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Review Article

CYP2D6, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2, AND BEYOND: PHARMACOGENOMICS-GUIDED PERSONALIZATION IN BREAST CANCER MANAGEMENT

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ABSTRACT

Breast cancer is a serious worldwide health concern, and it is associated with high mortality and variable treatment response because of tumor heterogeneity and an individual difference in metabolism and toxicity of drugs. The development of pharmacogenomics (PGx) has been a potent instrument in overcoming these issues by incorporating individual genetic data into the decision-making process of the therapeutic process. This narrative review synthesizes evidence from PubMed-indexed studies published between 2010 and 2025 regarding the use of PGx determinants to affect endocrine therapy, immunotherapy, and chemotherapy in breast cancer. Polymorphism in CYP2D6 plays a potentially significant role in tamoxifen activation and endoxifen concentrations in hormone receptor-positive disease, and variants in CYP19A1, estrogen receptor 1, and estrogen receptor 2 also play a role in the efficacy and toxicity of aromatase inhibitor. The FCGR3A and FCGR2A polymorphisms of PI3K/AKT pathways, as well as human epidermal growth factor receptor 2 (HER2) structural changes, can predict the responsiveness to trastuzumab in HER2-positive breast cancer and determine how to use the new agents, such as trastuzumab deruxtecan and margetuximab. In the case of triple-negative breast cancer, the biomarkers, such as programmed death-ligand 1 expression, immune-related gene signature, human leukocyte antigen variants, and polygenic risk scores narrow immune checkpoint inhibitors selection and determine vulnerability to immune-related adverse events. Furthermore, germline mutations in DPYD, CYP2C8, ABCB1, UGT2B7, and anthracycline cardiotoxicity-related genes assist in the reduction in dose and toxicity of anthracycline. The increased use of PGx testing, multigene panels, and next-generation sequencing in both clinical research and clinical practice highlight the growing importance of this technology in precision oncology. Together, the PGx allow the use of more personalized therapy choice, reduce the adverse effects, and increase the overall outcome of treatment in breast cancer.

Keywords: Breast cancer, Pharmacogenomics, CYP2D6, HER2, Precision oncology.

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INTRODUCTION

Cancer is the most considerable burden on health in the world and has been a major cause of deaths throughout the world [1-3]. The rise in deaths is driven by ageing and shifting risk factors distributions brought about by socioeconomic development [4-6].

Breast cancer is one of the primary causes of cancer related disease and mortality amongst women (Fig. 1). It represents more than 11% of all cancer groups in women and is highly prevalent in the nations with high Human Development Index. Although screening and treatment have got better, breast cancer remains a significant burden on global public health, causing a significant portion of death and disability in the world [7-11].

Some of the management strategies are surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, and immunotherapy [12-15]. The response to therapy is, however, very unpredictable owing to the biological differences of the breast cancer. Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-positive, and triple negative types of breast cancer vary in prognosis, aggressiveness, and sensitivity to treatment [16-21]. The primary problems are drug resistance, unpredictable therapeutic effect, and adverse drug reactions, to drugs, such as cardiotoxicity or neuropathy. Genetic variability also has an effect; such as the CYP2D6 polymorphisms have the potential to decrease tamoxifen activation and thus reduce its efficacy in Estrogen receptor (ER)-positive breast cancer [22].

Personalized medicine and pharmacogenomics (PGx) provide a potential solution to overcome such limitations. Clinicians can use molecular profiling by understanding the effects of genetic variations on metabolism, efficacy, and toxicity to customize treatment based on a specific molecular profile [23-26]. Genotyping of CYP2D6 can be used to guide the choice of endocrine therapy, HER2 changes should guide the use of trastuzumab or other anti-HER2 therapies, and BRCA1/2 mutations can be used to support the use of PARP inhibitors. Besides, the PGx profiling can be used to predict risks of these types of toxicities caused by chemotherapy and achieve safer and more effective treatment planning [27,28].

The present next-generation sequencing and multigene panel testing enables tumor profiling in a comprehensive manner, that is, with respect to the complexities of the molecules and undergoes precision therapy. The combination of these genomic understanding and clinical variables also optimizes the choice of treatment, results, and side effects. Consequently, PGx is transforming the traditional one-size-fits-all, breast cancer care model through to a more personalized, precision oncology model [24,29-32].

