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Review

Integrating Germline and Somatic Pharmacogenomics to Predict Tamoxifen Response in Breast Cancer

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Abstract

Tamoxifen remains a cornerstone in the treatment of estrogen receptor-positive (ER+) breast cancer; however, variability in patient response underscores the necessity of a pharmacogenomic approach. This review integrates germline and somatic pharmacogenomics to elucidate the molecular determinants of tamoxifen metabolism, efficacy, and resistance. Germline polymorphisms, particularly in *CYP2D6*, *CYP3A4/5*, *UGT2B7*, and *SULT1A1*, significantly influence endoxifen levels, driving therapeutic variability across ethnic populations. Moreover, somatic mutations, notably in *ESR1*, *TP53*, and enhancer regions, confer acquired resistance and affect treatment outcomes. Ethnicity-specific distributions of these variants further highlight the inadequacy of a one-size-fits-all dosing strategy. Although CPIC and DPWG guidelines focus on *CYP2D6* genotyping, they do not incorporate critical somatic data and phase II metabolism. To achieve truly personalized tamoxifen therapy, clinical algorithms must evolve to integrate germline and somatic profiles,

enabling predictive, population-aware, and mutation-guided endocrine treatment. This review advocates for expanded multi-omics frameworks and multiethnic databases to optimize tamoxifen use and overcome endocrine resistance globally.

Keywords
Tamoxifen; pharmacogenomics; breast cancer; ethnic variability; precision medicine

1. Introduction

Tamoxifen, a nonsteroidal triphenylethylene derivative, competes with estrogen to inhibit estrogen receptor (ER) activity associated with tumor cell growth. Tamoxifen's antiestrogenic activity, mediated by ER, is well-established. It is the primary reason for tamoxifen treatment in ER-positive breast cancers, and it has been approved by the U.S. Food and Drug Administration (FDA) for use in women and men with breast cancer. Consequently, tamoxifen has become a standard hormone therapy for preventing relapse in ER-positive cancers [1]. Consistent with this, ASCO guidelines recommend tamoxifen for treating hormone receptor-positive metastatic breast cancer in various situations, including in premenopausal patients [2].

The early use of tamoxifen is urgent due to its proven effectiveness in reducing breast cancer incidence. A study by Khallouki et al. [3] demonstrated tamoxifen's ability as an efficient chemopreventive agent, showing a 43% reduction in breast cancer risk in users versus nonusers over 5 years. Tamoxifen is most effective when administered to premenopausal women with a family history of cancer or cancer-predisposing genetic mutations [3]. Therefore, tamoxifen can be used as the primary hormonal therapy for estrogen receptor-positive (ER+) breast cancer [4].

However, its effectiveness depends heavily on the patient's metabolic processes. Tamoxifen is a prodrug that must be metabolized by the xenobiotic detoxification system into the active metabolite endoxifen [5]. Therefore, genetic variation at the germline and somatic levels may affect the effectiveness of this therapy and how patients respond to it [6].

Germline genetic variations in the CYP2D6*4, *10, and *17 genes can decrease or eliminate enzymatic activity, reducing endoxifen levels in the body. Patients can be classified as poor metabolizer phenotypes based on the combination of alleles. These individuals have a higher risk of breast cancer recurrence due to the inability to convert tamoxifen into its active form, which significantly decreases its therapeutic effectiveness [7]. Beyond germline variations, somatic mutations within tumor cells also influence tamoxifen responsiveness [8]. For example, mutations in the ESR1 gene can lead to ligand-independent activation of the estrogen receptor, resulting in resistance to selective estrogen receptor modulators such as tamoxifen [9].

Both germline and somatic mutations significantly contribute to variability in cancer therapy response. Somatic mutations often act as oncogenic drivers and can generate resistance to targeted therapies by activating alternative signaling pathways or modifying molecular targets. In contrast, germline mutations affect pharmacokinetics and pharmacodynamics, as well as predisposition to intrinsic resistance. Together, these factors can hinder therapeutic effectiveness. A major factor in therapeutic failure is the mismatch between a patient's genetic profile and a drug's mechanism of

action, which emphasizes the need to integrate germline and somatic analyses into personalized therapeutic approaches [10].

Germline variants are crucial for understanding hereditary cancer predisposition. However, their interpretation is often hindered by the classification of many variants as variants of uncertain significance (VUS), which limits their clinical utility [11]. Conversely, somatic mutations, reflecting tumor-specific genetic alterations, provide valuable information about tumorigenic mechanisms and potential therapeutic targets [12]. Combining germline and somatic data enables clinicians to reclassify VUS more accurately, identify actionable pathogenic variants, and better understand the penetrance and expressivity of hereditary cancer genes. Consequently, joint analysis refines diagnostic precision and enhances treatment stratification, enabling personalized, effective therapeutic strategies for cancer patients [13]. These insights underscore the need to incorporate both germline and somatic genetic profiling into clinical decision-making to tailor tamoxifen therapy, improving efficacy and reducing resistance [14].

The distribution of genetic variants affecting response to tamoxifen, such as CYP2D6, varies widely among populations. For instance, alleles with low enzymatic activity have been observed in up to 50% of Asian and African populations. The prevalence of intermediate metabolizers is 35%, 45.38%, and 15% among Malays, Chinese, and Indians, respectively. These differences suggest that pharmacogenomics-based therapeutic guidelines cannot be generalized without considering ethnic context. Similarly, somatic mutation profiles that contribute to therapy resistance or sensitivity may differ between populations. Meanwhile, Caucasians generally exhibit a wide range of metabolism [15]. These variations confirm that therapeutic algorithms developed from only one population will be inaccurate and lack global biological coverage. Therefore, biopsying tumors from various ethnic groups is important for mapping the somatic mutation landscape and building a personalized therapeutic algorithm system based on complete genetic profiles. This underscores the importance of a global database to avoid population bias in clinical guidelines.

