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Review Paper

Pharmacogenomics in Breast Cancer Therapy: A Review

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ABSTRACT

Breast cancer is one of the most frequently diagnosed cancers among women worldwide and remains a major public health concern despite continuous advances in diagnosis and treatment. Patients often show considerable variation in their response to anticancer drugs because of differences in their genetic makeup. Pharmacogenomics, which studies the influence of genetic variations on drug response, has become an essential component of personalized medicine. It helps clinicians select the most appropriate therapy, optimize drug dosage, and reduce the risk of adverse drug reactions. In breast cancer, genetic biomarkers such as BRCA1, BRCA2, HER2 (ERBB2), CYP2D6, PIK3CA, ESR1, and DPYD play an important role in guiding treatment decisions. These biomarkers support the use of targeted therapy, endocrine therapy, chemotherapy, and immunotherapy according to the molecular characteristics of individual patients. Pharmacogenomic-guided treatment improves therapeutic outcomes, minimizes toxicity, and enhances the quality of life. This review highlights the principles of pharmacogenomics, major genetic biomarkers, their clinical applications in breast cancer therapy, current challenges, and future perspectives in precision oncology [1–8].

INTRODUCTION

Breast cancer is the most common malignancy among women and is one of the leading causes of cancer-related deaths worldwide. According to recent global cancer statistics, millions of new cases are diagnosed each year, making breast cancer a major healthcare challenge [1–3]. Improvements in screening programs, imaging techniques, surgery, chemotherapy, endocrine therapy, and targeted therapy have significantly increased survival rates. However, many patients still experience disease recurrence, drug resistance, or severe treatment-related toxicity [4–6].

Traditionally, patients with similar clinical features received similar treatment regimens. Clinical experience has shown that the effectiveness and safety of these therapies vary considerably among individuals. Some patients

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achieve an excellent response, whereas others develop resistance or serious adverse effects. These differences are largely influenced by inherited and acquired genetic variations that affect drug metabolism and tumor biology [7–10].

Pharmacogenomics integrates pharmacology with genomics to understand how genetic differences influence drug efficacy, metabolism, and toxicity. By identifying clinically relevant genetic biomarkers before treatment, healthcare professionals can select the most suitable therapy for each patient. This personalized approach has become an important component of precision medicine and is increasingly incorporated into breast cancer management [7,8].

Several genes, including BRCA1, BRCA2, HER2 (ERBB2), CYP2D6, PIK3CA, ESR1, and DPYD, have demonstrated significant clinical value in predicting treatment response, identifying drug toxicity, and selecting targeted therapies. As genomic technologies continue to advance, pharmacogenomics is expected to further improve treatment outcomes and patient survival [11–20].

Pharmacogenomics: An Overview

Pharmacogenomics is the study of how genetic variations influence an individual's response to medications. Its primary objective is to provide the right drug, at the right dose, for the right patient, thereby maximizing therapeutic benefit while reducing adverse drug reactions [7–10].

Genetic differences affect both pharmacokinetics and pharmacodynamics. Pharmacokinetics involves the absorption, distribution, metabolism, and excretion of drugs, whereas pharmacodynamics refers to the interaction of drugs with their biological targets. Variations in genes encoding drug-metabolizing enzymes, transport proteins, and receptors may alter drug effectiveness and safety [8,9].

A well-known example in breast cancer is the CYP2D6 gene. Tamoxifen is administered as a prodrug and requires metabolic activation by the CYP2D6 enzyme to form its active metabolite, endoxifen. Patients carrying reduced-function CYP2D6 variants produce lower endoxifen concentrations, which may reduce the effectiveness of tamoxifen therapy [11–13].

With advances in genomic sequencing and molecular diagnostics, pharmacogenomics has become an essential component of precision oncology. It enables clinicians to personalize treatment strategies according to each patient's genetic profile, improving treatment outcomes while minimizing unnecessary toxicity and healthcare costs [7,8].

