Pharmacogenomics: Personalized medicine and its impact on breast cancer

Omar Obaid Alharbi
KSA, National Guard Health Affairs

Abstract---Background: Personalized medicine in breast cancer aims to optimize treatment by classifying cancer subtypes and tailoring therapy based on individual patient profiles, including genetic and epigenetic factors. Pharmacogenomics plays a crucial role in this strategy by investigating how genetic variations affect drug metabolism and therapy response. Aim: This article reviews the impact of pharmacogenomics on personalized medicine for breast cancer, focusing on different molecular subtypes and their responses to targeted therapies. Methods: The study involved a comprehensive review of current literature, examining the molecular classification of breast cancer, the role of genetic and epigenetic factors, and advancements in pharmacogenomics. Key resources, including open-source databases and clinical trials, were analyzed to understand treatment resistance and efficacy. Results: Breast cancer is categorized into molecular subtypes such as hormone receptor-positive, HER2-positive, and triple-negative. Each subtype exhibits distinct responses to therapies. For instance, hormone receptor-positive cancers benefit from endocrine therapies, while HER2-positive cancers respond to targeted antibodies. Triple-negative breast cancer, characterized by its heterogeneity, shows varied responses to platinum-based compounds and PARP inhibitors. The study highlights the challenges of drug resistance and the potential of personalized therapies to overcome these issues. Conclusion: Pharmacogenomics significantly enhances personalized medicine for breast cancer by enabling tailored treatments based on genetic profiles. Despite progress, challenges such as drug resistance and tumor heterogeneity remain. Future advancements in genetic and genomic understanding, along with the integration of personalized strategies, are crucial for improving treatment outcomes.

Keywords---pharmacogenomics, breast cancer, personalized medicine, drug resistance, molecular subtypes, targeted therapies.
Introduction

Providing optimal treatment in personalized medicine for breast cancer is critically important. This strategy facilitates the classification of cancer subtypes, thereby enabling the selection of the most appropriate treatment regimen based on patient-specific factors, including medical history and therapy response [1][2]. Pharmacological strategies, such as pharmacogenetics and pharmacodynamics, are instrumental in tailoring therapeutic decisions. These approaches assist clinicians in choosing suitable drugs and dosages to minimize adverse effects and enhance treatment efficacy. The systematic investigation of drug absorption, distribution, and metabolism, influenced by genetic and epigenetic variations, is vital for therapeutic success [3]. Alongside genetic polymorphisms, epigenetic factors, microbiome changes, and demographic attributes contribute to multi-drug resistance [4–6]. Historically, pharmacogenetics and pharmacogenomics examine the impact of genetic variations on drug metabolism and the overall genomic response to medications [7]. These methodologies are increasingly utilized in oncology to mitigate toxicity while optimizing the effectiveness of targeted therapies and chemotherapy. They are also pivotal in drug development, leveraging genetic profiling and innovative techniques.