2. Method

This review was conducted as a comprehensive narrative synthesis of the current evidence on germline and somatic pharmacogenomics associated with tamoxifen therapy in breast cancer. Relevant literature between 2013 and 2026 was identified through a non-systematic, yet targeted, search of PubMed, Google Scholar, and Scopus databases using combinations of the following keywords: *“tamoxifen”*, *“polymorphism”*, *“pharmacogenomics”*, *“germline mutation”*, *“somatic mutation”*, *“precision medicine”*, *“breast cancer”*, and *“endocrine resistance”*. Articles were selected based on their relevance to the objectives of the review, which aimed to integrate data on germline variants (particularly CYP450-related) and somatic alterations (such as ESR1, TP53, and PIK3CA) in relation to tamoxifen metabolism, response, and clinical outcomes.

We also included authoritative clinical pharmacogenetic guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), and U.S. FDA to provide a regulatory and translational context. We applied no restrictions on study design, sample size, or publication date, but preferred peer-reviewed human studies and original data that directly addressed gene-drug-outcome relationships.

Data from selected articles were synthesized narratively and summarized in comparative tables. Where possible, we highlighted mutation frequencies and population-specific patterns to reflect

interethnic variability. No formal bias assessment tool was used, as this review did not aggregate effect sizes but instead explored and integrated current knowledge in the field.

3. Discussion

3.1 Metabolism of Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), functions as a prodrug that requires extensive hepatic biotransformation to exert its antiestrogenic effects in estrogen receptor-positive (ER+) breast cancer. Tamoxifen metabolism involves a sequential two-phase process: Phase I oxidative metabolism, primarily mediated by cytochrome P450 (CYP) enzymes, and Phase II conjugation reactions for metabolite detoxification and elimination (Figure 1; Table 1). Phase I metabolism converts tamoxifen into several hydroxylated and demethylated metabolites with distinct biological potencies. Notably, CYP3A4/5 catalyzes the initial conversion to N-desmethyltamoxifen, which is subsequently hydroxylated by CYP2D6 to form endoxifen, the most pharmacologically active metabolite with up to 100-fold higher affinity for ER compared to tamoxifen itself [16, 17].

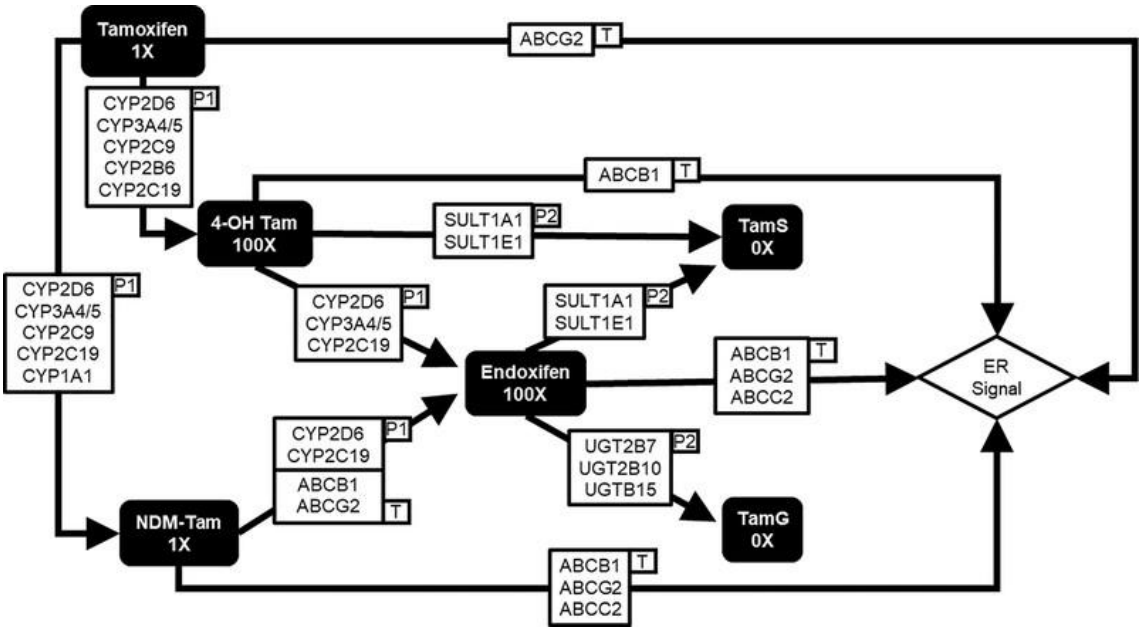

Figure 1 Tamoxifen metabolism pathway and its conversion to active or inactive metabolites [17]. The metabolic cascade of tamoxifen is illustrated with black boxes representing tamoxifen and its key metabolites, each annotated with their relative affinities for the estrogen receptor (ER). Directional arrows indicate the enzymatic transformations between metabolites and their interactions with the ER signaling pathway. Superimposed white boxes along these arrows denote the polymorphic genes encoding the metabolic or transport enzymes responsible for each conversion step. These gene boxes are marked with flags to categorize their functional roles: P1 for phase I metabolism, P2 for phase II metabolism, and T for transport processes. Additional abbreviations include: 4-OH Tam (4-hydroxy tamoxifen), NDM-Tam (N-desmethyltamoxifen), TamS (tamoxifen sulfate), and TamG (tamoxifen glucuronide).