Breast Cancer

Breast cancer develops when normal breast cells acquire genetic alterations that result in uncontrolled cell growth and tumor formation. Most breast cancers arise from the epithelial cells lining the milk ducts (ductal carcinoma), while a smaller proportion originates from the milk-producing lobules (lobular carcinoma) [1,25,26].

Breast cancer is a heterogeneous disease and is classified according to the expression of hormone receptors and HER2 status. Molecular classification plays an important role in selecting appropriate treatment and predicting prognosis.

Risk Factors

The major risk factors associated with breast cancer include:

- Increasing age
- Family history of breast or ovarian cancer
- BRCA1 and BRCA2 gene mutations
- Early menarche and late menopause
- Obesity
- Alcohol consumption
- Smoking
- Physical inactivity
- Hormone replacement therapy
- Exposure to ionizing radiation [1–5]

Molecular Classification of Breast Cancer

Table: Molecular Classification of Breast Cancer and Its Therapeutic Implications

Molecular Subtype	Receptor Status	Frequency (Approx.)	Characteristics	Prognosis	Standard Treatment Options	Therapeutic Implications
Luminal A	ER+ PR+ HER2− Ki-67 low	40–50%	• Hormone receptor positive • HER2 negative • Low Ki-67 expression • Slow growing tumors	Excellent	• Endocrine therapy (Tamoxifen, AI) • Surgery • Radiotherapy • Chemotherapy (in selected high-risk cases)	• Highly responsive to endocrine therapy • Chemotherapy benefit is low • Less aggressive; long-term survival is high
Luminal B (HER2−)	ER+ PR low/− HER2− Ki-67 high	15–20%	• Hormone receptor positive • HER2 negative • High Ki-67 expression • More proliferative than Luminal A	Intermediate	• Endocrine therapy • Chemotherapy • Surgery • Radiotherapy	• Endocrine therapy beneficial but less effective than Luminal A • Higher chance of recurrence • Chemotherapy improves outcomes
Luminal B (HER2+)	ER+ PR low/− HER2+ Any Ki-67	10–15%	• Hormone receptor positive • HER2 overexpression • High proliferation • More aggressive	Intermediate	• Endocrine therapy • Anti-HER2 therapy (Trastuzumab, Pertuzumab) • Chemotherapy • Surgery • Radiotherapy	• Requires both endocrine and anti-HER2 therapy • Higher pathologic complete response with targeted therapy
HER2-Enriched (Non-Luminal)	ER− PR− HER2+	15–20%	• HER2 overexpression • Hormone receptor negative • Aggressive behavior • High proliferation	Poor	• Anti-HER2 therapy (Trastuzumab, Pertuzumab, T-DM1, etc.) • Chemotherapy • Surgery • Radiotherapy	• Does not respond to endocrine therapy • Benefit from HER2-targeted agents and chemotherapy
Triple-Negative (Basal-like)	ER− PR− HER2−	10–15%	• Negative for ER, PR, HER2 • Basal-like phenotype • Highly aggressive • Early recurrence risk	Poor	• Chemotherapy (mainstay) • Immunotherapy (e.g., Pembrolizumab in PD-L1 positive) • Surgery • Radiotherapy	• No targeted endocrine or HER2 therapy • Chemotherapy is the main treatment • Immunotherapy helpful in selected patients

Table 1. Molecular classification of breast cancer and its therapeutic implications [4–6,25,26].

Breast cancer develops as a result of inherited or acquired genetic alterations that disrupt normal cell growth, DNA repair, and cell-cycle regulation. These genetic changes not only contribute to cancer development but also influence treatment response and prognosis. Identification of specific genetic biomarkers has become an essential part of precision medicine because it helps clinicians select the most effective therapy for individual patients [7–10].

