark Trials & Clinical Outcomes
		payloads via cleavable linkers	
PARP Inhibitors (e.g., Olaparib)	TNBC with Germline BRCA1/2 mutations	Exploits synthetic lethality in homologous recombination deficiency (HRD) or DNA repair-deficient cells	OlympiA/OlympiAD: Significantly prolongs progression-free and overall survival.
Trop-2-Targeted ADCs (e.g., Sacituzumab Govitecan)	Heavily pretreated metastatic TNBC	Bypasses traditional chemoresistance by targeting Trop-2 epithelial antigen to deliver SN-38	ASCENT: Marked improvement in survival outcomes for heavily pretreated, chemoresistant TNBC.

ARTICLE IN PRESS

5.8 Therapeutic Limitations and Mechanisms of Resistance

Despite the remarkable success of precision therapies, acquired drug resistance remains the primary cause of breast cancer mortality. Through a multi-omics lens, therapeutic resistance is rarely driven by a singular genetic event; rather, it manifests as a complex evolutionary adaptation characterized by subclonal selection, epigenetic regulation, and profound signaling pathway rewiring [201]. Under the selective pressure of targeted therapies, pre-existing drug-resistant subclones outcompete sensitive populations (clonal evolution). This process is heavily modulated by epigenetic regulation, such as genome-wide hypomethylation or specific histone modifications (e.g., EZH2 overexpression),

ARTICLE IN PRESS

which dynamically alter chromatin accessibility to promote an EMT-associated, therapy-tolerant persister cell state. Concurrently, profound signaling pathway rewiring allows tumors to bypass therapeutic blockades. [72].

Endocrine and Targeted Therapy Resistance: In HR+ breast cancers, prolonged endocrine therapy frequently induces selective pressure that results in ESR1 ligand-binding domain mutations (e.g., Y537S, D538G), leading to constitutive, estrogen-independent receptor activation [74,165]. Concurrently, transcriptomic plasticity allows tumors to bypass CDK4/6 inhibition via the compensatory hyperactivation of the PI3K/AKT/mTOR or FGFR signaling pathways [199]. Similarly, in HER2+ disease, profound intratumoral spatial heterogeneity, dynamic internalization of target antigens, and payload tolerance pose significant barriers to antibody-drug conjugates (ADCs), driving the survival of resistant subclones [200].

Immunotherapy Resistance and the TME: The efficacy of immunotherapy is profoundly limited by the tumor microenvironment (TME). Multi-omic profiling has identified that "immune-cold" breast cancers employ severe metabolic reprogramming to evade immune surveillance. The Warburg effect leads to excessive lactate accumulation and hypoxia within the TME, which physically and metabolically paralyzes infiltrating cytotoxic CD8+ T cells while recruiting immunosuppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [201]. Overcoming these multi-layered resistance mechanisms remains the most critical challenge in modern oncology, necessitating the shift towards dynamic, multi-omic monitoring (such as serial ctDNA tracking) to anticipate adaptive resistance before macroscopic clinical progression occurs.

6. Future Directions in Breast Cancer Treatment

6.1 AI-Enhanced Diagnostic Models

The integration of artificial intelligence (AI) with multi-modal imaging and radiomics holds significant promise for improving early-stage breast cancer detection [202]. AI models, particularly those utilizing deep learning algorithms, have the capacity to process large datasets from diagnostic imaging and clinical records, which can substantially increase the accuracy of early detection. Moreover, these AI-driven approaches can facilitate dynamic monitoring of residual molecular disease and micrometastases. By integrating patient-specific

ARTICLE IN PRESS

molecular profiles with real-time monitoring, AI could pave the way for more personalized treatment strategies, allowing for tailored therapeutic interventions that are both effective and timely.

6.2 Multi-Omics Integration in Therapy

A major challenge in breast cancer therapy lies in the underutilization of multi-omics data, including genomic, transcriptomic, proteomic, and metabolomic profiles. These datasets, when integrated, could provide a more comprehensive understanding of the tumor's heterogeneity and its molecular evolution. Future studies should focus on developing methods to seamlessly combine these diverse datasets for clinical application, with particular attention to utilizing single-cell RNA sequencing technologies. This approach may offer insights into tumor microenvironment (TME) interactions and mechanisms of therapeutic resistance, thereby identifying novel targets for intervention and improving the precision of therapeutic regimens.

6.3 Advancements in Immunotherapy

Immunotherapy, despite showing promising results in breast cancer, faces substantial challenges, especially in TNBC, which exhibits significant immune evasion mechanisms. To overcome these hurdles, future research must focus on optimizing immunotherapy regimens through combinations of immune checkpoint inhibitors, bispecific antibodies, and chimeric antigen receptor T-cell (CAR-T) therapies. Additionally, efforts to reprogram the TME to promote immune cell infiltration could enhance the effectiveness of immunotherapies, particularly in immune-cold tumors that are traditionally resistant to such treatments.

6.4 Innovations in Targeted Therapy

Recent innovations in antibody-drug conjugates (ADCs), designed to target specific tumor markers such as HER2, Trop-2, and ESR1 mutations, offer exciting new possibilities for overcoming drug resistance in breast cancer. Further investigation into the role of the PI3K/AKT/mTOR signaling pathway in therapy resistance could uncover additional therapeutic targets. The development of novel targeted agents, particularly those aimed at difficult-to-treat subtypes like TNBC, could enhance the precision of breast cancer therapy and improve clinical outcomes.

6.5 Integrating Traditional and Modern Therapeutic Modalities

ARTICLE IN PRESS

The potential for integrating Traditional Chinese Medicine (TCM) with modern oncological therapies presents a promising avenue for breast cancer treatment. Compounds derived from herbal sources have shown potential in modulating key molecular signaling pathways involved in tumor growth, metastasis, and immune evasion. Multi-center, randomized clinical trials are necessary to assess the clinical efficacy of combining TCM with modern cancer therapies. Such trials could provide the evidence required for broader integration of TCM into standard breast cancer treatment regimens.

6.6 Metabolic Reprogramming in Cancer Therapy

Metabolic alterations play a critical role in the pathogenesis of breast cancer, particularly in the context of glycolysis and lipid metabolism. Future research should prioritize targeting these metabolic pathways, including the Warburg effect and lipid metabolism, to reduce tumor resistance and increase the sensitivity of tumors to conventional therapies. By targeting the metabolic reprogramming that supports cancer cell survival and proliferation, new therapeutic strategies could be developed to complement existing treatment modalities.

To achieve true multi-omic integration, genomics and transcriptomics must be complemented by real-time metabolomic profiling. High-throughput techniques, such as mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy of patient serum, empower oncologists to monitor circulating oncometabolites (e.g., lactate, kynurenine) and lipidomic shifts during therapy. Because metabolic flux changes within hours to days of drug administration, metabolomics provides a near-instantaneous readout of therapeutic efficacy, far outpacing delayed radiographic or genomic (ctDNA) indicators. This allows for dynamic, real-time clinical decision-making, prompting the immediate switch to targeted metabolic inhibitors or alternative therapies before macroscopic relapse occurs [205].

6.7 Emerging Technologies for Precision Oncology

The next frontier in precision oncology relies heavily on the integration of emerging spatial and single-cell multi-omic technologies. Advanced spatial transcriptomics and highly multiplexed spatial proteomics (e.g., Imaging Mass Cytometry) offer unprecedented, spatially resolved maps of the tumor-immune interface, identifying exact molecular niches that foster drug resistance.

ARTICLE IN PRESS

Furthermore, the integration of these high-dimensional datasets with advanced artificial intelligence (AI) and machine learning algorithms will be paramount. Future clinical workflows must leverage these AI-driven multi-omic models not only to discover novel actionable targets but also to dynamically tailor individualized therapeutic regimens in real time, ultimately actualizing the true promise of precision oncology [209].

6.8 Real-World Implementation Challenges and Limitations

Despite the tremendous promise of multi-omics and precision oncology, several real-world implementation challenges persist. Firstly, economic and accessibility barriers: comprehensive multi-omic sequencing (e.g., spatial transcriptomics, serial ctDNA monitoring) entails exorbitant costs and requires sophisticated bioinformatics infrastructure, limiting its widespread adoption in resource-constrained or community oncology settings. Secondly, regulatory hurdles: transitioning novel multi-omic signatures from the laboratory to standard-of-care requires rigorous, large-scale prospective trials to meet strict FDA and EMA regulatory approvals.

Furthermore, inherent limitations exist within current methodologies and this review. While liquid biopsies provide a systemic snapshot, they may still fail to capture the entirety of extreme spatial intratumoral heterogeneity. Additionally, this review, while comprehensive, is inherently limited by the rapid, almost daily evolution of the oncology landscape; specific therapeutic guidelines and investigational trial data discussed herein are subject to swift updates. Overcoming these barriers requires a concerted global effort toward standardizing assays, decentralizing high-throughput technologies, and reforming insurance reimbursement frameworks to ensure equitable access to precision medicine.

7. Discussion and Conclusions

Despite the progress, several critical issues warrant discussion. First, the integration of multi-omics into clinic faces significant standardization hurdles; for instance, variant interpretation across platforms remains inconsistent, and metabolomic reference ranges are not yet clinically defined. Second, while PD-L1 and TMB are used as biomarkers for immunotherapy, their predictive power is imperfect, and immune-cold tumors may need alternative strategies like epigenetic priming. Third, the quality of evidence supporting TCM in breast cancer remains

ARTICLE IN PRESS

predominantly from small, single-center studies, necessitating rigorous multi-center RCTs. Finally, the cost-effectiveness of widespread multi-omic testing must be demonstrated to ensure equitable access. Only by critically addressing these gaps can multi-omics truly transform from a research tool into a standard-of-care component.

Taken together, the evidence reviewed here demonstrates that breast cancer, as a leading global health threat to women, demands an integrated understanding of its epidemiological, molecular, and clinical dimensions. This review has systematically summarized the multidimensional risk factors and molecular networks driving pathogenesis, and detailed how technological advances have driven a paradigm shift from traditional macroscopic evaluation to high-resolution, multi-omic molecular diagnostics. This integration has dramatically enhanced the early detection of minimal residual disease and reduced diagnostic latency. In parallel, treatment has evolved from conventional monotherapies to precision regimens combining targeted therapy, immunotherapy, novel endocrine agents, and traditional Chinese medicine, significantly improving patient outcomes. However, challenges such as drug resistance, metastasis control, and individualized treatment remain urgent issues.

Moving forward, emerging technologies such as single-cell and spatial transcriptomics will further unveil the tumor’s internal diversity, refining molecular subtyping beyond the current Luminal/HER2/TNBC framework. The ultimate conquest of breast cancer will require not only technological innovation and global collaboration, but also a transition from “disease treatment” to “health management.” For researchers and clinicians, strengthening the interface between basic research and clinical translation is essential to building dynamic treatment decision-making systems. For the public, maintaining regular physical activity, avoiding obesity, ensuring adequate sleep quality, reducing alcohol consumption, and maintaining proper vitamin intake remain foundational preventive measures. With continued interdisciplinary effort, the promise of precision oncology can be translated into tangible survival benefits for all patients.

Authors' contributions XC and YY Writing—original draft. PW made the Figures. JW, YZ, ZZ, JJ, HZ and XK searched the literature. HH, GJ and HF reviewed and edited the manuscript. All authors approved the final version.

ARTICLE IN PRESS

Funding This work was supported by the Excellent Young Teacher Training Program of Sanquan College of Xinxiang Medical University (SQ2025YQJH04), Backbone Henan Province Colleges and Universities Young Backbone teacher Training Program (2023GGJS201), Teachers Program of Sanquan College of Xinxiang Medical University (SQ2023GGJS06), Academic Technology Leader Program of Sanquan College of Xinxiang Medical University (SQ2023XSJSDTR01), Provincial key discipline project of Biology and Medicine of Sanquan College of Xinxiang Medical University (ZDXKXM003, ZDXKXM015).

Declarations

Ethical Approval and Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of supporting data Not applicable.

Competing interests No potential conflicts of interest are disclosed.

Acknowledgements All Figures created by https://BioRender.com

Clinical Trial Number: not applicable

List of abbreviations

HR Hormone Receptor

HER2 Human Epidermal Growth Factor Receptor 2

PR Progesterone Receptor

TNBC Triple-Negative Breast Cancer

TME Tumor Microenvironment

ER+ Estrogen Receptor-Positive

NACT Neoadjuvant Chemotherapy

BRCA1/2 Breast Cancer Gene 1/2

PARPi PARP Inhibitor

PI3K/AKT/mTOR Phosphoinositide 3-Kinase/Protein Kinase B/Mechanistic Target of Rapamycin

ESR1 Estrogen Receptor 1

AI Aromatase Inhibitor

ctDNA Circulating Tumor DNA

CSC Cancer Stem Cell

ARTICLE IN PRESS

ARTICLE IN PRESS

SASP Senescence-Associated Secretory Phenotype
TCA cycle Tricarboxylic Acid Cycle
BUS B-scan Ultrasonography
CT Computed Tomography
MRI Magnetic Resonance Imaging
IF Immunofluorescence
HDI Human Development Index
DCIS Ductal Carcinoma In Situ
IDC Invasive Ductal Carcinoma
ILC Invasive Lobular Carcinoma
IBC Inflammatory Breast Cancer
MPD Mammary Paget's Disease
MpBC Metaplastic Breast Carcinoma
HRR Homologous Recombination Repair
VUS Variants of Uncertain Significance
BCS Breast-Conserving Surgery
ADCs Antibody-Drug Conjugates
TCM Traditional Chinese Medicine

Reference

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024 May-Jun;74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4. PMID: 38572751.