Table 1 Key Enzymes and Transporters Involved in Tamoxifen Metabolism and Disposition.

Gen	Enzyme	Function
CYP2D6	CYP2D6	Converts tamoxifen to 4-hydroxytamoxifen and endoxifen
CYP3A4/5	CYP3A4/5	Converts tamoxifen to N-desmethyltamoxifen
CYP2C9, CYP2C19	CYP2C subfamily	Secondary hydroxylation pathway
UGT2B7	UDP-glucuronosyltransferase	Glucuronidation of 4-hydroxytamoxifen and endoxifen
SULT1A1	Sulfotransferase	Sulfation of active metabolites

The major metabolic pathway, responsible for approximately 90% of circulating endoxifen, proceeds via the sequential action of CYP3A4/5 and CYP2D6. In contrast, the minor pathway, which generates 4-hydroxytamoxifen via direct hydroxylation, contributes far less to endoxifen levels because alternative CYP enzymes are less efficient. Endoxifen and 4-hydroxytamoxifen exert potent antiestrogenic effects by competitively binding to ER and suppressing estrogen-driven transcriptional signaling, ultimately reducing tumor proliferation [17].

Following Phase I activation, tamoxifen metabolites undergo Phase II conjugation by enzymes such as UGT2B7 (glucuronidation) and SULT1A1 (sulfation), facilitating their excretion via renal and biliary pathways. These conjugation processes modulate drug bioavailability by decreasing the half-life of active metabolites, hence affecting therapeutic response. Importantly, all major enzymes involved in both metabolic phases exhibit polymorphic variation, which contributes to interindividual and interethnic variability in tamoxifen pharmacokinetics [16].

As illustrated in Figure 1, each enzymatic step is linked to specific polymorphic genes, whose variants can drastically influence metabolite formation. For example, CYP2D6 poor metabolizer genotypes (e.g., *4/*4, *5/*5, *10/*10) are associated with markedly reduced plasma endoxifen concentrations, translating into inferior clinical outcomes, including a higher risk of disease recurrence [16, 17]. On the other hand, individuals with *1/*1 or *1/*2 (normal metabolizers) achieve optimal endoxifen exposure and improved treatment efficacy. Despite this, some studies suggest that even patients with impaired CYP2D6 function may benefit from standard-dose tamoxifen, possibly due to the saturating levels achieved at conventional doses [17].

ATP-binding cassette (ABC) transporters, including ABCB1, ABCC2, and ABCG2, also play critical roles in regulating tamoxifen disposition. These transporters mediate the efflux of tamoxifen and its metabolites from hepatocytes and enterocytes, influencing systemic drug exposure, target tissue penetration, and ultimately therapeutic response [16]. For example, ABCB1 is expressed in 28-63% of breast tumours and has been shown to transport both tamoxifen and endoxifen, potentially modulating intratumoral drug concentrations.

Collectively, these insights underscore that the efficacy of tamoxifen therapy is a function of metabolic activation, systemic disposition, and cellular transport, all of which are governed by genetically polymorphic proteins. Therefore, personalized tamoxifen dosing and selection strategies based on integrated pharmacogenomic profiling considering both metabolic enzymes and transporters are essential for optimizing outcomes, particularly in ethnically diverse patient populations.

3.2 Germline Polymorphism in Tamoxifen Metabolism

As detailed in Table 2, germline polymorphisms in drug-metabolizing enzymes, particularly *CYP2D6*, play a pivotal role in modulating tamoxifen activition into its potent metabolite, endoxifen. The *CYP2D6* *10/*10 genotype, classified as an intermediate metabolizer (activity score 0.5), is highly prevalent in East and Southeast Asian populations, including Chinese (19.71%), Japanese (20.51%), Thai (44.5%), and Malaysian-Chinese (35.01%) [18]. This genotype is associated with reduced enzymatic activity and lower plasma endoxifen concentrations, contributing to suboptimal clinical outcomes [7].

Table 2 Summary of germline polymorphisms associated with tamoxifen metabolism, including their prevalence, affected populations, and clinical consequences.

Gene	Polymorphism	Enzyme Activity Score	Phenotype	Population	Clinical Effect	References
Phase I Metabolism						
CYP2D6	*2/*41	1.5	Normal Metabolizer	Iraqi (34.29%)	Effective	[19]
CYP2D6	*2XN/*39	3.0	Ultrarapid Metabolizer	Iraqi (9.29%)	More toxic and side effects reaction	[19]
CYP2D6	*2/*10	1.25	Normal Metabolizer	Chinese (15.51%), Japanese (8.92%), Korean (9.89%), Thai (8.90%), Malay-Malaysian (17.30%), Chinese-Malaysian (14.28%)	Effective	[18]
CYP2D6	*1/*1	2	Normal Metabolizer	Syrian (22.7%), Indonesian (0.09%), Chilean (33%), Chinese (36.54%), Japanese (31.37%), Korean (12.06%), Taiwanese (13.63%), Thai (8.14%), Filipino (20.12%), Vietnamese (68.72%), Malay-Malaysian (11.32%), Chinese-Malaysian (16.34%),	Effective	[15, 20, 21]