4.1 BRCA1 and BRCA2

BRCA1 and BRCA2 are tumor suppressor genes involved in repairing damaged DNA through homologous recombination. Germline mutations in these genes significantly increase the lifetime risk of breast and ovarian cancer. Patients carrying BRCA mutations are more likely to benefit from PARP inhibitors, such as olaparib and talazoparib, which selectively target cancer cells with defective DNA repair mechanisms [18,19].

4.2 HER2 (ERBB2)

The HER2 (ERBB2) gene encodes a receptor involved in cell growth and proliferation. Amplification or overexpression of HER2 occurs in approximately 15–20% of breast cancers and is associated with aggressive disease. Patients with HER2-positive tumors respond well to HER2-targeted therapies such as trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan [15–17].

4.3 PIK3CA

The PIK3CA gene encodes a catalytic subunit of phosphatidylinositol-3 kinase (PI3K). Mutations in this gene activate the PI3K/AKT signaling pathway, promoting tumor growth and survival. Patients with hormone receptor-positive, HER2-negative advanced breast cancer carrying PIK3CA mutations may benefit from the PI3K inhibitor alpelisib [20].

4.4 ESR1

The ESR1 gene encodes the estrogen receptor alpha. Mutations in ESR1 are commonly observed in metastatic breast cancer after prolonged endocrine therapy and are associated with resistance to aromatase inhibitors. Such patients may respond better to selective estrogen receptor degraders like fulvestrant [21–24].

4.5 CYP2D6

The CYP2D6 enzyme is responsible for converting tamoxifen into its active metabolite, endoxifen. Individuals with reduced CYP2D6 activity produce lower endoxifen concentrations, which may decrease the therapeutic effectiveness of tamoxifen. Pharmacogenomic testing can help identify patients who may require alternative endocrine therapy [11–13].

5. Pharmacogenomics in Breast Cancer Therapy

5.1 Role of Pharmacogenomics

Pharmacogenomics has transformed breast cancer management by enabling treatment to be tailored according to an individual's genetic profile. Instead of using the same treatment for all patients, clinicians can now select therapies based on genetic biomarkers that predict drug response, toxicity, and resistance. This personalized approach improves treatment effectiveness while minimizing unnecessary adverse effects [7,8].

The major objectives of pharmacogenomics are to:

- Select the most appropriate drug.
- Optimize drug dosage.
- Reduce adverse drug reactions.
- Prevent treatment resistance.
- Improve survival and quality of life [7–10].

5.2 Pharmacogenomics of Hormonal Therapy

Hormonal therapy is the standard treatment for hormone receptor-positive breast cancer.

Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) used in estrogen receptor-positive breast cancer. Since it is a prodrug, it requires activation by the CYP2D6 enzyme to form endoxifen, its active metabolite. Patients with reduced CYP2D6 activity may have lower endoxifen levels and a poorer response to treatment. Therefore, CYP2D6 genotyping may assist in selecting the most appropriate endocrine therapy [11–13].

Aromatase Inhibitors

Drugs such as anastrozole, letrozole, and exemestane reduce estrogen synthesis in postmenopausal women. Although variations in the CYP19A1 gene may influence treatment response, routine pharmacogenomic testing is not currently recommended [21–24].

Fulvestrant

Fulvestrant is a selective estrogen receptor degrader that blocks and degrades estrogen receptors. It is particularly useful in patients with ESR1 mutations who develop resistance to conventional endocrine therapy [21–24].

5.3 Pharmacogenomics of Chemotherapy

Despite the availability of targeted therapies, chemotherapy remains an important treatment option for many breast cancer patients. Genetic variations can influence both treatment response and toxicity.

DPYD and Fluoropyrimidines

The DPYD gene encodes dihydropyrimidine dehydrogenase (DPD), the enzyme responsible for metabolizing fluoropyrimidines such as 5-fluorouracil and capecitabine. Patients with reduced DPD activity are at increased risk of severe toxicity, including diarrhea, mucositis, neutropenia, and bone marrow suppression.