[2] Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, Pollack JR, Ross DT, Johnsen H, Akslen LA, Fluge O, Pergamenschikov A, Williams C, Zhu SX, Lønning PE, Børresen-Dale AL, Brown PO, Botstein D. Molecular portraits of human breast tumours. *Nature*. 2000 Aug 17;406(6797):747-52. doi: 10.1038/35021093. PMID: 10963602.

[3] Shan KS, Bonano-Rios A, Theik NWY, Hussein A, Blaya M. Molecular Targeting of the Phosphoinositide-3-Protein Kinase (PI3K) Pathway across Various Cancers. *Int J Mol Sci*. 2024 Feb 6;25(4):1973. doi: 10.3390/ijms25041973. PMID: 38396649; PMCID: PMC10888452.

[4] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011 Mar 4;144(5):646-74. doi: 10.1016/j.cell.2011.02.013. PMID: 21376230.

[5] Pavlova NN, Thompson CB. The Emerging Hallmarks of Cancer Metabolism. *Cell Metab*. 2016 Jan 12;23(1):27-47. doi: 10.1016/j.cmet.2015.12.006. PMID: 26771115; PMCID: PMC4715268.

ARTICLE IN PRESS

[6] Liang Y, Zhang H, Song X, Yang Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. *Semin Cancer Biol*. 2020 Feb;60:14-27. doi: 10.1016/j.semcancer.2019.08.012. Epub 2019 Aug 14. PMID: 31421262.

[7] Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, Harbeck N, Loibl S, Huang Bartlett C, Zhang K, Giorgetti C, Randolph S, Koehler M, Cristofanilli M; PALOMA3 Study Group. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2015 Jul 16;373(3):209-19. doi: 10.1056/NEJMoa1505270. Epub 2015 Jun 1. PMID: 26030518.

[8] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med*. 2018 Nov 29;379(22):2108-2121. doi: 10.1056/NEJMoa1809615. Epub 2018 Oct 20. PMID: 30345906.

[9] Gottesman MM. Mechanisms of cancer drug resistance. *Annu Rev Med*. 2002;53:615-27. doi: 10.1146/annurev.med.53.082901.103929. PMID: 11818492.

[10] Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ. Palbociclib and Letrozole in Advanced Breast Cancer. *N Engl J Med*. 2016 Nov 17;375(20):1925-1936. doi: 10.1056/NEJMoa1607303. PMID: 27959613.

[11] Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, Gelber RD, de Azambuja E, Fielding A, Balmaña J, Domchek SM, Gelmon KA, Hollingsworth SJ, Korde LA, Linderholm B, Bandos H, Senkus E, Suga JM, Shao Z, Pippas AW, Nowecki Z, Huzarski T, Ganz PA, Lucas PC, Baker N, Loibl S, McConnell R, Piccart M, Schmutzler R, Steger GG, Costantino JP, Arahmani A, Wolmark N, McFadden E, Karantza V, Lakhani SR, Yothers G, Campbell C, Geyer CE Jr; OlympiA Clinical Trial Steering Committee and Investigators. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3. PMID: 34081848; PMCID: PMC9126186.

[12] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015 Oct 3;386(10001):1341-1352. doi: 10.1016/S0140-6736(15)61074-1. Epub 2015 Jul 23. PMID: 26211827.

[13] Ibragimova MK, Tsyganov MM, Kravtsova EA, Tsydenova IA, Litviakov NV. Organ-Specificity of Breast Cancer Metastasis. *Int J Mol Sci*. 2023 Oct 26;24(21):15625. doi: 10.3390/ijms242115625. PMID: 37958607; PMCID: PMC10650169.

[14] Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2019 Aug 1;30(8):1194-1220. doi: 10.1093/annonc/mdz173. Erratum in: Ann Oncol. 2019 Oct 1;30(10):1674. doi: 10.1093/annonc/mdz189. Erratum in: Ann Oncol. 2021 Feb;32(2):284. doi: 10.1016/j.annonc.2020.08.2158. PMID: 31161190.

ARTICLE IN PRESS

[15] Qi YJ, Su GH, You C, Zhang X, Xiao Y, Jiang YZ, Shao ZM. Radiomics in breast cancer: Current advances and future directions. *Cell Rep Med*. 2024 Sep 17;5(9):101719. doi: 10.1016/j.xcrm.2024.101719. PMID: 39293402; PMCID: PMC11528234.

[16] Makki J. Diversity of Breast Carcinoma: Histological Subtypes and Clinical Relevance. *Clin Med Insights Pathol*. 2015 Dec 21;8:23-31. doi: 10.4137/CPath.S31563. PMID: 26740749; PMCID: PMC4689326.

[17] Kim R, Kawai A, Wakisaka M, Shimoyama M, Yasuda N, Ito M, Kin T, Arihiro K. Outcomes in patients with non-invasive breast carcinoma. *Cancer Rep (Hoboken)*. 2023 Apr;6(4):e1768. doi: 10.1002/cnr2.1768. Epub 2022 Dec 9. PMID: 36494178; PMCID: PMC10075290.

[18] Posner MC, Wolmark N. Non-invasive breast carcinoma. *Breast Cancer Res Treat*. 1992;21(3):155-64. doi: 10.1007/BF01974998. PMID: 1325215.

[19] Sokolova A, Lakhani SR. Lobular carcinoma in situ: diagnostic criteria and molecular correlates. *Mod Pathol*. 2021 Jan;34(Suppl 1):8-14. doi: 10.1038/s41379-020-00689-3. Epub 2020 Oct 6. PMID: 33024303.

[20] Mohsin SK, O'Connell P, Allred DC, Libby AL. Biomarker profile and genetic abnormalities in lobular carcinoma in situ. *Breast Cancer Res Treat*. 2005 Apr;90(3):249-56. doi: 10.1007/s10549-004-4493-8. PMID: 15830138.

[21] Foote FW, Stewart FW. Lobular carcinoma in situ: A rare form of mammary cancer. *Am J Pathol*. 1941 Jul;17(4):491-496.3. doi: 10.3322/canjclin.32.4.234. PMID: 19970575; PMCID: PMC1965212.

[22] Chuba PJ, Hamre MR, Yap J, Severson RK, Lucas D, Shamsa F, Aref A. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. *J Clin Oncol*. 2005 Aug 20;23(24):5534-41. doi: 10.1200/JCO.2005.04.038. PMID: 16110014.

[23] King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, Oskar S, Guerini-Rocco E, Boafo C, Gooch JC, De Brot M, Reis-Filho JS, Morrogh M, Andrade VP, Sakr RA, Morrow M. Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk. *J Clin Oncol*. 2015 Nov 20;33(33):3945-52. doi: 10.1200/JCO.2015.61.4743. Epub 2015 Sep 14. PMID: 26371145; PMCID: PMC4934644.

[24] Delaloge S, Khan SA, Wesseling J, Whelan T. Ductal carcinoma in situ of the breast: finding the balance between overtreatment and undertreatment. *Lancet*. 2024 Jun 22;403(10445):2734-2746. doi: 10.1016/S0140-6736(24)00425-2. Epub 2024 May 9. PMID: 38735296.

[25] Farante G, Toesca A, Magnoni F, Lissidini G, Vila J, Mastropasqua M, Viale G, Penco S, Cassano E, Lazzeroni M, Bonanni B, Leonardi MC, Ripoll-Orts F, Curigliano G, Orecchia R, Galimberti V, Veronesi P. Advances and controversies in management of breast ductal carcinoma in situ (DCIS). *Eur J Surg Oncol*. 2022 Apr;48(4):736-741. doi: 10.1016/j.ejso.2021.10.030. Epub 2021 Nov 9. PMID: 34772587.

[26] Bychkovsky BL, Myers S, Warren LEG, De Placido P, Parsons HA. Ductal Carcinoma In Situ. *Hematol Oncol Clin North Am*. 2024 Aug;38(4):831-849. doi: 10.1016/j.hoc.2024.05.014. PMID: 38960507.

ARTICLE IN PRESS

ARTICLE IN PRESS

[27] Grimm LJ, Rahbar H, Abdelmalak M, Hall AH, Ryser MD. Ductal Carcinoma in Situ: State-of-the-Art Review. *Radiology*. 2022 Feb;302(2):246-255. doi: 10.1148/radiol.211839. Epub 2021 Dec 21. PMID: 34931856; PMCID: PMC8805655.

[28] Harris LN, Ismaila N, McShane LM, Andre F, Collyar DE, Gonzalez-Angulo AM, Hammond EH, Kuderer NM, Liu MC, Mennel RG, Van Poznak C, Bast RC, Hayes DF; American Society of Clinical Oncology. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016 Apr 1;34(10):1134-50. doi: 10.1200/JCO.2015.65.2289. Epub 2016 Feb 8. PMID: 26858339; PMCID: PMC4933134.

[29] Prabhakaran S, Rizk VT, Ma Z, Cheng CH, Berglund AE, Coppola D, Khalil F, Mulé JJ, Soliman HH. Evaluation of invasive breast cancer samples using a 12-chemokine gene expression score: correlation with clinical outcomes. *Breast Cancer Res*. 2017 Jun 19;19(1):71. doi: 10.1186/s13058-017-0864-z. PMID: 28629479; PMCID: PMC5477261.

[30] Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G. Breast cancer. *Lancet*. 2005 May 14-20;365(9472):1727-41. doi: 10.1016/S0140-6736(05)66546-4. PMID: 15894099.

[31] Allison KH. Molecular pathology of breast cancer: what a pathologist needs to know. *Am J Clin Pathol*. 2012 Dec;138(6):770-80. doi: 10.1309/AJCPIV9IQ1MRQMOO. PMID: 23161709.

[32] Shea EKH, Koh VCY, Tan PH. Invasive breast cancer: Current perspectives and emerging views. *Pathol Int*. 2020 May;70(5):242-252. doi: 10.1111/pin.12910. Epub 2020 Feb 10. PMID: 32039524.

[33] Simpson PT, Reis-Filho JS, Gale T, Lakhani SR. Molecular evolution of breast cancer. *J Pathol*. 2005 Jan;205(2):248-54. doi: 10.1002/path.1691. PMID: 15641021.

[34] Mouabbi JA, Hassan A, Lim B, Hortobagyi GN, Tripathy D, Layman RM. Invasive lobular carcinoma: an understudied emergent subtype of breast cancer. *Breast Cancer Res Treat*. 2022 Jun;193(2):253-264. doi: 10.1007/s10549-022-06572-w. Epub 2022 Mar 26. PMID: 35347549.

[35] Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res*. 2004;6(3):R149-56. doi: 10.1186/bcr767. Epub 2004 Feb 17. PMID: 15084238; PMCID: PMC400666.

[36] McCart Reed AE, Kalinowski L, Simpson PT, Lakhani SR. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. *Breast Cancer Res*. 2021 Jan 7;23(1):6. doi: 10.1186/s13058-020-01384-6. PMID: 33413533; PMCID: PMC7792208.

[37] Gessain G, Joyon N, Petit T, Cotteret S, Lacroix-Triki M. Uncommon invasive lobular carcinoma with papillary architecture-clinicopathologic and molecular characterization with review of the literature. *Virchows Arch*. 2023 Nov;483(5):723-729. doi: 10.1007/s00428-023-03526-5. Epub 2023 Mar 16. PMID: 36928170.

[38] Tsagkaraki IM, Kourouniotis CD, Gomatou GL, Syrigos NK, Kotteas EA. Orbital metastases of invasive lobular breast carcinoma. *Breast Dis*. 2019;38(3-4):85-91. doi: 10.3233/BD-190398. PMID: 31640079.

ARTICLE IN PRESS

ARTICLE IN PRESS

[39] Somiari RI, Sullivan A, Russell S, Somiari S, Hu H, Jordan R, George A, Katenhusen R, Buchowiecka A, Arciero C, Brzeski H, Hooke J, Shriver C. High-throughput proteomic analysis of human infiltrating ductal carcinoma of the breast. *Proteomics*. 2003 Oct;3(10):1863-73. doi: 10.1002/pmic.200300560. PMID: 14625848.