				Malay-Singaporean (10.31%), Chinese-Singaporean (6.96%), Indian-Singaporean (21.78%), Caucasians (22.8%), African-American (51%)		
CYP2D6	*1/*2	2	Normal Metabolizer	Syrian (38.1%), Chinese (5.17%), Japanese (11.83%), Korean (5.78%), Thai (5.42%), Chinese Malaysian (9.52%), Indian Malaysian (14.28%), Malay-Singaporean (10.31%), Indian-Singaporean (17.31%)	Effective	[15, 20, 21]
CYP2D6	*2/*2	2	Normal Metabolizer	Indian-Malaysian (14.28%)	Effective	[18]
CYP2D6	*1/*41	1.5	Normal Metabolizer	Syrian (14.4%)	Effective	[15]
CYP2D6	*1/*10	1.25	Normal Metabolizer	Chinese (40.92%), Japanese (35.24%), Korean (27.32%), Taiwanese (23.10%), Thai (19.37%), Filipino (56.09%), Vietnamese (61.97%), Malay-Malaysian (34.59%), Chinese-Malaysian (37.74%), Malay-Singaporean (9.52%), Chinese-Singaporean (8.9%), Caucasians (14%)	Effective	[21]

CYP2D6	*1/*4	1	Intermediate Metabolizer	Chilean (7%) Caucasian (12.1%)	Ineffective	[20, 21]
CYP2D6	*2/*4	1	Intermediate Metabolizer	Caucasians (10.5%)	Ineffective	[21]
CYP2D6	*10/*10	0.5	Intermediate Metabolizer	Chinese (19.71%), Japanese (20.51%), Korean (21.03%), Taiwanese (56.06%), Thai (44.50%), Filipino (14.63%), Vietnamese (14.08%), Malay-Malaysian (26.41%), Chinese-Malaysian (35.01%), Malay-Singaporean (7.93%)	Ineffective	[18]
CYP2D6	*1/*5	1	Intermediate Metabolizer	Japanese (6.40%), Vietnamese (12.67%)	Reduce endoxifen level	[18]
CYP2D6	*1/*17	1.5	Normal to Intermediate Metabolizer	African-American (11.6%)	Slightly reduced endoxifen formation	[21]
CYP3A4	*1/*1	2	Normal Metabolizer	Chilean (35%)	Effective	[20]
CYP3A4	*1/*1B	2	Normal Metabolizer	Chilean (5%)	Effective	[20]
CYP3A5	*1/*3	1	Intermediate Metabolizer	Chilean (18%), Chinese (32.30%), Japanese (35.59%), Korean (31.42%), Taiwanese (43.88%), Thai (43.58%), Malay-Singaporean (50%), Chinese-Singaporean (33.65%), Indian-Singaporean (46.46%),	Ineffective	[18, 20]

				Vietnamese (47.22%)		
CYP3A5	*3/*3	0	Poor Metabolizer	Chilean (22%), Chinese (54.90%), Japanese (58.40%), Korean (62.85%), Taiwanese (47.22%), Thai (37.17%), Malay-Singaporean (34.82%), Chinese-Singaporean (57.28%), Indian-Singaporean (39.03%), Vietnamese (43.05%)	Greatly reduced endoxifen formation	[18, 20]
CYP3A5	*1/*1	2	Normal Metabolizer	Chinese (12.79%), Japanese (5.99%), Korean (5.71%), Taiwanese (8.88%), Thai (19.23%), Malay-Singaporean (15.17%), Chinese-Singaporean (9.06%), Indian-Singaporean (14.49%), Vietnamese (9.72%)	Effective	[18]
CYP2C9	*1/*1	2	Normal Metabolizer	Chinese (90.91%), Japanese (95.10%), Korean (91.49%), Taiwanese (93.97%), Vietnamese (95.54%), Indonesians (92.62%), Thai (95.16%), Malay-Malaysian (91.76%),	Effective	[18]

				Chinese-Malaysian (91.39), Indian-Malaysian (85%), Malay-Singaporean (88.88%), Chinese-Singaporean (94.69), Indian-Singaporean (69.27%)		
CYP2C9	*1/*2	1.5	Intermediate Metabolizer	Indian-Singaporean (7.26%)	No clinically significant effect expected	[18]
CYP2C9	*1/*3	1	Intermediate Metabolizer	Chinese (6.45%), Korean (7.75%), Taiwanese (5.78%), Indonesians (7.37%), Malay-Malaysian (5.88%), Chinese-Malaysian (7.52%), Indian-Malaysian (10%), Malay-Singaporean (10.31%), Chinese-Singaporean (5.84%), Indian-Singaporean (20.11%)	No impact expected on tamoxifen metabolism	[18]
CYP2C19	*1/*1	2	Normal Metabolizer	Chinese (43.76%), Japanese (39.74%), Korean (38.73%), Taiwanese (36.51%), Vietnamese (55.01%), Thai (44.64%), Burmese (44.09%), Karen (51.14%), Malay-Singaporean (42.85%), Chinese-Singaporean (52.53%), Indian-Singaporean (21.78%)	Effective	[18]

CYP2C19	*1/*2	1	Intermediate Metabolizer	Chinese (39.10%), Japanese (37.85%), Korean (36.88%), Taiwanese (44.94%), Vietnamese (43.45%), Thai (42.23%), Burmese (39.37%), Karen (39.69%), Malay-Singaporean (38.09%), Chinese-Singaporean (41.88%), Indian-Singaporean (30.72%)	Slightly reduced 4-OH-TAM	[18]
CYP2C19	*1/*3	1	Intermediate Metabolizer	Chinese (5.46%), Japanese (14.23%), Korean (10.03%), Taiwanese (6.74%), Vietnamese (8.01%), Thai (4.21%), Burmese (5.51%), Chinese-Singaporean (7.7%)	Slightly reduced 4-OH-TAM	[18]
CYP2C19	*2/*2	0	Poor Metabolizer	Chinese (8.82%), Japanese (7.87%), Korean (7.09%), Taiwanese (8.42%), Vietnamese (5.06%), Thailand (6.61%), Burmese (9.44%), Karen (7.63%), Malay-Singaporean (7.14%),	Influence 4-OH-TAM levels	[18]