Molecular Classification

Breast cancer is categorized into five molecular classes based on molecular stratification: 1) hormone receptor-positive (luminal A and luminal B), 2) HER2-positive, 3) basal-like, 4) normal-like, and 5) claudin-low, which corresponds to triple-negative breast cancer (TNBC) with medullary and metaplastic differentiation [8][9][10][11][12][13]. Each molecular subtype demonstrates distinct treatment responses [9][10]. The luminal A subtype, which constitutes 40%-60% of cases and is predominantly ER+/PR+ and HER2-negative, exhibits a low pathological grade and proliferation rate, showing minimal response to chemotherapy but sensitivity to endocrine therapy [8][14][15][16][17]. Luminal B (ER+/PR+ and HER2-positive) represents 15% of cases, with higher pathological grades and proliferation rates, benefiting more from chemotherapy than anti-estrogen drugs [14][15][18]. HER2-positive tumors, making up 10% of cases, present a high pathological grade and, although chemosensitive, had poor prognoses until targeted therapies emerged [14][15][19][20][21]. Basal-like tumors, accounting for 10–25% of cases, overlap with TNBC and exhibit aggressive behavior and poor prognosis, though they are chemosensitive [13][19][22–24]. The normal-like subtype, comprising 3–10% of cases, shows intermediate prognosis, with some studies suggesting that these may be technical artifacts [12][25]. Claudin-low tumors, predominantly TNBC and constituting 7–14% of cases, show reduced expression of claudin and E-cadherin genes, with 15% expressing ER and 15% overexpressing HER2 [12][26]. These tumors exhibit an intermediate response to chemotherapy [12][13]. Despite significant advancements in therapeutic strategies for breast cancer, challenges such as both de novo and acquired resistance remain. A thorough understanding of the molecular mechanisms underlying different breast cancer subgroups is essential for developing more effective treatment approaches. Targeting specific molecules or mutated genes offers promising potential for personalized therapies. Enhanced insights into these mechanisms can drive innovative drug development and
therapeutic strategies, potentially overcoming current limitations and improving patient outcomes. As personalized medicine evolves, integrating molecular knowledge into clinical practice will be critical in addressing the complexities of breast cancer treatment and resistance.

**Heterogeneity Resources**

The heterogeneity observed in breast cancer subtypes is a leading cause of therapeutic failure and unpredictable outcomes. Variations in genetic and epigenetic features within a subset of cancer cells can alter prognosis and drug responsiveness [5][29]. This heterogeneity can be categorized as intra-tumoral—where it affects cells within a single tumor—or inter-tumoral, affecting cells from the same cancer subtype across different patients. Intra-tumor heterogeneity may be "spatial," affecting specific regions of the tumor, or "temporal," involving changes in cells over time, from the primary tumor to metastatic sites. Heterogeneity at the morphological level is assessed through histopathological comparisons and grading systems [30]. At the genetic level, variations include copy number alterations (CNVs), gene overexpression or down-regulation, and mutations such as missense, nonsense, and frameshift [5]. Open-source databases like COSMIC and TCGA provide comprehensive data on high-throughput techniques and genetic variations. These databases categorize heterogeneity into local and systemic sources [5]. The COSMIC database offers extensive information from numerous breast cancer tumors analyzed across different platforms, detailing various analyses, mutations, CNVs, and expression levels. This variability, whether spatial or temporal, contributes to diverse tumor responses to treatment regimens.

The pharmacogenomics approach identifies genetic variations in driver genes that promote selective tumor growth. This information aids clinicians in choosing effective therapeutic regimens to counteract resistance. Considerations include selecting appropriate drug combinations and targeting subclonal populations that may develop adaptive responses or experience toxicity [3]. Accurate detection of subclonal populations, such as through ex vivo tumor culture methods, remains a critical challenge [31][32]. Passenger mutations, present in genes that support tumor survival, are acquired during normal cell states or after neoplastic transformation [5]. Additionally, genes associated with cancer development may not always be mutated but can be inactivated through epigenetic mechanisms.

Hereditary breast cancer is linked to genetic mutations in genes such as BRCA1, BRCA2, PALB2, TP53, CDH1, and PTEN, which are associated with increased breast cancer risk [33]. Epigenetic mechanisms also play a significant role, as evidenced by the frequent hypermethylation and silencing of the tumor suppressor gene RASSF1A in breast cancer [34]. Familial breast cancer is often attributed to mutations in BRCA1 and BRCA2, while sporadic cases show a 10–15% rate of BRCA1 methylation. Key molecular pathways involved in breast cancer progression include the PI3K/AKT/mTOR and RAS/RAF/MEK pathways, which are frequently aberrantly activated and linked to drug resistance [35]. Clinical trials are exploring PI3K inhibitors targeting these pathways, and PTEN inactivation by epigenetic mechanisms may extend the use of effective inhibitors.
for PTEN-deficient cancers. Additionally, PPP2R2B, a negative regulator of AKT, is often subject to promoter methylation in breast cancer [36].