[40] Masinghe SP, Faluyi OO, Kerr GR, Kunkler IH. Breast radiotherapy for occult breast cancer with axillary nodal metastases--does it reduce the local recurrence rate and increase overall survival? *Clin Oncol (R Coll Radiol)*. 2011 Mar;23(2):95-100. doi: 10.1016/j.clon.2010.10.001. Epub 2010 Nov 5. PMID: 21115330.

[41] Kuzmiak CM, Calhoun BC. Pure Mucinous Carcinoma of the Breast: Radiologic-Pathologic Correlation. *J Breast Imaging*. 2023 Mar 20;5(2):180-187. doi: 10.1093/jbi/wbac084. PMID: 38416927.

[42] Romaniuk A, Lyndin M, Sikora V, Lyndina Y, Panasovska K. Histological and immunohistochemical features of medullary breast cancer. *Folia Med Cracov*. 2015;55(2):41-8. PMID: 26839242.

[43] Mateo AM, Pezzi TA, Sundermeyer M, Kelley CA, Klimberg VS, Pezzi CM. Chemotherapy Significantly Improves Survival for Patients with T1c-T2N0M0 Medullary Breast Cancer: 3739 Cases From the National Cancer Data Base. *Ann Surg Oncol*. 2017 Apr;24(4):1050-1056. doi: 10.1245/s10434-016-5649-6. Epub 2016 Nov 2. PMID: 27807728.

[44] Malyuchik SS, Kiyamova RG. Medullary breast carcinoma. *Exp Oncol*. 2008 Jun;30(2):96-101. PMID: 18566570.

[45] Joglekar-Javadekar M, Van Laere S, Bourne M, Moalwi M, Finetti P, Vermeulen PB, Birnbaum D, Dirix LY, Ueno N, Carter M, Rains J, Ramachandran A, Bertucci F, van Golen KL. Characterization and Targeting of Platelet-Derived Growth Factor Receptor alpha (PDGFRA) in Inflammatory Breast Cancer (IBC). *Neoplasia*. 2017 Jul;19(7):564-573. doi: 10.1016/j.neo.2017.03.002. Epub 2017 Jun 10. PMID: 28609680; PMCID: PMC5470553.

[46] Bonnier P, Charpin C, Lejeune C, Romain S, Tubiana N, Beedassy B, Martin PM, Serment H, Piana L. Inflammatory carcinomas of the breast: a clinical, pathological, or a clinical and pathological definition? *Int J Cancer*. 1995 Aug 9;62(4):382-5. doi: 10.1002/ijc.2910620404. PMID: 7635562.

[47] Le-Petross HT, Balema W, Woodward WA. Why diagnosing inflammatory breast cancer is hard and how to overcome the challenges: a narrative review. *Chin Clin Oncol*. 2021 Dec;10(6):58. doi: 10.21037/cco-21-116. PMID: 35016512.

[48] Woodward WA, Cristofanilli M. Inflammatory breast cancer. *Semin Radiat Oncol*. 2009 Oct;19(4):256-65. doi: 10.1016/j.semradonc.2009.05.008. PMID: 19732690.

[49] Wang X, Semba T, Phi LTH, Chainitikun S, Iwase T, Lim B, Ueno NT. Targeting Signaling Pathways in Inflammatory Breast Cancer. *Cancers (Basel)*. 2020 Sep 1;12(9):2479. doi: 10.3390/cancers12092479. PMID: 32883032; PMCID: PMC7563157.

[50] Bonnier P, Charpin C, Lejeune C, Romain S, Tubiana N, Beedassy B, Martin PM, Serment H, Piana L. Inflammatory carcinomas of the breast: a clinical, pathological, or a clinical and pathological definition? *Int J Cancer*. 1995 Aug 9;62(4):382-5. doi: 10.1002/ijc.2910620404. PMID: 7635562.

ARTICLE IN PRESS

[51] Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nat Rev Cancer*. 2011 Dec 23;12(1):68-78. doi: 10.1038/nrc3181. PMID: 22193408; PMCID: PMC4972490.

[52] Hsu LC, White RL. BRCA1 is associated with the centrosome during mitosis. *Proc Natl Acad Sci U S A*. 1998 Oct 27;95(22):12983-8. doi: 10.1073/pnas.95.22.12983. PMID: 9789027; PMCID: PMC23679.

[53] Xu X, Weaver Z, Linke SP, Li C, Gotay J, Wang XW, Harris CC, Ried T, Deng CX. Centrosome amplification and a defective G2-M cell cycle checkpoint induce genetic instability in BRCA1 exon 11 isoform-deficient cells. *Mol Cell*. 1999 Mar;3(3):389-95. doi: 10.1016/s1097-2765(00)80466-9. PMID: 10198641.

[54] Abbott DW, Thompson ME, Robinson-Benion C, Tomlinson G, Jensen RA, Holt JT. BRCA1 expression restores radiation resistance in BRCA1-defective cancer cells through enhancement of transcription-coupled DNA repair. *J Biol Chem*. 1999 Jun 25;274(26):18808-12. doi: 10.1074/jbc.274.26.18808. PMID: 10373498.

[55] Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, Evans DG, Izatt L, Eeles RA, Adlard J, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Tischkowitz M, Douglas F, Hodgson S, Walker L, Porteous ME, Morrison PJ, Side LE, Kennedy MJ, Houghton C, Donaldson A, Rogers MT, Dorkins H, Miedzybrodzka Z, Gregory H, Eason J, Barwell J, McCann E, Murray A, Antoniou AC, Easton DF; EMBRACE. Cancer risks for BRCA1 and BRCA2 mutation carriers: results from prospective analysis of EMBRACE. *J Natl Cancer Inst*. 2013 Jun 5;105(11):812-22. doi: 10.1093/jnci/djt095. Epub 2013 Apr 29. PMID: 23628597.

[56] Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, Kyle S, Meuth M, Curtin NJ, Helleday T. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature*. 2005 Apr 14;434(7035):913-7. doi: 10.1038/nature03443. Erratum in: Nature. 2007 May 17;447(7142):346. PMID: 15829966.

[57] Filippini SE, Vega A. Breast cancer genes: beyond BRCA1 and BRCA2. *Front Biosci (Landmark Ed)*. 2013 Jun 1;18(4):1358-72. doi: 10.2741/4185. PMID: 23747889.

[58] Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005 Apr 14;434(7035):917-21. doi: 10.1038/nature03445. PMID: 15829967.

[59] O'Connor MJ. Targeting the DNA Damage Response in Cancer. *Mol Cell*. 2015 Nov 19;60(4):547-60. doi: 10.1016/j.molcel.2015.10.040. PMID: 26590714.

[60] Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, Masuda N, Delaloge S, Li W, Armstrong A, Wu W, Goessl C, Runswick S, Domchek SM. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. 2019 Apr 1;30(4):558-566. doi: 10.1093/annonc/mdz012. PMID: 30689707; PMCID: PMC6503629.

[61] Shahbandi A, Nguyen HD, Jackson JG. TP53 Mutations and Outcomes in Breast Cancer: Reading beyond the Headlines. *Trends Cancer*. 2020 Feb;6(2):98-110. doi: 10.1016/j.trecan.2020.01.007. Epub 2020 Feb 5. PMID: 32061310; PMCID: PMC7931175.

ARTICLE IN PRESS

ARTICLE IN PRESS

[62] Kaur RP, Vasudeva K, Kumar R, Munshi A. Role of p53 Gene in Breast Cancer: Focus on Mutation Spectrum and Therapeutic Strategies. *Curr Pharm Des*. 2018;24(30):3566-3575. doi: 10.2174/1381612824666180926095709. PMID: 30255744.

[63] Kudo R, Safonov A, Jones C, Moiso E, Dry JR, Shao H, Nag S, da Silva EM, Yildirim SY, Li Q, O'Connell E, Patel P, Will M, Fushimi A, Benitez M, Bradic M, Fan L, Nakshatri H, Sudhan DR, Denz CR, Huerga Sanchez I, Reis-Filho JS, Goel S, Koff A, Weigelt B, Khan QJ, Razavi P, Chandarlapaty S. Long-term breast cancer response to CDK4/6 inhibition defined by TP53-mediated geroconversion. *Cancer Cell*. 2024 Nov 11;42(11):1919-1935.e9. doi: 10.1016/j.ccell.2024.09.009. Epub 2024 Oct 10. Erratum in: Cancer Cell. 2024 Nov 11;42(11):1983. doi: 10.1016/j.ccell.2024.10.013. PMID: 39393354.

[64] Magri J, Gasparetto A, Conti L, Calautti E, Cossu C, Ruiu R, Barutello G, Cavallo F. Tumor-Associated Antigen xCT and Mutant-p53 as Molecular Targets for New Combinatorial Antitumor Strategies. *Cells*. 2021 Jan 8;10(1):108. doi: 10.3390/cells10010108. PMID: 33430127; PMCID: PMC7827209.

[65] Yadav S, Boddicker NJ, Na J, Polley EC, Hu C, Hart SN, Gnanaolivu RD, Larson N, Holtegaard S, Huang H, Dunn CA, Teras LR, Patel AV, Lacey JV, Neuhausen SL, Martinez E, Haiman C, Chen F, Ruddy KJ, Olson JE, John EM, Kurian AW, Sandler DP, O'Brien KM, Taylor JA, Weinberg CR, Anton-Culver H, Ziogas A, Zirpoli G, Goldgar DE, Palmer JR, Domchek SM, Weitzel JN, Nathanson KL, Kraft P, Couch FJ. Contralateral Breast Cancer Risk Among Carriers of Germline Pathogenic Variants in ATM, BRCA1, BRCA2, CHEK2, and PALB2. *J Clin Oncol*. 2023 Mar 20;41(9):1703-1713. doi: 10.1200/JCO.22.01239. Epub 2023 Jan 9. PMID: 36623243; PMCID: PMC10022863.

[66] Kalinsky K, Jacks LM, Heguy A, Patil S, Drobnjak M, Bhanot UK, Hedvat CV, Traina TA, Solit D, Gerald W, Moynahan ME. PIK3CA mutation associates with improved outcome in breast cancer. *Clin Cancer Res*. 2009 Aug 15;15(16):5049-59. doi: 10.1158/1078-0432.CCR-09-0632. Epub 2009 Aug 11. PMID: 19671852.

[67] Martínez-Sáez O, Chic N, Pascual T, Adamo B, Vidal M, González-Farré B, Sanfeliu E, Schettini F, Conte B, Brasó-Maristany F, Rodríguez A, Martínez D, Galván P, Rodríguez AB, Martinez A, Muñoz M, Prat A. Frequency and spectrum of PIK3CA somatic mutations in breast cancer. *Breast Cancer Res*. 2020 May 13;22(1):45. doi: 10.1186/s13058-020-01284-9. PMID: 32404150; PMCID: PMC7222307.

[68] Cantley LC. The phosphoinositide 3-kinase pathway. *Science*. 2002 May 31;296(5573):1655-7. doi: 10.1126/science.296.5573.1655. PMID: 12040186.

[69] André F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, Rubovszky G, Yamashita T, Kaufman B, Lu YS, Inoue K, Pápai Z, Takahashi M, Ghaznawi F, Mills D, Kaper M, Miller M, Conte PF, Iwata H, Rugo HS. Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: final overall survival results from SOLAR-1. *Ann Oncol*. 2021 Feb;32(2):208-217. doi: 10.1016/j.annonc.2020.11.011. Epub 2020 Nov 25. PMID: 33246021.

[70] Zhang QX, Borg A, Wolf DM, Oesterreich S, Fuqua SA. An estrogen receptor mutant with strong hormone-independent activity from a metastatic breast cancer. *Cancer Res*. 1997 Apr 1;57(7):1244-9. PMID: 9102207.

ARTICLE IN PRESS

[71] Herzog SK, Fuqua SAW. ESR1 mutations and therapeutic resistance in metastatic breast cancer: progress and remaining challenges. *Br J Cancer*. 2022 Feb;126(2):174-186. doi: 10.1038/s41416-021-01564-x. Epub 2021 Oct 7. PMID: 34621045; PMCID: PMC8770568.

[72] Barone I, Iacopetta D, Covington KR, Cui Y, Tsimelzon A, Beyer A, Andò S, Fuqua SA. Phosphorylation of the mutant K303R estrogen receptor alpha at serine 305 affects aromatase inhibitor sensitivity. *Oncogene*. 2010 Apr 22;29(16):2404-14. doi: 10.1038/onc.2009.520. Epub 2010 Jan 25. PMID: 20101208; PMCID: PMC2922934.

[73] Fuqua SA, Gu G, Rechoum Y. Estrogen receptor (ER) α mutations in breast cancer: hidden in plain sight. *Breast Cancer Res Treat*. 2014 Feb;144(1):11-9. doi: 10.1007/s10549-014-2847-4. Epub 2014 Feb 1. PMID: 24487689; PMCID: PMC4123761.