				Chinese-Singaporean (10.71%), Indian-Singaporean (14.52%)		
CYP2C19	*1/*17	2.5	Rapid Metabolizer	Indian-Singaporean (15.08%)	Increased clearance of esterogens	[18]
CYP2C19	*2/*17	1.5	Poor Metabolizer	Indian-Singaporean (13.9%)	Clinical relevance unclear	[18]
Phase II Metabolism						
SULT1A1	*1/*1	2	Normal Metabolizer	Chilean (8%)	Normal sulfatase activity	[20]
SULT1A1	*1/*2	1.5	Normal Metabolizer	Chilean (18%)	Intermediate-Normal sulfatase activity	[20]
SULT1A1	*2/*2	1	Intermediate Metabolizer	Chilean (12%)	Decreased sulfatase activity	[20]
UGT2B7	*1/*1	2	Normal Metabolizer	Caucasians (22.5%)	Normal glucuronidation	[22]
UGT2B7	*1/*2	2	Normal Metabolizer	Chilean (18%), Caucasians (49.7%)	Normal or slightly increased glucuronidation	[20, 22]
UGT2B7	*2/*2	2	Normal Metabolizer	Chilean (18%) Caucasians (27.8%)	Increased glucuronidation	[20, 22]
UGT2B15	*1/*2	1.5	Normal Metabolizer	Chilean (33%)	Intermediate glucuronidation capacity	[20]
TRANSPORTER						
ABCC2	-1774delG	-	Decreased function	Asians (20.2-34.3%)	Reduced MRP2 efflux activity	[23]
ABCC2	-24C>T	-	Decreased function	Asians (17.4-32.6%), Caucasians (18.1-22.5%)	Decreased transporter expression	[23]
ABCC2	1249G>A	-	Decreased function	Asians (9.7-10.9%), Caucasians (15.5-24.3%)	Impaired drug/metabolite clearance	[23]

In contrast, *CYP2D6* *1/*1 and *1/*2 genotypes, considered normal metabolizers (activity score 2.0), are commonly found in Vietnamese (68.72%), Japanese (31.37%), and Caucasian (22.8%) cohorts, correlating with effective therapeutic responses [15, 21]. Interestingly, ultrarapid metabolizers (*CYP2D6* *2XN/*39; score 3.0) are notably detected in 9.29% of Iraqi patients, predisposing them to elevated endoxifen levels and increased risk of adverse drug reactions [19]. Conversely, *CYP2D6* *4/*4 and *4/*5, associated with poor metabolism, are more common among Caucasians (10-12%), leading to insufficient drug activation and higher recurrence risk [20, 21].

Beyond *CYP2D6*, polymorphisms in *CYP3A5* also contribute to variability in phase I metabolism. The *3/*3 genotype, indicative of a poor metabolizer phenotype, is frequently observed in Japanese (58.4%) and Chinese (54.9%) populations, and may impair the formation of N-desmethyltamoxifen, a precursor to endoxifen [18]. Additionally, phase II conjugation enzymes such as UGT2B7 and SULT1A1 display population-specific variations. For instance, the *SULT1A1* *2/*2 genotype, linked to decreased sulfonation activity, is found in 12% of Chilean patients, which may impair detoxification of active metabolites and prolong systemic exposure [20].

Moreover, polymorphisms in ABCC2, a key transporter in hepatic efflux, vary significantly among Asians, with the -1774delG variant occurring in up to 34.3% of individuals, potentially reducing biliary excretion of tamoxifen metabolites [23]. These population-specific genetic patterns underscore the need for personalized tamoxifen dosing strategies based on ethnicity-informed pharmacogenomic profiles.

Taken together, the findings in Table 2 support the integration of multiethnic genetic data into tamoxifen therapy to optimize efficacy and minimize toxicity. Ignoring these polymorphic patterns could result in underdosing or overtreatment, particularly in populations with high frequencies of reduced-function alleles such as *CYP2D6 10*, *41*, or *3*.

3.3 Somatic Mutation in Tamoxifen Metabolism

Despite its long-standing role as a cornerstone of endocrine therapy in hormone receptor-positive breast cancer, tamoxifen continues to show variable efficacy across patient populations. While factors such as drug metabolism and adherence are often considered, increasing attention is now being directed toward tumor-intrinsic mechanisms of resistance. Among these, somatic mutations acquired during disease progression have emerged as critical yet underexplored determinants of therapeutic failure. Unlike germline variants, which inform predisposition and metabolism, somatic alterations in tumor DNA can directly rewire signaling pathways, alter drug targets, and drive resistance even in initially responsive cases. However, the routine clinical assessment of somatic mutations remains limited, particularly in settings where personalized medicine has yet to be fully integrated. This underscores a pressing need to better characterize the landscape of somatic mutations in patients receiving tamoxifen, not only to improve prognostication but also to inform the development of adaptive, mutation-guided therapeutic strategies.

As summarized in Table 3, somatic mutations in the *ESR1* gene and its regulatory landscape represent key mechanisms of acquired resistance to tamoxifen in ER-positive breast cancer. The most recurrent are the Y537S and D538G substitutions, predominantly observed in post-treatment metastatic tumors from Western populations, with frequencies reaching up to 12% [24, 25]. These mutations cause ligand-independent activation of ERα, stabilizing the receptor in an agonist

conformation that diminishes the efficacy of selective estrogen receptor modulators (SERMs), including tamoxifen.