In gene families, mutations and methylation overlaps can lead to variable responses, as exemplified by RUNX1 mutations and RUNX3 inactivation through epigenetic mechanisms [15][37]. DNA methylation analysis in blood samples using bisulfite-based PCR techniques is a powerful tool for investigating these variations [15]. Tumor heterogeneity is further influenced by the tumor microenvironment, including tumor-associated macrophages, fibroblasts, bone marrow-derived cells, lymphatic growth factors, chemokines, cytokines, and exosomes, which contribute to tumor growth and metastasis [5]. Future advancements in genetic, genomic, and immunologic consultation are anticipated to guide oncologists in devising tailored treatment strategies. Pharmacogenomics will play a crucial role in the development of personalized therapies, enhancing treatment efficacy and overcoming resistance challenges.

Pharmacogenetics in Breast Cancer Subtypes

Estrogen Receptor Positive (ER+) Subtype

Estrogen receptor-positive (ER+) breast cancer is the most prevalent subtype and is characterized by the expression of estrogen receptors, which serve as a predictive marker for patient monitoring and disease-free status [38][39]. This subtype typically benefits from hormonal therapies, such as the synthetic estrogen analog tamoxifen (TAM). TAM binds to the estrogen receptor and disrupts the classical signaling pathway that promotes ductal hyperplasia, thereby altering the tumor microenvironment and affecting the invasive state of the cancer [38][39]. ER overexpression also engages non-classical functions that affect genomic activity independently of hormones, through growth factor signaling pathways like FGFR, IGFR, and GPCRs, which activate intracellular kinases and phosphatases. Research has demonstrated that kinases influence ER phosphorylation, which correlates with either sensitivity or resistance to endocrine therapies [40]. Baron et al. have reviewed phosphorylation sites and mRNA splicing regions in ER, linking these to drug responses.

The interaction between ER and other transcription factors, such as C-Fos/C-Jun (AP-1), Sp1, and NF-KB, contributes to tumor cell proliferation, angiogenesis, and metastasis [40]. In addition to TAM, Fulvestrant, an ER down-regulator, has been approved for ER+ breast cancer treatment. Fulvestrant binds to ER, preventing its dimerization and promoting its degradation. Aromatase inhibitors like Anastrozole, which block estrogen conversion from adrenal androgens, are also used, particularly in postmenopausal women [39]. TAM’s efficacy is consistent regardless of menopausal status. Variations in hormone receptor subtypes, such as progesterone receptor (PR) expression, influence treatment outcomes. ER+ tumors that also express PR generally have a better prognosis, while PR-negative tumors, which do not respond as well to TAM, benefit from Anastrozole [41].

Primary endocrine resistance occurs in approximately 50% of ER+ cases, with an additional 50% developing acquired resistance over time. Factors contributing to resistance include mutation rates, methylation, acetylation, downregulation of ERα, overexpression of ERβ, and interactions between ER and growth factor
signaling pathways [40][42]. ARN-810, a selective ERα antagonist, targets ESR1 mutations, providing efficacy where traditional endocrine therapies fall short [43]. ESR1 mutations in the ligand-binding domain (e.g., Y537S, Y537N, Y537C, and D538G) are linked to ligand-independent transcriptional activity and are a major resistance mechanism in recurrent and metastatic cancer [44][46]. These mutations, though rare in primary tumors, are prevalent in over 20% of cases with recurrence and are more common in metastatic cancer compared to primary cases. Detection of ESR1 mutations in plasma cfDNA can guide treatment strategies, with Fulvestrant showing improved tumor-free survival in ESR1-mutant cases [48][49]. The combination of Fulvestrant with Palbociclib has been beneficial for metastatic cancer patients with ER mutations [50]. The COSMIC database reports that ESR1 mutation Y537S affects IGF1R phosphorylation, correlating with shorter overall survival and resistance to targeted therapies [51][42]. Other mutations, such as K303R, reduce TAM sensitivity through AKT phosphorylation [52]. Additionally, PIK3CA mutations are common in ER+ cases, with the Luminal B subtype showing moderate PTEN reduction and enhanced PI3K signaling. Combination therapies involving mTOR, AKT, or MEK inhibitors with Fulvestrant improve outcomes, as Luminal B tumors are more aggressive and resistant compared to Luminal A [53][54].