[74] Li S, Shen D, Shao J, Crowder R, Liu W, Prat A, He X, Liu S, Hoog J, Lu C, Ding L, Griffith OL, Miller C, Larson D, Fulton RS, Harrison M, Mooney T, McMichael JF, Luo J, Tao Y, Goncalves R, Schlosberg C, Hiken JF, Saied L, Sanchez C, Giuntoli T, Bumb C, Cooper C, Kitchens RT, Lin A, Phommaly C, Davies SR, Zhang J, Kavuri MS, McEachern D, Dong YY, Ma C, Pluard T, Naughton M, Bose R, Suresh R, McDowell R, Michel L, Aft R, Gillanders W, DeSchryver K, Wilson RK, Wang S, Mills GB, Gonzalez-Angulo A, Edwards JR, Maher C, Perou CM, Mardis ER, Ellis MJ. Endocrine-therapy-resistant ESR1 variants revealed by genomic characterization of breast-cancer-derived xenografts. *Cell Rep*. 2013 Sep 26;4(6):1116-30. doi: 10.1016/j.celrep.2013.08.022. Epub 2013 Sep 19. PMID: 24055055; PMCID: PMC3881975.

[75] Jeselsohn R, Yelensky R, Buchwalter G, Frampton G, Meric-Bernstam F, Gonzalez-Angulo AM, Ferrer-Lozano J, Perez-Fidalgo JA, Cristofanilli M, Gómez H, Arteaga CL, Giltnane J, Balko JM, Cronin MT, Jarosz M, Sun J, Hawryluk M, Lipson D, Otto G, Ross JS, Dvir A, Soussan-Gutman L, Wolf I, Rubinek T, Gilmore L, Schnitt S, Come SE, Pusztai L, Stephens P, Brown M, Miller VA. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor-positive breast cancer. *Clin Cancer Res*. 2014 Apr 1;20(7):1757-1767. doi: 10.1158/1078-0432.CCR-13-2332. Epub 2014 Jan 7. PMID: 24398047; PMCID: PMC3998833.

[76] Brett JO, Spring LM, Bardia A, Wander SA. ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res*. 2021 Aug 15;23(1):85. doi: 10.1186/s13058-021-01462-3. PMID: 34392831; PMCID: PMC8365900.

[77] Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. *Clin Breast Cancer*. 2004 Apr;5(1):63-9. doi: 10.3816/cbc.2004.n.011. PMID: 15140287.

[78] Gradishar WJ, O'Regan R, Rimawi MF, Nordstrom JL, Rosales MK, Rugo HS. Margetuximab in HER2-positive metastatic breast cancer. *Future Oncol*. 2023 May;19(16):1099-1112. doi: 10.2217/fon-2022-1040. Epub 2023 May 12. PMID: 37170847.

[79] Takada M, Toi M. Neoadjuvant treatment for HER2-positive breast cancer. *Chin Clin Oncol*. 2020 Jun;9(3):32. doi: 10.21037/cco-20-123. Epub 2020 Jun 3. PMID: 32527117.

ARTICLE IN PRESS

[80] Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell*. 1999 Oct 29;99(3):247-57. doi: 10.1016/s0092-8674(00)81656-6. PMID: 10555141.

[81] Ma L, Li C, Yin H, Huang J, Yu S, Zhao J, Tang Y, Yu M, Lin J, Ding L, Cui Q. The Mechanism of DNA Methylation and miRNA in Breast Cancer. *Int J Mol Sci*. 2023 May 27;24(11):9360. doi: 10.3390/ijms24119360. PMID: 37298314; PMCID: PMC10253858.

[82] Esteve-Puig R, Bueno-Costa A, Esteller M. Writers, readers and erasers of RNA modifications in cancer. *Cancer Lett*. 2020 Apr 1;474:127-137. doi: 10.1016/j.canlet.2020.01.021. Epub 2020 Jan 25. PMID: 31991154.

[83] Baylin SB, Jones PA. A decade of exploring the cancer epigenome - biological and translational implications. *Nat Rev Cancer*. 2011 Sep 23;11(10):726-34. doi: 10.1038/nrc3130. PMID: 21941284; PMCID: PMC3307543.

[84] Kresovich JK, Gann PH, Erdal S, Chen HY, Argos M, Rauscher GH. Candidate gene DNA methylation associations with breast cancer characteristics and tumor progression. *Epigenomics*. 2018 Apr 1;10(4):367-378. doi: 10.2217/epi-2017-0119. Epub 2018 Mar 12. PMID: 29528252; PMCID: PMC5925433.

[85] Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, He C, Zhang Y. Tet proteins can convert 5-methylcytosine to 5-formylcytosine and 5-carboxylcytosine. *Science*. 2011 Sep 2;333(6047):1300-3. doi: 10.1126/science.1210597. Epub 2011 Jul 21. PMID: 21778364; PMCID: PMC3495246.

[86] Good CR, Panjarian S, Kelly AD, Madzo J, Patel B, Jelinek J, Issa JJ. TET1-Mediated Hypomethylation Activates Oncogenic Signaling in Triple-Negative Breast Cancer. *Cancer Res*. 2018 Aug 1;78(15):4126-4137. doi: 10.1158/0008-5472.CAN-17-2082. Epub 2018 Jun 11. PMID: 29891505; PMCID: PMC6072603.

[87] Szczepanek J, Skorupa M, Jarkiewicz-Tretyn J, Cybulski C, Tretyn A. Harnessing Epigenetics for Breast Cancer Therapy: The Role of DNA Methylation, Histone Modifications, and MicroRNA. *Int J Mol Sci*. 2023 Apr 13;24(8):7235. doi: 10.3390/ijms24087235. PMID: 37108398; PMCID: PMC10138995.

[88] Creyghton MP, Cheng AW, Welstead GG, Kooistra T, Carey BW, Steine EJ, Hanna J, Lodato MA, Frampton GM, Sharp PA, Boyer LA, Young RA, Jaenisch R. Histone H3K27ac separates active from poised enhancers and predicts developmental state. *Proc Natl Acad Sci U S A*. 2010 Dec 14;107(50):21931-6. doi: 10.1073/pnas.1016071107. Epub 2010 Nov 24. PMID: 21106759; PMCID: PMC3003124.

[89] Feng J, Meng X. Histone modification and histone modification-targeted anti-cancer drugs in breast cancer: Fundamentals and beyond. *Front Pharmacol*. 2022 Sep 15;13:946811. doi: 10.3389/fphar.2022.946811. PMID: 36188615; PMCID: PMC9522521.

[90] Berezikov E, Guryev V, van de Belt J, Wienholds E, Plasterk RH, Cuppen E. Phylogenetic shadowing and computational identification of human microRNA genes. *Cell*. 2005 Jan 14;120(1):21-4. doi: 10.1016/j.cell.2004.12.031. PMID: 15652478.

[91] Cho WC. MicroRNAs: potential biomarkers for cancer diagnosis, prognosis and targets for therapy. *Int J Biochem Cell Biol*. 2010 Aug;42(8):1273-81. doi: 10.1016/j.biocel.2009.12.014. Epub 2009 Dec 22. PMID: 20026422.

ARTICLE IN PRESS

[92] Teo MT, Landi D, Taylor CF, Elliott F, Vaslin L, Cox DG, Hall J, Landi S, Bishop DT, Kiltie AE. The role of microRNA-binding site polymorphisms in DNA repair genes as risk factors for bladder cancer and breast cancer and their impact on radiotherapy outcomes. *Carcinogenesis*. 2012 Mar;33(3):581-6. doi: 10.1093/carcin/bgr300. Epub 2011 Dec 12. PMID: 22166496; PMCID: PMC3291859.

[93] Cho WC. Great potential of miRNAs as predictive and prognostic markers for cancer. *Expert Rev Mol Diagn*. 2012 May;12(4):315-8. doi: 10.1586/erm.12.21. PMID: 22616694.

[94] Rama AR, Lara P, Mesas C, Quiñonero F, Vélez C, Melguizo C, Prados J. Circular Sponge against miR-21 Enhances the Antitumor Activity of Doxorubicin against Breast Cancer Cells. *Int J Mol Sci*. 2022 Nov 26;23(23):14803. doi: 10.3390/ijms232314803. PMID: 36499129; PMCID: PMC9736351.

[95] Zhang Y, Wang Y, Xue J, Liang W, Zhang Z, Yang X, Qiao Z, Jiang Y, Wang J, Cao X, Chen P. Co-treatment with miR-21-5p inhibitor and Aurora kinase inhibitor reversine suppresses breast cancer progression by targeting sprouty RTK signaling antagonist 2. *Bioengineered*. 2022 Jan;13(1):455-468. doi: 10.1080/21655979.2021.2009410. PMID: 34967265; PMCID: PMC8805969.

[96] Asefi N, Fazilat A, Oghabi T, Jafarbeik Iravani N, Majidzadeh-A K, Hasannejad F. Epithelial-mesenchymal-associated non-coding RNAs as Breast cancer metastasis biomarkers. Cell Cycle. 2025 Nov-Dec;24(21-24):440-467. doi: 10.1080/15384101.2025.2576512. Epub 2025 Oct 18. PMID: 41108105; PMCID: PMC12710946.

[97] Solaimani M, Hosseinzadeh S, Abasi M. Non-coding RNAs, a double-edged sword in breast cancer prognosis. Cancer Cell Int. 2025 Apr 1;25(1):123. doi: 10.1186/s12935-025-03679-0. PMID: 40170036; PMCID: PMC11959806.

ARTICLE IN PRESS

[98] Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, Naghavi M. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *Lancet*. 2011 Oct 22;378(9801):1461-84. doi: 10.1016/S0140-6736(11)61351-2. Epub 2011 Sep 14. PMID: 21924486.

[99] Chi D, Singhal H, Li L, Xiao T, Liu W, Pun M, Jeselsohn R, He H, Lim E, Vadhi R, Rao P, Long H, Garber J, Brown M. Estrogen receptor signaling is reprogrammed during breast tumorigenesis. *Proc Natl Acad Sci U S A*. 2019 Jun 4;116(23):11437-11443. doi: 10.1073/pnas.1819155116. Epub 2019 May 20. PMID: 31110002; PMCID: PMC6561257.

[100] Fu X, Pereira R, Liu CC, De Angelis C, Shea MJ, Nanda S, Qin L, Mitchell T, Cataldo ML, Veeraraghavan J, Sethunath V, Giuliano M, Gutierrez C, Győrffy B, Trivedi MV, Cohen O, Wagle N, Nardone A, Jeselsohn R, Rimawi MF, Osborne CK, Schiff R. High FOXA1 levels induce ER transcriptional reprogramming, a pro-metastatic secretome, and metastasis in endocrine-resistant breast cancer. *Cell Rep*. 2023 Aug 29;42(8):112821. doi: 10.1016/j.celrep.2023.112821. Epub 2023 Jul 18. PMID: 37467106.

ARTICLE IN PRESS

[101] Templeton AJ, Diez-Gonzalez L, Ace O, Vera-Badillo F, Seruga B, Jordán J, Amir E, Pandiella A, Ocaña A. Prognostic relevance of receptor tyrosine kinase expression in breast cancer: a meta-analysis. *Cancer Treat Rev*. 2014 Oct;40(9):1048-55. doi: 10.1016/j.ctrv.2014.08.003. Epub 2014 Sep 3. PMID: 25217796.

[102] Butti R, Das S, Gunasekaran VP, Yadav AS, Kumar D, Kundu GC. Receptor tyrosine kinases (RTKs) in breast cancer: signaling, therapeutic implications and challenges. *Mol Cancer*. 2018 Feb 19;17(1):34. doi: 10.1186/s12943-018-0797-x. PMID: 29455658; PMCID: PMC5817867.

[103] Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. *Cell*. 2010 Jun 25;141(7):1117-34. doi: 10.1016/j.cell.2010.06.011. PMID: 20602996; PMCID: PMC2914105.

[104] Brewer JR, Mazot P, Soriano P. Genetic insights into the mechanisms of Fgf signaling. *Genes Dev*. 2016 Apr 1;30(7):751-71. doi: 10.1101/gad.277137.115. PMID: 27036966; PMCID: PMC4826393.

[105] Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science*. 2009 May 22;324(5930):1029-33. doi: 10.1126/science.1160809. PMID: 19460998; PMCID: PMC2849637.

[106] Vander Heiden MG, DeBerardinis RJ. Understanding the Intersections between Metabolism and Cancer Biology. *Cell*. 2017 Feb 9;168(4):657-669. doi: 10.1016/j.cell.2016.12.039. PMID: 28187287; PMCID: PMC5329766.

[107] Chandel NS. Glycolysis. *Cold Spring Harb Perspect Biol*. 2021 May 3;13(5):a040535. doi: 10.1101/cshperspect.a040535. PMID: 33941515; PMCID: PMC8091952.

[108] Garcia SN, Guedes RC, Marques MM. Unlocking the Potential of HK2 in Cancer Metabolism and Therapeutics. *Curr Med Chem*. 2019;26(41):7285-7322. doi: 10.2174/0929867326666181213092652. PMID: 30543165.