Table 3 Summary of key somatic mutations associated with tamoxifen resistance, including their prevalence, affected populations, molecular pathways involved, and clinical consequences.

Somatic Variation	Specific Population	Prevalence in Population (%)	Effect on Tamoxifen Therapy	Molecular Pathway Involved	Additional Clinical Effect	References
ESR1 Y537S	United Kingdom, Italy, USA (ER+ metastatic BC)	~5-12% in metastatic cases	Confers acquired resistance to tamoxifen through constitutive ERα activation	Rho-GDI/PTEN signaling; mitochondrial metabolism; glycolysis	Enhanced ATP production, mammosphere formation, stemness (↑ ALDH)	[24, 25]
ESR1 D538G	North America, Europe	~2-5%	Reduces tamoxifen binding efficacy and promotes estrogen-independent activation	Helix 12 conformational stabilization (ER LBD)	Sustained ER activity in absence of ligand	[24]
ESR1 Y537N	USA, Italy	~12%	Partial resistance to tamoxifen; context-dependent	Cross-talk with IGF1R pathway	Increased PI3K signaling (↑ PIK3R1/R3), reduced antiproliferative response to tamoxifen	[26]
CDKN1A (p21) loss	USA (MCF-7 and patient biopsy)	Not quantified	Tamoxifen paradoxically stimulates tumor growth via ER hyperphosphorylation	CDK/cyclin signaling; ERα S118 phosphorylation	Increased ER-regulated gene expression, SERM-induced tumor proliferation	[27]
ZNF143 C>T mutation (non-coding)	European (BRCA-EU cohort, N = 560 ER+ BC)	Detected in ≥2 patients	Reduces tamoxifen sensitivity by disrupting ER binding site	Altered chromatin loop formation; distal gene regulation	Increased expression of oncogenic distal targets, tamoxifen resistance	[28]

Notably, Y537S is linked to metabolic reprogramming, including increased mitochondrial respiration and glycolysis, as well as activation of the Rho-GDI/PTEN signaling pathway, which collectively promote stemness and apoptosis resistance [25]. In contrast, D538G similarly confers estrogen-independent activity but is more associated with conformational stabilization of Helix 12 within the ligand-binding domain [24].

The Y537N mutation, while less potent, reveals context-dependent tamoxifen resistance, primarily through interaction with IGF1R/PI3K signaling, suggesting that tumor background and signaling milieu are decisive modifiers of endocrine response [26].

Beyond protein-coding regions, non-coding mutations such as the recurrent ZNF143 C>T substitution at estrogen receptor binding sites (ERBS) significantly alter chromatin architecture, enhance distal oncogene expression, and reduce sensitivity to tamoxifen, as shown by Yang et al. [28]. These findings, also detailed in Table 3, broaden the resistance paradigm to include epigenomic topology and enhancer activity, which have been underexplored in endocrine therapy resistance.

Another notable mechanism, independent of direct ER alteration, involves loss of CDKN1A (p21). This event leads to hyperphosphorylation of ERα at Ser118 and paradoxically stimulates tumor growth upon tamoxifen exposure, effectively converting tamoxifen from antagonist to agonist under specific molecular contexts [27]. As shown in Table 3, this reinforces the relevance of cell cycle regulators in determining endocrine outcomes.

Taken together, these data emphasize the necessity of integrating somatic mutation screening both in coding and non-coding regions into therapeutic algorithms for ER+ breast cancer. The mutations outlined in Table 3 represent candidate biomarkers for therapeutic stratification, guiding clinicians toward selecting between tamoxifen, SERDs, or combination therapies with IGF1R or PI3K/AKT inhibitors, especially in resistant or metastatic settings.

3.4 Germline and Somatic Genetic Variants

Table 4 summarizes germline and somatic genetic variants related to tamoxifen pharmacokinetics and therapeutic outcomes across diverse ethnic populations. The table highlights differences in allele frequencies, mutation patterns, and their predicted clinical implications under standard tamoxifen dosing.

Table 4 Ethnicity-Specific Germline and Somatic Variants Associated with Tamoxifen Response and Prognosis at Standard Dose.

Country	Germline		References	Somatic	References	Potential Combination Effect on Tamoxifen Response/Prognosis at Normal Dose
	Phase I	Phase II				
Caucasoid						
United Kingdom	CYP2D6*4, *5, and *6 (PM ~25%)		[29]	ESR1 Y537S (endocrine resistance biomarkers → tamoxifen resistance) TP53 codon 179 (R248W) (biomarker of uncontrolled cell proliferation)	[30, 31]	Predictors of therapy failure (with decreased patient survival)
Algerian	CYP2D6*2 >2 copies (UM ~33.03%) CYP2D6*5 (PM ~1.03%)		[32]	TP53 codon 179 (R248W) (biomarker of uncontrolled cell proliferation)	[31, 33]	Predictors of therapeutic success (with risk of toxicity, side effects, and decreased patient survival) Predictors of therapy failure (with decreased patient survival)
Iraqi	CYP2D6*10, *17, and *41 (IM ~55.03%) CYP2D6*2XN (UM ~10.75%)		[19, 32]	TP53 overekspresi (biomarker of cancer progression)	[33]	Predictors of therapy failure (Time to onset is long with decreased patient survival) Predictors of therapeutic success (with risk of toxicity, side effects, and decreased patient survival)