Pharmacogenetics plays a crucial role in the management of ER+ breast cancer by identifying genetic variations that influence drug responses and resistance mechanisms. The variability in ER+ breast cancer subtypes necessitates tailored therapeutic approaches to address primary and acquired resistance. Advanced therapies, such as Fulvestrant and PI3K inhibitors, combined with targeted strategies for specific mutations, represent promising advancements in overcoming resistance. Despite significant progress, challenges remain in predicting and managing resistance, emphasizing the need for continued research into biomarkers and personalized treatments. The integration of pharmacogenomics into clinical practice holds the potential to enhance treatment efficacy and patient outcomes, particularly for those with resistant or advanced disease. Addressing drug resistance remains a critical focus to improve long-term survival and quality of life for ER+ breast cancer patients.

**HER2 Positive Breast Cancer**  
**HER2 Amplification and Resistance**

HER2-positive breast cancer, characterized by the overexpression of the HER2 receptor, accounts for over 14% of metastatic cases. This amplification is linked to increased cell proliferation, angiogenesis, invasion, and reduced apoptosis [64]. In HER2-negative tumors, compensatory oncogenes such as BRF2 and DSN1 may be amplified or overexpressed, providing a neoplastic advantage [29].

HER2+ patients respond well to targeted therapies, including HER2 antibodies and kinase inhibitors such as lapatinib, pertuzumab, trastuzumab, ado-trastuzumab, and emtansine [65]. Trastuzumab (Herceptin™) was the first humanized monoclonal antibody developed against HER2 and received FDA approval as a targeted therapy for breast cancer [66][67]. Clinical studies have shown that combining trastuzumab with standard chemotherapy often results in better outcomes than chemotherapy alone [68][70]. However, resistance to
trastuzumab can develop, predominantly due to mechanisms related to HER2 signaling pathways, and is associated with mutations in PIK3CA, RAS, Src, NF-KB, and inactivating mutations in PTEN \[71\][75].

Resistance to trastuzumab can also occur due to truncated isoforms of HER2 that lack the trastuzumab target epitope, resulting in stable HER2 homodimers \[76\][77][78]. Additionally, overexpression of EGFR and HER-3, and their interactions with adhesion molecules like MUC1-C or MUC4, contribute to resistance \[73\][80]. Strategies to overcome resistance include:

1. PI3K and mTOR Pathway Inhibitors: Pan PI3K inhibitors, specific PIK3CA inhibitors, AKT inhibitors, and mTOR inhibitors can address resistance due to PIK3CA alterations.
2. Lapatinib: Combines with trastuzumab to overcome high levels of p95HER2.
3. Tyrosine Kinase Inhibitors: Target IGF1R tyrosine kinase receptor.
4. MET Inhibitors: Address MET alterations.
5. Immune Checkpoint Inhibitors: Target low immune responses \[81\].

Trastuzumab-DM1 (T-DM1), a novel monoclonal antibody conjugated with maytansine, requires high HER2 expression for efficacy. Low intra-tumor HER2 levels and poor internalization of the HER2-drug can lead to resistance \[83\][84]. CYD985, another antibody-drug conjugate, has shown promise in T-DM1-pretreated patients \[85\]. Lapatinib inhibits EGFR and HER2 autophosphorylation, and its combination with trastuzumab targets both intracellular and extracellular HER2 domains \[86\][88]. However, resistance to lapatinib can occur due to HER2 overexpression and AXL activation \[89\][90]. Pertuzumab, which binds to a different HER2 extracellular domain than trastuzumab, inhibits HER2 dimerization and can partially reverse trastuzumab resistance \[91\][92]. Combining pertuzumab with lapatinib has shown effectiveness in overcoming resistance \[93\]. Ertumaxomab, still under clinical evaluation, might offer additional targeted therapy options \[93\]. Neratinib, a reversible tyrosine kinase inhibitor, has demonstrated improved disease-free survival in patients with recurrent and metastatic tumors \[94\][96]. Afatinib, another kinase inhibitor, has been effective in both preclinical and clinical studies, showing longer effects compared to other EGFR inhibitors \[97\][98][99].