The objective of this review is to clarify the impact of PGx on personalized care of breast cancer through the association between genetic variants and drug response. It underscores the promise of personalized medicine in transcending existing therapeutic challenges, and describes recent innovations that shape our changing paradigm of precision oncology – an inclusive new view of how genomic information can be made accessible to patients over time.

PGx OF ENDOCRINE THERAPY IN BREAST CANCER

Endocrine therapy persists as an essential component of the treatment for hormone receptor-positive breast cancer, and about 70% of the cases are of this type of breast cancer [33]. These therapies operate either by inhibiting estrogen synthesis or by blocking ERs, ultimately interrupting estrogen signaling [34]. Even though they are effective, variations in the Individual's response to the treatment, resistance development, and adverse reactions make clinical practice very difficult [35]. PGx offers a significant approach for discovering the genetic factors that affect drug metabolism, potency, efficacy, and toxicity. This technique helps in customizing the endocrine therapy of breast cancer [36].

Tamoxifen and CYP2D6

Tamoxifen is a selective estrogen receptor modulator widely used as adjuvant therapy for ER+ breast cancer in premenopausal and certain postmenopausal women [37]. It inhibits the estrogen from acting on the breast tissues, yet it can perform like estrogen in other tissues, such as the uterus and bones. Tamoxifen is inactive as such, but after metabolism in the body, it gets converted to its active form, that is, 4-hydroxytamoxifen and endoxifen, by the enzyme cytochrome P450 and primarily by CYP2D6 [31]. Endoxifen binds most effectively to the estrogen receptor and is primarily the component that makes the drug work against cancer [38] (Fig. 2).

Key genetic variations of CYP2D6

More than 100 recognized allelic mutations that have a major effect on enzyme function, the CYP2D6 gene is highly polymorphic [39]. These distinct characteristics divide peoples into various types of metabolizer phenotypes (Table 1).

Clinical evidence

Several studies have examined the relationship between CYP2D6 genotype, endoxifen levels, and tamoxifen outcomes. Early analyses showed that patients with reduced or poor CYP2D6 metabolism have lower endoxifen concentration and higher recurrence risk than extensive metabolizers [41,42]. A recent 2024–2025 meta-analytic update reported that poor metabolizers have an approximately 1.30–1.35-fold increased risk of recurrence or mortality [41]. Similarly, a large Swedish cohort demonstrated significantly higher breast-cancer-specific mortality in poor metabolizer receiving tamoxifen [42]. More recent population-based studies also found CYP2D6 variants linked to poorer survival or early tamoxifen discontinuation in premenopausal women [36,41].

However, findings remain inconsistent, as several randomized controlled trials and later analyses – including low dose tamoxifen studies – reported no significant association between CYP2D6 genotype, endoxifen levels, and clinical outcomes [43,44] (Table 2).

Controversies and limitations

A major obstacle involves the contraindicatory data about CYP2D6 genotyping and tamoxifen efficacy. A number of confounding variables have been suggested:

- Concomitance CYP2D6 inhibitors: Regardless of genotype, drugs, such as paroxetine, fluoxetine, and bupropion can inhibit CYP2D6, reducing endoxifen levels [45,46]
- Ethnic variability: Findings from the studies are impacted by the notable differences in polymorphism frequency and impact between ethnic groups
- Examine the constraints of the design: Inconsistent results are caused by retrospective analysis, small sample size, and lack of standardized assays.

Despite of these controversies, it is generally accepted that CYP2D6 polymorphisms influence endoxifen concentrations; however, there is uncertainty over how this translates into the clinical judgment [47].

Clinical implementations and guidelines

Based on the CYP2D6 genotype, PGx guidelines, including those from the Dutch Pharmacogenetics Working Group and the clinical PGx implementation Consortium (CPIC), recommend tamoxifen therapy [46,49].

As per CPIC guidelines (2020), alternative hormonal therapy, such as aromatase inhibitors (AIs) (for postmenopausal women) or ovarian suppression with AIs (for premenopausal women) may be taken into consideration for poor metabolizers [49].