	CYP2D6*4, *3B, and *7 (PM ~9.13%)					Predictors of therapy failure (with decreased patient survival)
Bangladesh	CYP3A5*3 (UM ~45.88%)	SULT1A1*2 (PM ~34.02%)	[34]			Predictors of therapeutic success (with risk of toxicity and side effects)
	CYP2D6*10 (IM ~57.09%)	UGT2B7*2 (PM ~52.32%)				Predictors of therapy failure (Time to onset is long with high risk of side effects and toxicity)
			Mongoloid			
Chilean	CYP3A4*1/*1B (UM ~12.5%)	SULT1A1*1/*2 (PM~50%)	[20]			Predictors of therapeutic success (with risk of toxicity and side effects)
China	CYP2D6*10 (IM ~16% in the Uygur and 33% in the Han patients).		[35]	PIK3CA ~22.1% (E39K, E542K, H1047R) (breast cancer cell proliferation biomarker)	[36]	Predictors of therapy failure (Time to onset is long with decreased patient survival)
			Negroid			
Black/ African American	CYP2D6*17 (IM ~21%)		[37]	TP53 mutations occur in stage III B/AA patients ~48%; they occur in TNBC ~73% (biomarkers of dysregulation of cell cycle control and apoptosis)	[38]	Predictors of therapy failure (Time to onset is long, with decreased patient survival)
	CYP2D6 *29 (PM ~7.9%)					Predictors of therapy failure (with decreased patient survival)

Among Caucasoid populations, particularly in the United Kingdom, poor metabolizer alleles CYP2D6*4, *5, and *6 are prevalent (~25%), accompanied by somatic mutations such as ESR1 Y537S and TP53 R248W. These variants have been identified as biomarkers of endocrine resistance and dysregulated cell proliferation, respectively [29-31]. Their co-existence is associated with tamoxifen resistance and reduced survival, underscoring the need for molecular stratification prior to treatment initiation.

In Algerian patients, the table shows a high frequency of CYP2D6*2 gene duplications (UM ~33.03%), which may lead to accelerated drug metabolism. However, TP53 R248W mutations suggest cellular-level resistance [33]. Despite the potential for therapeutic success, the combination of these variants may increase the risk of toxicity and poor prognosis. Interestingly, CYP2D6*5 (PM ~1.03%) is also present in a minor fraction, reflecting intra-population heterogeneity in metabolic capacity.

The Iraqi population exhibits a high prevalence of CYP2D6*10, 17, and 41* (IM ~55.03%) and somatic *TP53* overexpression, both of which are indicated in the table as predictors of delayed therapeutic onset and decreased survival [19]. Despite the presence of ***CYP2D6*2XN (UM ~10.75%), suggesting a subset of ultrarapid metabolizers, the overall profile leans toward therapeutic failure unless individualized dosing is considered.

In Bangladeshi patients, the table identifies a distinct profile with CYP3A5*3 (UM ~45.88%), SULT1A1*2 (PM ~34.02%), and UGT2B7*2 (PM ~52.32%), indicating enhanced phase I activation but impaired phase II conjugation [34]. This imbalance can result in accumulation of active intermediates, increasing toxicity risk. Moreover, CYP2D6*10 (IM ~57.09%) is associated with delayed endoxifen formation and suboptimal therapeutic effect.

In Chilean individuals, polymorphisms such as CYP3A4*1/1B* (UM ~12.5%) and SULT1A1*1/2* (PM ~50%) are identified, with a predicted outcome of increased side effects despite potential therapeutic success [20]. Similarly, in Chinese populations, the CYP2D6*10 allele is present in 16% of Uygur and 33% of Han patients, as shown in the table. Concurrently, somatic PIK3CA mutations (E39K, E542K, H1047R) (~22.1%) are common and are linked to enhanced tumor cell proliferation, suggesting a multifactorial mechanism of tamoxifen resistance [36].

In the Black/African American population, the table reports CYP2D6*17 (IM ~21%) and CYP2D6*29 (PM ~7.9%), along with a high incidence of TP53 mutations in patients with stage III breast cancer (~48%) and triple-negative breast cancer (TNBC) (~73%) [37, 38]. These combined alterations are strong predictors of impaired drug metabolism, tumor progression, and poor clinical outcomes.

3.5 Current Clinical Pharmacogenetic Guidelines on Tamoxifen and Their Limitations

Despite the substantial body of evidence linking CYP2D6 genetic variability to tamoxifen metabolism and therapeutic response, current clinical pharmacogenetic guidelines remain narrowly focused on germline CYP2D6 variants and largely neglect the broader genomic landscape, including phase II metabolism, drug transporters, and somatic alterations in tumor DNA.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides phenotype-based dosing recommendations for tamoxifen therapy grounded in CYP2D6 activity score. According to CPIC, normal and ultrarapid metabolizers (activity score ≥1.5) are recommended to receive the standard tamoxifen dose (20 mg/day), while intermediate and poor metabolizers (activity score =

0-0.5) are advised to consider alternative hormonal therapies such as aromatase inhibitors (Ais: anastrozole) due to reduced endoxifen levels and increased recurrence risk. When AIs are contraindicated, high-dose tamoxifen (40 mg/day) may be used, although the resultant endoxifen levels may still fall short of therapeutic thresholds [39].

Similarly, the Dutch Pharmacogenetics Working Group (DPWG) supports alternative therapies in CYP2D6 intermediate and poor metabolizers, with specific dose-adjustment strategies or endoxifen monitoring protocols. DPWG even suggests dose increases up to 40-60 mg/day in poor metabolizers, provided endoxifen plasma levels are closely monitored. Notably, both guidelines acknowledge limitations in evidence quality, especially regarding populations harboring *CYP2D6* *10 alleles, which are common in Asians [39].