[109] Patra KC, Wang Q, Bhaskar PT, Miller L, Wang Z, Wheaton W, Chandel N, Laakso M, Muller WJ, Allen EL, Jha AK, Smolen GA, Clasquin MF, Robey B, Hay N. Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer. *Cancer Cell*. 2013 Aug 12;24(2):213-228. doi: 10.1016/j.ccr.2013.06.014. Epub 2013 Aug 1. Erratum in: Cancer Cell. 2013 Sep 9;24(3):399. PMID: 23911236; PMCID: PMC3753022.

[110] Hultsch S, Kankainen M, Paavolainen L, Kovanen RM, Ikonen E, Kangaspeska S, Pietiäinen V, Kallioniemi O. Association of tamoxifen resistance and lipid reprogramming in breast cancer. *BMC Cancer*. 2018 Aug 24;18(1):850. doi: 10.1186/s12885-018-4757-z. PMID: 30143015; PMCID: PMC6109356.

[111] Wang Y, Botolin D, Xu J, Christian B, Mitchell E, Jayaprakasam B, Nair MG, Peters JM, Busik JV, Olson LK, Jump DB. Regulation of hepatic fatty acid elongase and desaturase expression in diabetes and obesity. *J Lipid Res*. 2006 Sep;47(9):2028-41. doi: 10.1194/jlr.M600177-JLR200. Epub 2006 Jun 21. Erratum in: J Lipid Res. 2006 Oct;47(10):2353. Nair, Muraleedharan [corrected to Nair, Muraleedharan G]; Peters, Jeffery M [corrected to Peters, Jeffrey M]; Busik, Julia [corrected to Busik, Julia V]. PMID: 16790840; PMCID: PMC2764365.

[112] Jump DB. Fatty acid regulation of hepatic lipid metabolism. *Curr Opin Clin Nutr Metab Care*. 2011 Mar;14(2):115-20. doi: 10.1097/MCO.0b013e328342991c. PMID: 21178610; PMCID: PMC3356999.

ARTICLE IN PRESS

[113] Khwairakpam AD, Banik K, Girisa S, Shabnam B, Shakibaei M, Fan L, Arfuso F, Monisha J, Wang H, Mao X, Sethi G, Kunnumakkara AB. The vital role of ATP citrate lyase in chronic diseases. *J Mol Med (Berl)*. 2020 Jan;98(1):71-95. doi: 10.1007/s00109-019-01863-0. Epub 2019 Dec 19. PMID: 31858156.

[114] Ferraro GB, Ali A, Luengo A, Kodack DP, Deik A, Abbott KL, Bezwada D, Blanc L, Prideaux B, Jin X, Posada JM, Chen J, Chin CR, Amoozgar Z, Ferreira R, Chen IX, Naxerova K, Ng C, Westermark AM, Duquette M, Roberge S, Lindeman NI, Lyssiotis CA, Nielsen J, Housman DE, Duda DG, Brachtel E, Golub TR, Cantley LC, Asara JM, Davidson SM, Fukumura D, Dartois VA, Clish CB, Jain RK, Vander Heiden MG. FATTY ACID SYNTHESIS IS REQUIRED FOR BREAST CANCER BRAIN METASTASIS. *Nat Cancer*. 2021 Apr;2(4):414-428. doi: 10.1038/s43018-021-00183-y. Epub 2021 Apr 1. Erratum in: Nat Cancer. 2021 Nov;2(11):1243. doi: 10.1038/s43018-021-00283-9. PMID: 34179825; PMCID: PMC8223728.

[115] Gao FY, Li XT, Xu K, Wang RT, Guan XX. c-MYC mediates the crosstalk between breast cancer cells and tumor microenvironment. *Cell Commun Signal*. 2023 Jan 31;21(1):28. doi: 10.1186/s12964-023-01043-1. PMID: 36721232; PMCID: PMC9887805.

[116] Bagati A, Kumar S, Jiang P, Pyrdol J, Zou AE, Godicelj A, Mathewson ND, Cartwright ANR, Cejas P, Brown M, Giobbie-Hurder A, Dillon D, Agudo J, Mittendorf EA, Liu XS, Wucherpfennig KW. Integrin αvβ6-TGFβ-SOX4 Pathway Drives Immune Evasion in Triple-Negative Breast Cancer. *Cancer Cell*. 2021 Jan 11;39(1):54-67.e9. doi: 10.1016/j.ccell.2020.12.001. Epub 2020 Dec 31. PMID: 33385331; PMCID: PMC7855651.

[117] Harris MA, Savas P, Virassamy B, O'Malley MMR, Kay J, Mueller SN, Mackay LK, Salgado R, Loi S. Towards targeting the breast cancer immune microenvironment. *Nat Rev Cancer*. 2024 Aug;24(8):554-577. doi: 10.1038/s41568-024-00714-6. Epub 2024 Jul 5. PMID: 38969810.

[118] Nakamura A, Ohnuki K, Takahashi H, Usami S, Ishida Y, Shibata S, Umemura A, Kano A. Impact of breast size and composition on the accuracy of mammography and ultrasonography in breast cancer screening. *Breast Cancer*. 2025 Mar;32(2):385-392. doi: 10.1007/s12282-024-01664-5. Epub 2025 Jan 2. PMID: 39751707.

[119] Dustler M, Hellgren G, Timberg P. Comparing synthetic mammograms based on wide-angle digital breast tomosynthesis with digital mammograms. *J Med Imaging (Bellingham)*. 2025 Jan;12(Suppl 1):S13011. doi: 10.1117/1.JMI.12.S1.S13011. Epub 2025 Jan 20. PMID: 39840005; PMCID: PMC11745418.

[120] Thejas JD, Vinod S, Mohan DK, Dev B, Srinivasan JP, Raavi V, Perumal V. Low dose X-radiation induced DNA damage and its association with Glandular dose in women undergoing mammography. *Mutat Res Genet Toxicol Environ Mutagen*. 2025 Feb-Mar;902:503856. doi: 10.1016/j.mrgentox.2025.503856. Epub 2025 Feb 12. PMID: 40044375.

[121] Wu Z, Li H, Chen Z, Zhou H, Liang X, Huang X, Wang J, Chen T, Xu X, Yang Y. Encapsulated papillary carcinoma of breast: Comparative study of multimodal ultrasound manifestations and pathological features. *Clin Hemorheol Microcirc*. 2025 Feb 13:13860291241295587. doi: 10.1177/13860291241295587. Epub ahead of print. PMID: 39973435.

ARTICLE IN PRESS

[122] Sun J, Shen X, Zhang N, Zhang Q, Xing K, Liu Y. Combination of conventional ultrasound with quantitative and qualitative analyses of CEUS for the differentiation of benign and malignant breast solid lesions: A modified breast cancer model. *Asian J Surg*. 2024 Aug 29:S1015-9584(24)01844-X. doi: 10.1016/j.asjsur.2024.08.104. Epub ahead of print. PMID: 39214812.

[123] Ying L, Luo L, Li F, Zhou H, Tao X, Ling Y. Quantitative Perfusion Analysis of Contrast-enhanced Ultrasound Might Help Differentiate Benign and Malignant Solid Cystic Lesions of the Kidney: A Case Report and Literature Review. *Curr Med Imaging*. 2024;20:1-5. doi: 10.2174/0115734056244999231124113017. PMID: 38389366.

[124] Wang F, Wang W, Sun N, Ma L, Zhang Q. Diagnostic value of multimodal ultrasound strategies in the differentiation of non-mass-like breast lesions. *J Clin Ultrasound*. 2023 Jun;51(5):848-856. doi: 10.1002/jcu.23463. Epub 2023 Apr 7. PMID: 37026589.

[125] Kim J, Koh J, Park J. Utility of chest CT in the diagnosis of additional suspicious lesions on MRI in women with breast cancer. *Acta Radiol*. 2025 Feb 16:28418512513191O8. doi: 10.1177/02841851251319108. Epub ahead of print. PMID: 39956928.

[126] Jeong B, Lee YW, Lee SB, Kim J, Chung IY, Kim HJ, Ko BS, Lee JW, Son BH, Gwark S, Shin HJ, Yoo TK, Choi SH. Diagnostic yield of contrast-enhanced abdominal staging CT in patients with initially diagnosed breast cancer. *Eur J Radiol.* 2024 Feb;171:111295. doi: 10.1016/j.ejrad.2024.111295. Epub 2024 Jan 8. PMID: 38241854.

[127] Wen R, Dong J, Wang Y, Wang L. Combination of color Doppler ultrasound and CT for diagnosing breast cancer. *Am J Transl Res*. 2021 Sep 15;13(9):10771-10776. PMID: 34650754; PMCID: PMC8507029.

[128] Aripoli A, Beeler J, Clark L, Walter C, Inciardi M, Huppe A, Gatewood J, Irani N, Carroll M, Norris T, Barton A, Ackerman P, Winblad O. Incidental Breast Cancer on Chest CT: Is the Radiology Report Enough? *J Breast Imaging*. 2021 Sep 16;3(5):591-596. doi: 10.1093/jbi/wbab040. PMID: 38424942.

[129] Özdemir A, Güven M, Binici S, Uygur S, Toktaş O. Impact of 18F-FDG PET/CT in the management decisions of breast cancer board on early-stage breast cancer. *Clin Transl Oncol*. 2024 May;26(5):1139-1146. doi: 10.1007/s12094-023-03331-1. Epub 2023 Oct 17. PMID: 37848693.

[130] Ahmadpour S, Hosseinimehr SJ. Recent developments in peptide-based SPECT radiopharmaceuticals for breast tumor targeting. *Life Sci*. 2019 Dec 15;239:116870. doi: 10.1016/j.lfs.2019.116870. Epub 2019 Sep 13. PMID: 31525426.

[131] McMillan AB, Bradshaw TJ. Artificial Intelligence-Based Data Corrections for Attenuation and Scatter in Position Emission Tomography and Single-Photon Emission Computed Tomography. *PET Clin*. 2021 Oct;16(4):543-552. doi: 10.1016/j.cpet.2021.06.010. Epub 2021 Aug 5. PMID: 34364816; PMCID: PMC10562009.

[132] Jiang Y, Gai Y, Long Y, Liu Q, Liu C, Zhang Y, Lan X. Application and Evaluation of [99mTc]-Labeled Peptide Nucleic Acid Targeting MicroRNA-155 in Breast Cancer Imaging. *Mol Imaging*. 2020 Jan-Dec;19:1536012120916124. doi: 10.1177/1536012120916124. PMID: 32559121; PMCID: PMC7307583.

ARTICLE IN PRESS

[133] Hansen AR, Bedard PL. Clinical application of high-throughput genomic technologies for treatment selection in breast cancer. *Breast Cancer Res*. 2013;15(5):R97. doi: 10.1186/bcr3558. PMID: 24135425; PMCID: PMC3979162.

[134] Ma L, Liang Z, Zhou H, Qu L. Applications of RNA Indexes for Precision Oncology in Breast Cancer. *Genomics Proteomics Bioinformatics*. 2018 Apr;16(2):108-119. doi: 10.1016/j.gpb.2018.03.002. Epub 2018 May 9. PMID: 29753129; PMCID: PMC6112337.

[135] Pasculli B, Barbano R, Parrella P. Epigenetics of breast cancer: Biology and clinical implication in the era of precision medicine. *Semin Cancer Biol*. 2018 Aug;51:22-35. doi: 10.1016/j.semcancer.2018.01.007. Epub 2018 Jan 12. PMID: 29339244.

[136] Liang SB, Fu LW. Application of single-cell technology in cancer research. *Biotechnol Adv*. 2017 Jul;35(4):443-449. doi: 10.1016/j.biotechadv.2017.04.001. Epub 2017 Apr 5. PMID: 28390874.

[137] Mirza Z, Karim S. Nanoparticles-based drug delivery and gene therapy for breast cancer: Recent advancements and future challenges. *Semin Cancer Biol*. 2021 Feb;69:226-237. doi: 10.1016/j.semcancer.2019.10.020. Epub 2019 Nov 5. PMID: 31704145.

[138] Fan R, Tao X, Zhai X, Zhu Y, Li Y, Chen Y, Dong D, Yang S, Lv L. Application of aptamer-drug delivery system in the therapy of breast cancer. *Biomed Pharmacother*. 2023 May;161:114444. doi: 10.1016/j.biopha.2023.114444. Epub 2023 Feb 27. PMID: 36857912.

[139] Shahdordizadeh M , Yazdian-Robati R , Ramezani M , Abnous K , Taghdisi SM . Aptamer application in targeted delivery systems for diagnosis and treatment of breast cancer. *J Mater Chem B*. 2016 Dec 28;4(48):7766-7778. doi: 10.1039/c6tb02564a. Epub 2016 Nov 21. PMID: 32263769.