**Triple-Negative Breast Cancer (TNBC)**

Triple-negative breast cancer (TNBC) encompasses three subtypes: normal-like, basal-like, and non-basal-like. About 75% of basal-like cancers are triple-negative, and 80% of these cases exhibit TP53 mutations (nonsense and frameshift) \[100\]. Basal-like and non-basal TN cancers show distinct mutations related to homologous recombination deficiency (HRD) and repair (HRR). Homologous recombination is crucial for repairing double-strand DNA breaks (DSBs), and clinical trials have highlighted HRD as a predictor of therapeutic response \[100\][102].

COSMIC database analysis identifies several genes involved in TNBC variations, including TP53, BRCA1, PIK3CA, RB, and PTEN. In TN tumors, TP53 and BRCA1 mutations do not correlate, though BRCA1 methylation has been associated with
TP53 mutations [103][104]. Increased PIK3CA mutations, loss of PTEN and INPP4B, and EGFR overexpression activate the PI3K pathway. In basal-like tumors, 72% are RB-/P16+ with high p53 expression, correlating with high proliferation. Mutations in BRCA1, PTEN, and ERBB2 are linked to a higher risk of metastasis [100].

Platinum-based compounds, which induce DSBs, are relevant for treating cells with defective DNA repair mechanisms. PARP inhibitors are effective in cancers with defective DSB repair by blocking PARP1 activity, leading to accumulation of unrepaired single-strand breaks and DSBs, particularly in BRCA1 or BRCA2 defective cells [15]. While PARP inhibitors showed initial promise in TNBC, subsequent trials have not consistently confirmed these results, making it unclear which subsets of TNBC or inherited BRCA mutations benefit from these treatments [106][107]. Platinum-based agents, such as cisplatin, target lesions that are ineffectively repaired due to DSB formation, but mutations in TP53 can lead to cisplatin resistance [108]. Targeted therapies combined with chemotherapy may overcome PI3K/AKT/mTOR pathway mutations in TNBC [5].

**Chemotherapy in Breast Cancer Treatment**

Chemotherapy remains a cornerstone in the treatment of both primary and metastatic breast cancer, utilizing a range of systemic medications to target and eliminate cancer cells [108]. Several classes of chemotherapy drugs are used, each with distinct mechanisms and challenges:

1. Anthracyclines: This class includes doxorubicin, epirubicin, and mitoxantrone. Anthracyclines are known for their pleiotropic effects, inducing cell death through various mechanisms [109][110][112]. Resistance to anthracyclines often arises from increased expression of P-glycoprotein, leading to drug efflux [113]. Strategies to overcome resistance include the use of novel topoisomerase II inhibitors like fostriecin and merbarone, non-cross-resistant drugs, and modifications in drug delivery [114][119].
2. Taxanes: Paclitaxel, docetaxel, and nab-paclitaxel are taxanes that bind to microtubules, inhibiting mitosis and disrupting cell division [120]. Resistance mechanisms include alterations in beta-tubulin expression and upregulation of caveolin-1. Overcoming resistance involves using agents like cyclosporine A, PC833, and verapamil, as well as new microtubule inhibitors like ixabepilone and eribulin [121][123].
3. Antimetabolites: Drugs such as methotrexate (MTX) and 5-fluorouracil (5-FU) target specific enzymes involved in DNA synthesis. Resistance to MTX can result from decreased drug uptake, increased efflux, and reduced polyglutamation [126][134]. 5-FU resistance is often due to alterations in its metabolism [135]. Strategies to overcome resistance include manipulating drug metabolism, using high doses, and developing new antimetabolites [136].
4. Alkylating Agents and Platinum-based Drugs: These drugs alkylate DNA, forming reactive intermediates that interfere with DNA repair [109]. Tumors may develop resistance through decreased drug accumulation, increased drug inactivation, and enhanced DNA repair mechanisms [137][139].
alkaloids (e.g., vincristine, vinblastine) also face multidrug resistance due to decreased drug accumulation, with potential solutions including DNA polymerase alpha inhibitors like gemcitabine [141][142].