DPYD testing before treatment helps clinicians adjust drug dosage or select alternative therapy [14].

Anthracyclines

Anthracyclines such as doxorubicin and epirubicin are widely used in breast cancer treatment. Genetic factors may influence treatment response and susceptibility to cardiotoxicity, although routine pharmacogenomic testing has not yet become standard clinical practice [25,26].

Taxanes

Paclitaxel and docetaxel inhibit cell division by stabilizing microtubules. Genetic variations in ABCB1, CYP2C8, and CYP3A4 may affect drug metabolism and toxicity; however, their routine clinical use requires further evidence [25,26].

5.4 Pharmacogenomics of Targeted Therapy

Targeted therapy has significantly improved the management of breast cancer by specifically acting on molecular abnormalities present in tumor cells. Pharmacogenomic testing helps identify patients who are most likely to benefit from these therapies, leading to better treatment outcomes and fewer unnecessary side effects [15–20].

HER2-Targeted Therapy

HER2-positive breast cancer is characterized by overexpression of the HER2 receptor, resulting in rapid tumor growth. Patients with HER2-positive tumors respond well to targeted agents such as trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan. Therefore, HER2 testing is mandatory before initiating these treatments [15–17].

PARP Inhibitors

Patients carrying BRCA1 or BRCA2 mutations have impaired DNA repair mechanisms. PARP inhibitors, including olaparib and talazoparib, block an alternative DNA repair pathway, causing selective death of BRCA-mutated cancer cells while sparing normal cells [18,19].

PI3K Inhibitors

Mutations in the PIK3CA gene activate the PI3K signaling pathway, promoting tumor growth. The PI3K inhibitor alpelisib, combined with endocrine therapy, has shown improved outcomes in patients with hormone receptor-positive, HER2-negative advanced breast cancer carrying PIK3CA mutations [20].

5.5 Pharmacogenomics of Immunotherapy

Immunotherapy has emerged as a promising treatment option, particularly for triple-negative breast cancer (TNBC). The immune checkpoint inhibitor pembrolizumab is recommended for selected patients with PD-L1-positive tumors. Biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) may help predict the likelihood of response to immunotherapy and support personalized treatment decisions [25,26].

6. Clinical Applications of Pharmacogenomics

- Pharmacogenomics has several important clinical applications in breast cancer management:
- Selection of the most appropriate anticancer drug based on genetic profile.
- Individualization of drug dosage to improve safety and efficacy.
- Prediction of treatment response and resistance.
- Reduction of adverse drug reactions through genetic testing.
- Identification of hereditary cancer syndromes, particularly BRCA mutations.
- Support for targeted therapy and precision medicine.
- Improved patient survival and quality of life.

- Facilitation of genetic counseling for affected families [7–20].

Table 2. Major pharmacogenomic biomarkers used in personalized breast cancer therapy.

Table 3. Major Pharmacogenomic Biomarkers Used in Personalised Breast Cancer Therapy