[140] Wang S, Shen X, Chen G, Zhang W, Tan B. Application and development of CRISPR-Cas12a methods for the molecular diagnosis of cancer: A review. *Anal Chim Acta*. 2025 Mar 1;1341:343603. doi: 10.1016/j.aca.2024.343603. Epub 2024 Dec 30. PMID: 39880493.

[141] Elliott MJ, Kim J, Dou A, Fuentes Antrás J, Amir E, Nadler MB, Van de Laar E, Yu C, Cheikh R, Silvestro A, Siu LL, Bedard PL, Berman HK, Cescon DW. Comprehensive tumor-agnostic evaluation of genomic and epigenomic-based approaches for the identification of circulating tumor DNA in early-stage breast cancer. ESMO Open. 2025 Jun;10(6):105286. doi: 10.1016/j.esmoop.2025.105286. Epub 2025 Jun 4. PMID: 40472659; PMCID: PMC12172975.

[142] Radovich M, Jiang G, Hancock BA, Chitambar C, Nanda R, Falkson C, Lynce FC, Gallagher C, Isaacs C, Blaya M, Paplomata E, Walling R, Daily K, Mahtani R, Thompson MA, Graham R, Cooper ME, Pavlick DC, Albacker LA, Gregg J, Solzak JP, Chen YH, Bales CL, Cantor E, Shen F, Storniolo AMV, Badve S, Ballinger TJ, Chang CL, Zhong Y, Savran C, Miller KD, Schneider BP. Association of Circulating Tumor DNA and Circulating Tumor Cells After Neoadjuvant Chemotherapy With Disease Recurrence in Patients With Triple-Negative Breast Cancer: Preplanned Secondary Analysis of the BRE12-158 Randomized Clinical Trial. JAMA Oncol. 2020 Sep 1;6(9):1410-1415. doi: 10.1001/jamaoncol.2020.2295. PMID: 32644110; PMCID: PMC7349081.

ARTICLE IN PRESS

ARTICLE IN PRESS

[143] Bidard FC, Peeters DJ, Fehm T, Nolé F, Gisbert-Criado R, Mavroudis D, Grisanti S, Generali D, Garcia-Saenz JA, Stebbing J, Caldas C, Gazzaniga P, Manso L, Zamarchi R, de Lascoiti AF, De Mattos-Arruda L, Ignatiadis M, Lebofsky R, van Laere SJ, Meier-Stiegen F, Sandri MT, Vidal-Martinez J, Politaki E, Consoli F, Bottini A, Diaz-Rubio E, Krell J, Dawson SJ, Raimondi C, Rutten A, Janni W, Munzone E, Carañana V, Agelaki S, Almici C, Dirix L, Solomayer EF, Zorzino L, Johannes H, Reis-Filho JS, Pantel K, Pierga JY, Michiels S. Clinical validity of circulating tumour cells in patients with metastatic breast cancer: a pooled analysis of individual patient data. Lancet Oncol. 2014 Apr;15(4):406-14. doi: 10.1016/S1470-2045(14)70069-5. Epub 2014 Mar 11. PMID: 24636208.

[144] Qiu P, Yu X, Zheng F, Gu X, Huang Q, Qin K, Hu Y, Liu B, Xu T, Zhang T, Chen G, Liu Y. Advancements in liquid biopsy for breast Cancer: Molecular biomarkers and clinical applications. Cancer Treat Rev. 2025 Sep;139:102979. doi: 10.1016/j.ctrv.2025.102979. Epub 2025 Jun 14. PMID: 40540857.

[145] Venetis K, Pescia C, Cursano G, Frascarelli C, Mane E, De Camilli E, Munzone E, Dellapasqua S, Criscitiello C, Curigliano G, Guerini Rocco E, Fusco N. The Evolving Role of Genomic Testing in Early Breast Cancer: Implications for Diagnosis, Prognosis, and Therapy. *Int J Mol Sci*. 2024 May 24;25(11):5717. doi: 10.3390/ijms25115717. PMID: 38891906; PMCID: PMC11172282.

[146] Arun B, Couch FJ, Abraham J, Tung N, Fasching PA. BRCA-mutated breast cancer: the unmet need, challenges and therapeutic benefits of genetic testing. *Br J Cancer*. 2024 Nov;131(9):1400-1414. doi: 10.1038/s41416-024-02827-z. Epub 2024 Aug 30. PMID: 39215191; PMCID: PMC11519381.

[147] Calabrese A, von Arx C, Tafuti AA, Pensabene M, De Laurentiis M. Prevention, diagnosis and clinical management of hereditary breast cancer beyond BRCA1/2 genes. *Cancer Treat Rev*. 2024 Sep;129:102785. doi: 10.1016/j.ctrv.2024.102785. Epub 2024 Jun 11. PMID: 38870570.

[148] Bhardwaj PV, Abdou YG. Germline Genetic Testing in Breast Cancer: Systemic Therapy Implications. *Curr Oncol Rep*. 2022 Dec;24(12):1791-1800. doi: 10.1007/s11912-022-01340-x. Epub 2022 Oct 18. PMID: 36255604.

[149] Katz SJ, Abrahamse P, Furgal A, Hodan R, Tocco RS, Ward KC, Hamilton AS, Wallner LP, Kurian AW. Genetic Counseling, Testing, and Family Communication Into Survivorship After Diagnosis of Breast Cancer. *J Clin Oncol*. 2024 Sep 10;42(26):3123-3129. doi: 10.1200/JCO.24.00122. Epub 2024 Jul 15. PMID: 39008790; PMCID: PMC11377164.

[150] Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. *Lancet*. 2021 May 8;397(10286):1750-1769. doi: 10.1016/S0140-6736(20)32381-3. Epub 2021 Apr 1. Erratum in: Lancet. 2021 May 8;397(10286):1710. doi: 10.1016/S0140-6736(21)00838-2. PMID: 33812473.

[151] King TA, Morrow M. Surgical issues in patients with breast cancer receiving neoadjuvant chemotherapy. *Nat Rev Clin Oncol*. 2015 Jun;12(6):335-43. doi: 10.1038/nrclinonc.2015.63. Epub 2015 Apr 7. PMID: 25850554.

[152] Bedard PL, Cardoso F. Can some patients avoid adjuvant chemotherapy for early-stage breast cancer? *Nat Rev Clin Oncol*. 2011 May;8(5):272-9. doi: 10.1038/nrclinonc.2011.19. Epub 2011 Mar 1. PMID: 21364525.

[153] Roché H, Vahdat LT. Treatment of metastatic breast cancer: second line and beyond. *Ann Oncol*. 2011 May;22(5):1000-1010. doi: 10.1093/annonc/mdq429. Epub 2010 Oct 21. PMID: 20966181.

ARTICLE IN PRESS

ARTICLE IN PRESS

[154] Azim HA Jr, de Azambuja E, Colozza M, Bines J, Piccart MJ. Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann Onco*l. 2011 Sep;22(9):1939-1947. doi: 10.1093/annonc/mdq683. Epub 2011 Feb 2. PMID: 21289366.

[155] Murray S, Briasoulis E, Linardou H, Bafaloukos D, Papadimitriou C. Taxane resistance in breast cancer: mechanisms, predictive biomarkers and circumvention strategies. *Cancer Treat Rev*. 2012 Nov;38(7):890-903. doi: 10.1016/j.ctrv.2012.02.011. Epub 2012 Mar 31. PMID: 22465195.

[156] von Minckwitz G, Martin M. Neoadjuvant treatments for triple-negative breast cancer (TNBC). *Ann Oncol*. 2012 Aug;23 Suppl 6:vi35-9. doi: 10.1093/annonc/mds193. PMID: 23012300.

[157] Krauss K, Stickeler E. Endocrine Therapy in Early Breast Cancer. *Breast Care (Basel)*. 2020 Aug;15(4):337-346. doi: 10.1159/000509362. Epub 2020 Jul 21. PMID: 32982643; PMCID: PMC7490651.

[158] Johnston SJ, Cheung KL. Endocrine Therapy for Breast Cancer: A Model of Hormonal Manipulation. *Oncol Ther*. 2018 Dec;6(2):141-156. doi: 10.1007/s40487-018-0062-x. Epub 2018 Jul 10. PMID: 32700026; PMCID: PMC7360014.

[159] Walsh EM, Nunes R, Wilkinson MJ, Santa-Maria CA. Extended Endocrine Therapy for Early-Stage Breast Cancer: How Do We Decide? *Curr Oncol Rep*. 2020 Oct 5;22(12):123. doi: 10.1007/s11912-020-00988-7. PMID: 33015752.

[160] Burstein HJ. Adjuvant endocrine therapy in postmenopausal women: making treatment choices based on the magnitude of benefit. *Breast*. 2019 Nov;48 Suppl 1:S89-S91. doi: 10.1016/S0960-9776(19)31132-4. PMID: 31839170.

[161] Azim HA, Dawood S, El-Saghir N, Kassem L, Azim HA Jr. Understanding the benefits and challenges of first-line cyclin-dependent kinases 4 and 6 inhibitors in advanced breast cancer among postmenopausal women. *Breast J*. 2020 Apr;26(4):630-642. doi: 10.1111/tbj.13637. Epub 2019 Nov 10. PMID: 31709685.

[162] Ziyeh S, Wong L, Basho RK. Advances in Endocrine Therapy for Hormone Receptor-Positive Advanced Breast Cancer. *Curr Oncol Rep*. 2023 Jul;25(7):689-698. doi: 10.1007/s11912-023-01393-6. Epub 2023 Apr 1. PMID: 37004700.

[163] Goldner M, Pandolfi N, Maciel D, Lima J, Sanches S, Pondé N. Combined endocrine and targeted therapy in luminal breast cancer. *Expert Rev Anticancer Ther*. 2021 Nov;21(11):1237-1251. doi: 10.1080/14737140.2021.1960160. Epub 2021 Sep 7. PMID: 34338570.

[164] McAndrew NP, Finn RS. Management of ER positive metastatic breast cancer. *Semin Oncol*. 2020 Oct;47(5):270-277. doi: 10.1053/j.seminoncol.2020.07.005. Epub 2020 Aug 29. PMID: 32958261.

[165] Rasha F, Sharma M, Pruitt K. Mechanisms of endocrine therapy resistance in breast cancer. *Mol Cell Endocrinol*. 2021 Jul 15;532:111322. doi: 10.1016/j.mce.2021.111322. Epub 2021 May 15. PMID: 34000350.

[166] Li Y, Kong X, Xuan L, Wang Z, Huang YH. Prolactin and endocrine therapy resistance in breast cancer: The next potential hope for breast cancer treatment. *J Cell Mol Med*. 2021 Nov;25(22):10327-10348. doi: 10.1111/jcmm.16946. Epub 2021 Oct 15. PMID: 34651424; PMCID: PMC8581311.

ARTICLE IN PRESS

ARTICLE IN PRESS

[167] Corti C, De Angelis C, Bianchini G, Malorni L, Giuliano M, Hamilton E, Jeselsohn R, Jhaveri K, Curigliano G, Criscitiello C. Novel endocrine therapies: What is next in estrogen receptor positive, HER2 negative breast cancer? *Cancer Treat Rev*. 2023 Jun;117:102569. doi: 10.1016/j.ctrv.2023.102569. Epub 2023 Apr 28. PMID: 37146385.

[168] Valenza C, Curigliano G. Positioning oral selective estrogen receptor degraders in patients with metastatic breast cancer. Eur J Cancer. 2025 Oct 1;228:115739. doi: 10.1016/j.ejca.2025.115739. Epub 2025 Aug 21. PMID: 40850315.

[169] Luo W, Ali YF, Liu C, Wang Y, Liu C, Jin X, Zhou G, Liu NA. Particle Therapy for Breast Cancer: Benefits and Challenges. *Front Oncol*. 2021 May 5;11:662826. doi: 10.3389/fonc.2021.662826. PMID: 34026640; PMCID: PMC8131859.

[170] Han MC, Choi SH, Hong CS, Kim YB, Koom WS, Kim JS, Cho J, Wee CW, Kim C, Park JW, Han S, Lee H, Yoon HI, Lee IJ, Keum KC. The first Korean carbon-ion radiation therapy facility: current status of the Heavy-ion Therapy Center at the Yonsei Cancer Center. *Radiat Oncol J*. 2024 Dec;42(4):295-307. doi: 10.3857/roj.2024.00206. Epub 2024 Dec 20. PMID: 39748530; PMCID: PMC11701461.

[171] Yu B, Li KW, Fan Y, Pei X. Value of Carbon-Ion Radiation Therapy for Breast Cancer. *Int J Part Ther*. 2024 Aug 30;14:100629. doi: 10.1016/j.ijpt.2024.100629. PMID: 39309411; PMCID: PMC11415881.