In contrast, the U.S. Food and Drug Administration (FDA) label for tamoxifen remains conservative. It acknowledges the role of CYP2D6 in tamoxifen activation but does not endorse routine genotyping due to "limited and conflicting data." The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) echo this position, advising against CYP2D6 genotyping for routine clinical decision-making [39].

These recommendations reflect a fundamental limitation: they consider only one-dimension CYP2D6 of tamoxifen pharmacogenomics, neglecting other influential factors. For example, polymorphisms in CYP3A4/5, UGT2B7, SULT1A1, and transporters like ABCC2 can modulate bioavailability and elimination of tamoxifen and endoxifen, especially in underrepresented ethnic populations such as South Asians and Southeast Asians. Additionally, somatic mutations including *ESR1*, *TP53*, *PIK3CA*, and enhancer region variants have been increasingly implicated in acquired tamoxifen resistance but remain absent from clinical guidelines.

Thus, while current guidelines offer useful starting points for personalized endocrine therapy, their narrow focus on CYP2D6 germline variants limits their predictive value and clinical utility, particularly in diverse and metastatic patient populations. There is a clear need for an expanded framework that integrates multi-omics data, including somatic mutations, to improve therapeutic precision and address endocrine resistance mechanisms.

4. Future Directions

The evolving understanding of both germline and somatic pharmacogenomics in breast cancer signals a paradigm shift toward truly individualized tamoxifen therapy. However, to translate this knowledge into clinical impact, several critical avenues remain.

First, there is an urgent need for prospective, multi-ethnic cohort studies that combine germline pharmacogenetic testing (e.g., *CYP2D6*, *CYP3A4/5*, *UGT2B7*, *SULT1A1*) with tumor genomic profiling (e.g., *ESR1*, *TP53*, *PIK3CA*) in patients receiving tamoxifen. Such integrated designs would help establish combinatorial genomic risk models that predict treatment response, resistance, or recurrence more accurately than CYP2D6 alone.

Second, the development of clinically validated scoring systems that integrate pharmacokinetics (endoxifen levels), pharmacogenomics, and somatic mutation burden may help guide therapeutic decisions, particularly in cases where tamoxifen is considered in the presence of endocrine resistance mutations.

Third, updated clinical guidelines (e.g., CPIC, DPWG, NCCN) must begin incorporating somatic markers into their recommendations. The exclusive focus on CYP2D6 in current guidance does not

reflect the molecular complexity of tamoxifen response, especially in metastatic or recurrent settings.

Fourth, advancements in multi-omics technologies including transcriptomics, epigenomics, and single-cell sequencing should be leveraged to map dynamic changes in tumor evolution under tamoxifen pressure. This may reveal novel resistance mechanisms and identify rational drug combinations.

Lastly, more investment is needed in global pharmacogenomic infrastructure, especially in low- and middle-income countries, where germline variant diversity is poorly characterized, and somatic profiling is rarely implemented. Building population-specific databases and contextualized clinical algorithms will be essential for equity in precision oncology.

In sum, the future of tamoxifen therapy lies not in abandoning the drug, but in refining its use through integrated pharmacogenomics, ensuring that the right patients receive the right endocrine therapy, at the right dose, and at the right time.

5. Conclusion

Optimizing tamoxifen therapy in breast cancer requires a multidimensional approach that transcends current pharmacogenetic practices centered solely on germline *CYP2D6* polymorphisms. While guidelines from CPIC and DPWG have made significant strides in stratifying tamoxifen dosing based on *CYP2D6* activity scores, these frameworks fall short of accounting for the broader genomic and ethnic complexity observed in global populations. Furthermore, somatic mutations, particularly in *ESR1*, *TP53*, and non-coding enhancer regions, play a pivotal role in driving acquired resistance yet remain absent from routine clinical assessment and pharmacogenetic guidelines.

This review highlights the need to integrate germline and somatic pharmacogenomic data to guide therapeutic decisions. The interaction between metabolic capacity (e.g., via *CYP2D6*, *UGT2B7*, *SULT1A1*) and tumor-specific mutations dictates not only drug efficacy but also toxicity profiles and long-term prognosis. Additionally, interethnic variability in allelic distribution reinforces the need for population-specific implementation of pharmacogenomic testing.

Moving forward, clinical practice must evolve from single-gene models toward multi-omics-informed frameworks that incorporate tumor genomics, metabolism, and real-time resistance mechanisms. Large-scale prospective studies, multiethnic genomic databases, and clinical trials stratified by pharmacogenomic profile are urgently needed to support this transition. Only through such integrative precision medicine can tamoxifen therapy reach its full therapeutic potential, minimizing recurrence and maximizing patient benefit in both early- and advanced-stage breast cancer.

Author Contributions

Syahrul Tuba responsible for Investigation, methodology, resources, and experimental validation. Luluk Sakdiyyah, Natanael Panjaitan, and F. Josse Pasca Pradana are responsible for software, manuscript drafting, data curation, formal analysis, project administration. Adi Priyono, Budi Sumaryono manuscript review and editing. All authors reviewed and approved the final manuscript.

Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

Artificial intelligence (AI) tools were used solely for basic grammar correction and language refinement in the preparation of this manuscript. Specifically, OpenAI's ChatGPT was employed to improve the readability and linguistic clarity of the English text. All scientific content, data interpretation, and conclusions were developed independently by the author. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript.

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