S. No.	Biomarker (Gene)	Biological Role	Associated Therapy	Pharmacogenomic Significance	Clinical Utility in Personalised Therapy
1.	**HER2** *(ERBB2)*	• Encodes the HER2 receptor tyrosine kinase. • Overexpression or amplification leads to increased cell proliferation and tumor growth.	**Trastuzumab,** Pertuzumab, Ado-trastuzumab emtansine (T-DM1), Lapatinib, Tucatinib	• HER2 gene amplification or overexpression predicts response to HER2-targeted therapies. • Absence of HER2 predicts lack of benefit.	• HER2 testing (IHC 3+ or FISH+) is essential to select patients for HER2-targeted therapy. • Avoids ineffective therapy and optimizes outcomes.
2.	**CYP2D6** *(Cytochrome P450 2D6)*	• Key enzyme involved in the metabolism of tamoxifen. • Converts tamoxifen (prodrug) to active metabolite endoxifen.	**Tamoxifen** (Endocrine therapy for ER-positive breast cancer)	• CYP2D6 poor/intermediate metabolizers have reduced endoxifen levels. • Associated with lower treatment efficacy and higher risk of recurrence.	• CYP2D6 genotyping helps identify patients who may have suboptimal response to tamoxifen. • Alternative endocrine therapy can be considered.
3.	**ESR1** *(Estrogen Receptor 1)*	• Encodes estrogen receptor alpha (ERα). • Mutations (especially in ligand-binding domain) can drive endocrine resistance.	**Aromatase inhibitors** (Letrozole, Anastrozole, Exemestane), Fulvestrant (Endocrine therapy)	• ESR1 activating mutations predict resistance to aromatase inhibitors. • May predict better response to selective estrogen receptor degraders (SERDs).	• ESR1 mutation testing in advanced/metastatic ER-positive breast cancer guides endocrine therapy selection. • Helps in tailoring therapy after progression.

Abbreviations: IHC – Immunohistochemistry; FISH – Fluorescence In Situ Hybridization; ER – Estrogen Receptor; SERDs – Selective Estrogen Receptor Degraders.

7. Advantages of Pharmacogenomics

- Pharmacogenomics has become an important component of personalized breast cancer treatment because it improves therapeutic outcomes while reducing unnecessary toxicity.
- Major advantages include:
- Improved treatment effectiveness by selecting the most suitable therapy.
- Reduced risk of serious adverse drug reactions.
- Personalized treatment based on the patient's genetic profile.
- Early identification of drug resistance.
- Better quality of life due to fewer treatment-related complications.
- More cost-effective use of healthcare resources by avoiding ineffective therapies [7–20].

8. Limitations and Challenges

- Despite its benefits, the widespread implementation of pharmacogenomics still faces several challenges.
- High cost of comprehensive genetic testing.
- Limited availability of molecular diagnostic facilities, especially in developing countries.
- Lack of awareness and training among healthcare professionals.
- Ethical, legal, and privacy concerns regarding genetic information.
- Tumor heterogeneity and the development of new mutations during disease progression.

- Limited clinical evidence for some emerging pharmacogenomic biomarkers [7,8,25,26].

9. FUTURE PERSPECTIVES

- The future of pharmacogenomics is closely linked to advances in genomic technologies and precision medicine.
- Key developments include:
- Next-Generation Sequencing (NGS): Enables simultaneous analysis of multiple cancer-related genes, providing comprehensive genomic information.
- Liquid Biopsy: Detects circulating tumor DNA from blood samples, allowing non-invasive monitoring of disease progression and treatment response.
- Artificial Intelligence (AI): Assists in analyzing complex genomic data and supports personalized treatment decisions.
- Comprehensive Genomic Profiling: Combines multiple biomarkers to improve the accuracy of treatment selection.
- Precision Oncology: Integration of pharmacogenomics with molecular diagnostics, targeted therapy, and immunotherapy is expected to further improve long-term survival and quality of life [7,8,25,26].

CONCLUSION

Pharmacogenomics has transformed the management of breast cancer by enabling treatment strategies that are tailored to each patient's genetic profile. Genetic biomarkers such as BRCA1, BRCA2, HER2, CYP2D6, PIK3CA, ESR1, and DPYD play a vital role in predicting treatment response, minimizing drug toxicity, and guiding the selection of targeted and endocrine therapies. Personalized treatment has improved clinical outcomes, reduced unnecessary adverse effects, and enhanced patients' quality of life. Although challenges such as high testing costs, limited accessibility, and ethical concerns remain, continuous advances in genomic technologies are making pharmacogenomic testing more practical and widely available. In the future, integration of pharmacogenomics with artificial intelligence, comprehensive genomic profiling, and precision oncology is expected to further improve individualized breast cancer care and establish personalized medicine as the standard approach to treatment [7–26].

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