[172] Durante M, Debus J, Loeffler JS. Physics and biomedical challenges of cancer therapy with accelerated heavy ions. *Nat Rev Phys*. 2021 Dec;3(12):777-790. doi: 10.1038/s42254-021-00368-5. Epub 2021 Sep 17. PMID: 34870097; PMCID: PMC7612063.

[173] Smith CEP, Prasad V. Targeted Cancer Therapies. *Am Fam Physician*. 2021 Feb 1;103(3):155-163. PMID: 33507053.

[174] Cipriano É, Mesquita A. Emerging Therapeutic Drugs in Metastatic Triple-Negative Breast Cancer. *Breast Cancer (Auckl)*. 2021 Mar 22;15:11782234211002491. doi: 10.1177/11782234211002491. PMID: 33814914; PMCID: PMC7989121.

[175] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N, Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022 Jul 7;387(1):9-20. doi: 10.1056/NEJMoa2203690. Epub 2022 Jun 5. PMID: 35665782; PMCID: PMC10561652.

[176] Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, Brufsky A, Sardesai SD, Kalinsky K, Zelnak AB, Weaver R, Traina T, Dalenc F, Aftimos P, Lynce F, Diab S, Cortés J, O'Shaughnessy J, Diéras V, Ferrario C, Schmid P, Carey LA, Gianni L, Piccart MJ, Loibl S, Goldenberg DM, Hong Q, Olivo MS, Itri LM, Rugo HS; ASCENT Clinical Trial Investigators. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021 Apr 22;384(16):1529-1541. doi: 10.1056/NEJMoa2028485. PMID: 33882206.

ARTICLE IN PRESS

ARTICLE IN PRESS

[177] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

[178] Nik Amirah Auni NMA, Mohd Redzwan N, Yahya MM, Wong KK. Antibody-drug conjugates in breast cancer: From therapeutic and immune activation mechanisms to resistance prevention. Int Rev Immunol. 2025;44(6):420-442. doi: 10.1080/08830185.2025.2545364. Epub 2025 Aug 19. PMID: 40827372.

[179] Goldner M, Pandolfi N, Maciel D, Lima J, Sanches S, Pondé N. Combined endocrine and targeted therapy in luminal breast cancer. *Expert Rev Anticancer Ther*. 2021 Nov;21(11):1237-1251. doi: 10.1080/14737140.2021.1960160. Epub 2021 Sep 7. PMID: 34338570.

[180] Zhu K, Wu Y, He P, Fan Y, Zhong X, Zheng H, Luo T. PI3K/AKT/mTOR-Targeted Therapy for Breast Cancer. *Cells*. 2022 Aug 12;11(16):2508. doi: 10.3390/cells11162508. PMID: 36010585; PMCID: PMC9406657.

[181] Garay JP, Smith R, Devlin K, Hollern DP, Liby T, Liu M, Boddapati S, Watson SS, Esch A, Zheng T, Thompson W, Babcock D, Kwon S, Chin K, Heiser L, Gray JW, Korkola JE. Sensitivity to targeted therapy differs between HER2-amplified breast cancer cells harboring kinase and helical domain mutations in PIK3CA. *Breast Cancer Res*. 2021 Aug 3;23(1):81. doi: 10.1186/s13058-021-01457-0. PMID: 34344439; PMCID: PMC8336338.

[182] Elizabeth MS, Cristina SBJ, Christian CG. Immunotherapy in Combination with Chemotherapy for Triple-negative Breast Cancer. *Mini Rev Med Chem*. 2024;24(4):431-439. doi: 10.2174/1389557523666230517152538. PMID: 37198990.

[183] Emens LA, Loi S. Immunotherapy Approaches for Breast Cancer Patients in 2023. *Cold Spring Harb Perspect Med*. 2023 Apr 3;13(4):a041332. doi: 10.1101/cshperspect.a041332. PMID: 37011999; PMCID: PMC10071416.

[184] Yang T, Kang L, Li D, Song Y. Immunotherapy for HER-2 positive breast cancer. *Front Oncol*. 2023 Mar 16;13:1097983. doi: 10.3389/fonc.2023.1097983. PMID: 37007133; PMCID: PMC10061112.

[185] Agostinetto E, Montemurro F, Puglisi F, Criscitiello C, Bianchini G, Del Mastro L, Introna M, Tondini C, Santoro A, Zambelli A. Immunotherapy for HER2-Positive Breast Cancer: Clinical Evidence and Future Perspectives. *Cancers (Basel)*. 2022 Apr 25;14(9):2136. doi: 10.3390/cancers14092136. PMID: 35565264; PMCID: PMC9105460.

[186] Kundu M, Butti R, Panda VK, Malhotra D, Das S, Mitra T, Kapse P, Gosavi SW, Kundu GC. Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. *Mol Cancer*. 2024 May 7;23(1):92. doi: 10.1186/s12943-024-01990-4. PMID: 38715072; PMCID: PMC11075356.

[187] Sueangoen N, Thuwajit P, Yenchitsomanus PT, Thuwajit C. Public neoantigens in breast cancer immunotherapy (Review). *Int J Mol Med*. 2024 Jul;54(1):65. doi: 10.3892/ijmm.2024.5388. Epub 2024 Jun 21. PMID: 38904202; PMCID: PMC11188978.

ARTICLE IN PRESS

ARTICLE IN PRESS

[188] Li H, Li J, Zhang Y, Zhao C, Ge J, Sun Y, Fu H, Li Y. The therapeutic effect of traditional Chinese medicine on breast cancer through modulation of the Wnt/β-catenin signaling pathway. *Front Pharmacol*. 2024 May 9;15:1401979. doi: 10.3389/fphar.2024.1401979. PMID: 38783943; PMCID: PMC11111876.

[189] Liu Y, Fang C, Luo J, Gong C, Wang L, Zhu S. Traditional Chinese Medicine for Cancer Treatment. *Am J Chin Med*. 2024;52(3):583-604. doi: 10.1142/S0192415X24500253. Epub 2024 May 8. PMID: 38716616.

[190] Zhang Y, Shi L. Traditional Chinese medicine combined with chemotherapy for breast cancer after operation: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2024 Nov 15;103(46):e40264. doi: 10.1097/MD.0000000000040264. PMID: 39560516; PMCID: PMC11575946.

[191] Tang Z, Tian X. Astragalus membranaceus: A Traditional Chinese Medicine with Multifaceted Impacts on Breast Cancer Treatment. *Biomolecules*. 2024 Oct 21;14(10):1339. doi: 10.3390/biom14101339. PMID: 39456271; PMCID: PMC11506204.

[192] Wu Q, Yan H, Kang Z. A Review of Traditional Chinese Medicine for Triple Negative Breast Cancer and the Pharmacological Mechanisms. *Am J Chin Med*. 2024;52(4):987-1011. doi: 10.1142/S0192415X2450040X. Epub 2024 Jun 14. PMID: 38879747.

[193] Zhao X, Luo T, Qiu Y, Yang Z, Wang D, Wang Z, Zeng J, Bi Z. Mechanisms of traditional Chinese medicine overcoming of radiotherapy resistance in breast cancer. *Front Oncol*. 2024 Jun 27;14:1388750. doi: 10.3389/fonc.2024.1388750. PMID: 38993643; PMCID: PMC11237312.

[194] Kindt CK, Ehmsen S, Traynor S, Policastro B, Nissen N, Jakobsen MK, Hundebøl MF, Johansen LE, Bak M, Arbajian E, Staaf J, Ditzel HJ, Alves CL. RET inhibition overcomes resistance to combined CDK4/6 inhibitor and endocrine therapy in ER+ breast cancer. *Front Oncol*. 2025 Jan 27;14:1497093. doi: 10.3389/fonc.2024.1497093. PMID: 39931212; PMCID: PMC11808005.

[195] Dou QQ, Sun TT, Wang GQ, Tong WB. Inetetamab combined with pyrotinib and chemotherapy in the treatment of breast cancer brain metastasis: A case report. *World J Clin Cases*. 2024 Jan 26;12(3):575-581. doi: 10.12998/wjcc.v12.i3.575. PMID: 38322469; PMCID: PMC10841958.

[196] Huang J, Chen X, Guo J, Song L, Mu Y, Zhao H, Du C. Apatinib combined with trastuzumab and albumin-bound paclitaxel for treatment of HER2+ breast cancer with brain metastases resistant to anti-HER2 TKIs: A case report. *Oncol Lett*. 2022 Dec 20;25(2):56. doi: 10.3892/ol.2022.13642. PMID: 36644147; PMCID: PMC9827463.

[197] Yang X, Ren H, Xu Y, Peng X, Yu W, Shen Z. Combination of radiotherapy and targeted therapy for HER2-positive breast cancer brain metastases. *Eur J Med Res*. 2023 Jan 16;28(1):27. doi: 10.1186/s40001-022-00894-7. PMID: 36642742; PMCID: PMC9841677.

[198] Wang Y, Minden A. Current Molecular Combination Therapies Used for the Treatment of Breast Cancer. *Int J Mol Sci*. 2022 Sep 20;23(19):11046. doi: 10.3390/ijms231911046. PMID: 36232349; PMCID: PMC9569555.

ARTICLE IN PRESS

[199] Spring LM, Wander SA, Andre F, Moy B, Turner NC, Bardia A. Cyclin-dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. Lancet. 2020 Mar 7;395(10226):817-827. doi: 10.1016/S0140-6736(20)30165-3. PMID: 32145796.

[200] Valle I, Grinda T, Antonuzzo L, Pistilli B. Antibody-drug conjugates in breast cancer: mechanisms of resistance and future therapeutic perspectives. NPJ Breast Cancer. 2025 Sep 29;11(1):102. doi: 10.1038/s41523-025-00829-5. PMID: 41022825; PMCID: PMC12480482.

[201] DePeaux K, Delgoffe GM. Metabolic barriers to cancer immunotherapy. Nat Rev Immunol. 2021 Dec;21(12):785-797. doi: 10.1038/s41577-021-00541-y. Epub 2021 Apr 29. PMID: 33927375; PMCID: PMC8553800.

[202] Qi YJ, Su GH, You C, Zhang X, Xiao Y, Jiang YZ, Shao ZM. Radiomics in breast cancer: Current advances and future directions. *Cell Rep Med*. 2024 Sep 17;5(9):101719. doi: 10.1016/j.xcrm.2024.101719. PMID: 39293402; PMCID: PMC11528234.

[203] Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, Denkert C, Park YH, Hui R, Harbeck N, Takahashi M, Foukakis T, Fasching PA, Cardoso F, Untch M, Jia L, Karantza V, Zhao J, Aktan G, Dent R, O'Shaughnessy J; KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821. doi: 10.1056/NEJMoa1910549. PMID: 32101663.

[204] Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol. 2022 Feb;19(2):91-113. doi: 10.1038/s41571-021-00565-2. Epub 2021 Nov 9. PMID: 34754128.

[205] Vellan CJ, Natesan V, Jayapalan JJ. Metabolomics Biomarkers for Breast Cancer: An updated perspective. Clin Breast Cancer. 2025 Aug;25(6):e765-e778. doi: 10.1016/j.clbc.2025.05.005. Epub 2025 May 8. PMID: 40441981.

[206] Wu SZ, Al-Eryani G, Roden DL, Junankar S, Harvey K, Andersson A, Thennavan A, Wang C, Torpy JR, Bartonicek N, Wang T, Larsson L, Kaczorowski D, Weisenfeld NI, Uytingco CR, Chew JG, Bent ZW, Chan CL, Gnanasambandapillai V, Dutertre CA, Gluch L, Hui MN, Beith J, Parker A, Robbins E, Segara D, Cooper C, Mak C, Chan B, Warrier S, Ginhoux F, Millar E, Powell JE, Williams SR, Liu XS, O'Toole S, Lim E, Lundeberg J, Perou CM, Swarbrick A. A single-cell and spatially resolved atlas of human breast cancers. Nat Genet. 2021 Sep;53(9):1334-1347. doi: 10.1038/s41588-021-00911-1. Epub 2021 Sep 6. PMID: 34493872; PMCID: PMC9044823.

[207] Andersson A, Larsson L, Stenbeck L, Salmén F, Ehinger A, Wu SZ, Al-Eryani G, Roden D, Swarbrick A, Borg Å, Frisén J, Engblom C, Lundeberg J. Spatial deconvolution of HER2-positive breast cancer delineates tumor-associated cell type interactions. Nat Commun. 2021 Oct 14;12(1):6012. doi: 10.1038/s41467-021-26271-2. PMID: 34650042; PMCID: PMC8516894.

[208] Bardia A, Jhaveri K, Im SA, Pernas S, De Laurentiis M, Wang S, Martínez Jañez N, Borges G, Cescon DW, Hattori M, Lu YS, Hamilton E, Zhang Q, Tsurutani J, Kalinsky K, Rubini Liedke PE, Xu L, Fairhurst RM, Khan S, Denduluri N, Rugo HS, Xu B, Pistilli B; TROPION-Breast01 Investigators. Datopotamab Deruxtecan Versus Chemotherapy in Previously Treated Inoperable/Metastatic Hormone Receptor-Positive Human Epidermal Growth

ARTICLE IN PRESS

Factor Receptor 2-Negative Breast Cancer: Primary Results From TROPION-Breast01. J Clin Oncol. 2025 Jan 20;43(3):285-296. doi: 10.1200/JCO.24.00920. Epub 2024 Sep 12. PMID: 39265124; PMCID: PMC11771365.