**New Challenges in Precision Medicine**

Despite advances, significant challenges remain in precision medicine:

1. **Drug Safety and Efficacy**: The development of safe and effective drugs is critical. For instance, metformin, an antihyperglycemic drug, has shown potential in reducing cancer rates, including breast cancer [143]. It inhibits cancer cell proliferation and invasion, potentially through its effects on tumor suppressor microRNA miR-200c [144]. Understanding the molecular mechanisms of metformin and developing advanced generations of the drug could improve therapeutic outcomes [145].

2. **Personalized Medicine Factors**: Personalized approaches must consider factors like diet, psycho-social status, and hormonal influences. Vitamin D, which affects nearly all cells, plays a role in breast cancer prevention [146]. Epidemiological studies suggest that vitamin D and related genes impact disease risk. Psycho-social factors such as stress, depression, and anxiety also significantly influence breast cancer development and treatment response [147][149]. Dopamine and serotonin have emerged as potential targets, with studies showing changes in receptor gene expression related to spiritual interventions and serotonin levels [150][151].

3. **Microbiome Profiling**: The role of the microbiome in breast cancer etiology is gaining attention. Differences in bacterial profiles between tumor-adjacent tissues and healthy controls may provide insights into disease mechanisms [152].

4. **Systems Biology**: Modern diagnostics and therapeutics leverage systems biology, which integrates data from various sources to understand complex biological interactions. This approach aids in developing personalized treatments by analyzing interactions between cellular components and identifying novel biomarkers and therapeutic targets [153-155].

Overall, integrating these advancements into clinical practice will enhance the precision of breast cancer treatment and improve patient outcomes.

**Conclusion**

Pharmacogenomics has transformed the landscape of personalized medicine in breast cancer by enabling the development of targeted treatments based on individual genetic profiles. This approach has been instrumental in improving the efficacy of therapies and reducing adverse effects. Breast cancer’s classification into molecular subtypes—such as hormone receptor-positive (ER+), HER2-positive, and triple-negative—has facilitated a more precise application of treatments. Each subtype demonstrates distinct molecular characteristics and therapeutic responses, which are critical for designing effective treatment strategies. The integration of pharmacogenomics into clinical practice addresses the complexities of breast cancer, particularly in overcoming drug resistance and managing tumor heterogeneity. For ER+ breast cancer, targeted therapies like
tamoxifen and aromatase inhibitors have been beneficial, though resistance remains a significant challenge due to mutations and variations in hormone receptor expression. HER2-positive breast cancer has seen substantial improvements with targeted therapies like trastuzumab, but resistance due to mutations and alterations in signaling pathways continues to pose challenges. In triple-negative breast cancer (TNBC), the variability in responses to treatments such as platinum-based drugs and PARP inhibitors highlights the need for ongoing research and development. Despite these advancements, several challenges persist. Drug resistance, due to both genetic and epigenetic factors, and the intrinsic heterogeneity of tumors complicate treatment outcomes. The role of pharmacogenomics in addressing these issues is vital for developing more effective personalized therapies. Future research should focus on improving our understanding of tumor biology, enhancing the accuracy of genetic profiling, and integrating these insights into clinical practice. Overall, pharmacogenomics holds promise for advancing personalized medicine in breast cancer, offering hope for better-targeted treatments and improved patient outcomes. Continued innovation in genetic research and therapeutic strategies will be essential in addressing current limitations and achieving more precise and effective cancer care.

References


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