[209] Stylianakis D, Benjamin HA, Martella S, De Silva P, Stylianakis I, Denaro N, Leoni VP, Atzori L, Scartozzi M, Lambertini M, Solinas C, Willard-Gallo K. Spatial multiomics of the breast tumour microenvironment: State of the field, advancements and clinical implementation promises. Crit Rev Oncol Hematol. 2026 Feb;218:105082. doi: 10.1016/j.critrevonc.2025.105082. Epub 2025 Dec 11. PMID: 41389952.

[210] DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. Nat Rev Immunol. 2019 Jun;19(6):369-382. doi: 10.1038/s41577-019-0127-6. PMID: 30718830; PMCID: PMC7339861.

[211] Kieffer Y, Hocine HR, Gentric G, Pelon F, Bernard C, Bourachot B, Lameiras S, Albergante L, Bonneau C, Guyard A, Tarte K, Zinovyev A, Baulande S, Zalcman G, Vincent-Salomon A, Mechta-Grigoriou F. Single-Cell Analysis Reveals Fibroblast Clusters Linked to Immunotherapy Resistance in Cancer. Cancer Discov. 2020 Sep;10(9):1330-1351. doi: 10.1158/2159-8290.CD-19-1384. Epub 2020 May 20. PMID: 32434947.

[212] Garcia-Murillas I, Chopra N, Comino-Méndez I, Beaney M, Tovey H, Cutts RJ, Swift C, Kriplani D, Afentakis M, Hrebien S, Walsh-Crestani G, Barry P, Johnston SRD, Ring A, Bliss J, Russell S, Evans A, Skene A, Wheatley D, Dowsett M, Smith IE, Turner NC. Assessment of Molecular Relapse Detection in Early-Stage Breast Cancer. JAMA Oncol. 2019 Oct 1;5(10):1473-1478. doi: 10.1001/jamaoncol.2019.1838. Erratum in: JAMA Oncol. 2020 Jan 1;6(1):162. doi: 10.1001/jamaoncol.2019.6325. PMID: 31369045; PMCID: PMC6681568.

[213] Kalluri R, LeBleu VS. The biology**,** function**,** and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478):eaau6977. doi: 10.1126/science.aau6977. PMID: 32029601; PMCID: PMC7717626.

[214] Merker JD, Oxnard GR, Compton C, Diehn M, Hurley P, Lazar AJ, Lindeman N, Lockwood CM, Rai AJ, Schilsky RL, Tsimberidou AM, Vasalos P, Billman BL, Oliver TK, Bruinooge SS, Hayes DF, Turner NC. Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. Arch Pathol Lab Med. 2018 Oct;142(10):1242-1253. doi: 10.5858/arpa.2018-0901-SA. Epub 2018 Mar 5. PMID: 29504834.

[215] Moutafi M, Robbins CJ, Yaghoobi V, Fernandez AI, Martinez-Morilla S, Xirou V, Bai Y, Song Y, Gaule P, Krueger J, Bloom K, Hill S, Liebler DC, Fulton R, Rimm DL. Quantitative measurement of HER2 expression to subclassify ERBB2 unamplified breast cancer. Lab Invest. 2022 Oct;102(10):1101-1108. doi: 10.1038/s41374-022-00804-9. Epub 2022 May 20. PMID: 35595825.

[216] Michelon I, Dacoregio MI, Vilbert M, Priantti J, do Rego Castro CE, Vian L, Tarantino P, de Azambuja E, Cavalcante L. Antibody-drug conjugates in patients with advanced/metastatic HER2-low-expressing breast cancer: a systematic review and meta-analysis. Ther Adv Med Oncol. 2024 Nov 20;16:17588359241297079. doi: 10.1177/17588359241297079. PMID: 39574495; PMCID: PMC11580099.

[217] Lee CK, Jeong SH, Jang C, Bae H, Kim YH, Park I, Kim SK, Koh GY. Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation. Science. 2019 Feb 8;363(6427):644-649. doi: 10.1126/science.aav0173. Epub 2019 Feb 7. PMID: 30733421.

ARTICLE IN PRESS

[218] Elayeh E, Aleidi SM, Aboud O, Semreen MH, Bustanji YK, Dahabiyeh LA. Integrated Multi-Omics Approaches for Predicting Immune Checkpoint Inhibitor Response in NSCLC - Insights From Genomics, Proteomics, and Metabolomics. Lung Cancer (Auckl). 2025 Dec 16;16:167-198. doi: 10.2147/LCTT.S539777. PMID: 41424613; PMCID: PMC12717820.

[219] Sicklick JK, Kato S, Okamura R, Schwaederle M, Hahn ME, Williams CB, De P, Krie A, Piccioni DE, Miller VA, Ross JS, Benson A, Webster J, Stephens PJ, Lee JJ, Fanta PT, Lippman SM, Leyland-Jones B, Kurzrock R. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med. 2019 May;25(5):744-750. doi: 10.1038/s41591-019-0407-5. Epub 2019 Apr 22. PMID: 31011206; PMCID: PMC6553618.

[220] André F, Bachelot T, Commo F, Campone M, Arnedos M, Dieras V, Lacroix-Triki M, Lacroix L, Cohen P, Gentien D, Adélaide J, Dalenc F, Goncalves A, Levy C, Ferrero JM, Bonneterre J, Lefeuvre C, Jimenez M, Filleron T, Bonnefoi H. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol. 2014 Mar;15(3):267-74. doi: 10.1016/S1470-2045(13)70611-9. Epub 2014 Feb 7. PMID: 24508104.

[221] Trüb M, Zippelius A. Tertiary Lymphoid Structures as a Predictive Biomarker of Response to Cancer Immunotherapies. Front Immunol. 2021 May 12;12:674565. doi: 10.3389/fimmu.2021.674565. PMID: 34054861; PMCID: PMC8149953.

[222] Akai M, Noma K, Kato T, Nishimura S, Matsumoto H, Kawasaki K, Kunitomo T, Kobayashi T, Nishiwaki N, Kashima H, Kikuchi S, Ohara T, Tazawa H, Choyke PL, Kobayashi H, Fujiwara T. Fibroblast activation protein-targeted near-infrared photoimmunotherapy depletes immunosuppressive cancer-associated fibroblasts and remodels local tumor immunity. Br J Cancer. 2024 Jun;130(10):1647-1658. doi: 10.1038/s41416-024-02639-1. Epub 2024 Mar 30. PMID: 38555315; PMCID: PMC11091110.

ARTICLE IN PRESS

检 索 证 明

经检索《Science Citation Index Expanded》（SCI-EXPANDED）数据库、《Journal Citation Reports》（JCR）数据库和《中国科学院文献情报中心期刊分区表升级版》，以下 1 篇文献的收录简要信息、期刊的影响因子及分区如下：

标题: Integrating multi-omics and clinical management in breast cancer: a comprehensive review

作者: Cao, XX (Cao, Xiangxiang);Yang, YC (Yang, Yunchang);Wang, PB (Wang, Pengbo);Wang, JJ (Wang, Jinjin);Zhao, YK (Zhao, Yike);Zhang, ZC (Zhang, Zichun);Jiang, JQ (Jiang, Jiaqi);Zhang, HW (Zhang, Hanwen);Kang, XY (Kang, Xinyao);Feng, HG (Feng, Huigen);Ji, GJ (Ji, Guojie);Hu, HH (Hu, Huanhuan)

来源出版物: DISCOVER ONCOLOGY　卷:17　期:1　DOI:10.1007/s12672-026-05357-7　出版时间:JUN 6 2026　提前访问日期:JUN 2026

Web of Science 核心合集中的“被引频次”：0 次

期刊《DISCOVER ONCOLOGY》2025 年影响因子为 2.8。

经检索《中国科学院文献情报中心期刊分区表升级版》，2025 年分区如下：

刊名	Discover Oncology		
年份	2025		
ISSN/EISSN	2730-6011/2730-6011		
Review	否		
OA Journal Index（OAJ）	否		
Open Access	否		
Web of Science	SCIE		
	学科	分区	Top 期刊
小类	ENDOCRINOLOGY & METABOLISM 内分泌学与代谢	4	
小类	ONCOLOGY 肿瘤学	4	
大类	医学	4	否

特此证明

（详细内容见附件）

扫描二维码查看报告

书馆

教育 站 Z12

林卉

15 日

注：因 JCR 数据更新滞后，新出版论文的期刊影响因子以最新版 JCR 数据为参考。

第 1 条，共 1 条

标题: Integrating multi-omics and clinical management in breast cancer: a comprehensive review

作者: Cao, XX (Cao, Xiangxiang);Yang, YC (Yang, Yunchang);Wang, PB (Wang, Pengbo);Wang, JJ (Wang, Jinjin);Zhao, YK (Zhao, Yike);Zhang, ZC (Zhang, Zichun);Jiang, JQ (Jiang, Jiaqi);Zhang, HW (Zhang, Hanwen);Kang, XY (Kang, Xinyao);Feng, HG (Feng, Huigen);Ji, GJ (Ji, Guojie);Hu, HH (Hu, Huanhuan)

来源出版物: DISCOVER ONCOLOGY **卷:** 17 **期:**1 **DOI:** 10.1007/s12672-026-05357-7 **出版年:** JUN 6 2026 **提前访问日期**:JUN 2026

Web of Science 核心合集中的 "被引频次": 0

被引频次合计: 0

使用次数 (最近 180 天): 0

使用次数 (2013 年至今): 0

引用的参考文献数: 219

摘要: Unlike conventional reviews that d domains, this review uniquely integrates genomic, transcriptomic, proteomic, and metabolomic data to bridge the gap between advanced tum and actionable clinical management. Its objective is to provide a definitive translational roadmap that decodes TME reprogramming, surmount s personalized oncology. We dissect the multifaceted mechanisms driving therapeutic resistance and highlight the paradigm-shifting role of li mes) in dynamically monitoring minimal residual disease (MRD).

入藏号: WOS:001845869700004

PubMed ID: 42250175

语言: English

文献类型: Review

作者关键词: Breast cancer;Multi-Omics rapies;Tumor microenvironment

KeyWords Plus: CARCINOMA-IN-SI A; LOBULAR CARCINOMA; ENDOCRINE-THERAPY; DUCTAL CARCINOMA; ADJUVANT CHEMOTHERAPY; SINGLE-CELL; B ON

地址: [Cao, Xiangxiang; Yang, Yunchang; Wang, Pengbo; Wang, Jinjin; Zhao, Yike; Zhang, Zichun; Jiang, Jiaqi; Zhang, Hanwen; Feng, Huigen; Ji, Guojie; Hu, Huanhuan] North Henan Med Univ, Key Lab Fertil Preservat, Pingyuan Demonstrat Area, West Sect Changjiang Rd, Xinxiang 453003, Henan, Peoples R China;[Kang, Xinyao] Henan Univ, Kaifeng, Henan, Peoples R China

通讯作者地址: [Feng, Huigen; Ji, Guojie; Hu, Huanhuan] (corresponding author), North Henan Med Univ, Key Lab Fertil Preservat, Pingyuan Demonstrat Area, West Sect Changjiang Rd, Xinxiang 453003, Henan, Peoples R China

电子邮件地址: huigenfeng1963@163.com;jiguojie87@163.com;huhuanhuan1987@163.com

出版商:SPRINGER

出版商地址: ONE NEW YORK PLAZA, SUITE 4600, NEW YORK, NY, UNITED STATES

Web of Science Index : 《Science Citation Index Expanded》（SCI-EXPANDED）

Web of Science 类别: Oncology;Endocrinology & Metabolism

研究方向: Oncology;Endocrinology & Metabolism

IDS 号:MM6SC

eISSN: 2730-6011

来源出版物页码计数: 31

基金资助致谢: This work was supported by the Excellent Young Teacher Training Program of Sanquan College of Xinxiang Medical University (SQ2025YQJH04), Backbone Henan Province Colleges and Universities Young Backbone teacher Training Program (2023GGJS201), Teachers Program of Sanquan College of Xinxiang Medical University (SQ2023GGJS06), Academic Technology Leader Program of Sanquan College of Xinxiang Medical University (SQ2023XSJSDTR01), Provincial key discipline project of Biology and Medicine of Sanquan College of Xinxiang Medical University (ZDXKXM003, ZDXKXM015).

基金资助机构	授权号
north henan medical university	**SQ2025YQJH04**

ESI 高被引论文: N

ESI 热点论文: N

输出日期: 2026 年 09 月 15 日