However, because of conflicting data about its clinical utility, the Food and Drug Administration (FDA) does not currently advise routine CYP2D6 genotyping before tamoxifen therapy [50].

AIS: LETROZOLE, ANASTROZOLE, AND EXEMESTANE

Mechanism and PGx variability

AIs reduce the production of estrogen and its level in the blood by inhibiting the aromatase, which is encoded by the CYP19A1. Even though this enzyme is the target of all AIs, response rates, toxicity profiles (such as bone loss and musculoskeletal pain), and recurrence risk vary significantly from person to person [51]. Genetic variations linked to inflammation and estrogen metabolism have been linked in genome-wide association studies to side effects of AI, including osteoporosis and arthralgia [52].

CYP19A1 gene polymorphism

Polymorphisms in CYP19A1 can alter aromatase activity and, consequently, the production of estrogen. Notable variations are as follows:

- rs4646: Linked to both improved time-to-time progression and higher musculoskeletal toxicity, as well as altered plasma estrogen suppression
- rs10046: Associated with the variations in estrogen levels, aromatase gene expression, and AI response; however, results need to be verified
- rs700518: Correlated with the higher risk of bone loss and musculoskeletal adverse events in AI treatment.

Recent studies have shown that, especially when considering prognostic factors into consideration, not all CYO19A1 variants independently predict outcomes [53].

Estrogen receptor 1 (ESR1), and estrogen receptor 2 (ESR2) gene variants

A known mechanism of AI resistance is ligand-independent receptor activation caused by the mutations in the ligand-binding domain of ESR1, such as Y537S and D538G [54]. These somatic mutations are rare in initial tumors, but they become more prevalent in metastatic disease during extended AI therapy. Although germline mutations of ESR1 and ESR2 also affects the vasomotor symptoms and bone loss risk, their effect on clinical outcome differ [55].

Clinical associations and translation relevance

According to several GWAS research, CYP19A1 and ESR1/ESR2 genotyping may potentially allow for the classification of the patient at risk for higher toxicity or decreased efficacy, opening the path for AI treatment [56]. However, the lack of standardized, validated multigene panels and inconsistent research replication currently limits the practical application. The medical value of these PGx techniques is continues to be investigated in ongoing prospective trials [57].

Future directions in AIs PGx

Although genetic polymorphism in CYP19A1 and ESR1 have been shown to influence variation in the impact of AIs on efficacy and toxicity, low replication rates and small magnitudes of effect currently preclude their clinical application [58-60]. Further investigations should be based on large, prospective studies in multiethnic populations with standardized endpoints. The combination of germline PGx, tumor-acquired ESR1 mutations, longitudinal estrogen suppression profiles, and polygenic risk models could enhance the prediction of AI resistance and toxicities to enable personalization of endocrine therapy [61,62].

Table 1: CYPCD6 metabolizer phenotypes and their clinical implications [40]

Metabolizer type	Genetic makeup/example alleles	Enzyme activity	Activity score (AS)	Remarks
Poor metabolizers (PM)	Two non-functional alleles (e.g., CYP2D6*4/*4, *5/*5)	Absent or very low	0	Greatly reduced drug metabolism→higher risk of toxicity
Intermediate metabolizers (IM)	One reduced-function alleles (e.g., CYP2D6*10, *17, *41)	Decreased	0.25–1.0	Slower metabolism than normal→may need dose adjustment
Extensive metabolizers (EM)	Two normal-function alleles	Normal	1.25–2.25	Normal drug metabolism→standard dosing
Ultrarapid metabolizers (UM)	Gene duplication causing increased enzyme expression	Increased	>2.25	Faster metabolism→reduced efficacy or therapeutic failure

Table 2: Overview of conflicting evidence on CYP2D6-guided tamoxifen therapy

Study (Year)	Study design	Sample size	Population/ Ethnicity	Findings
2025	Retrospective, real-world cohort	3,218	Predominantly European ancestry	CYP2D6 poor metabolizers had significantly worse OS and BCSS; the effect strengthened with long follow-up and after accounting for CYP2D6 inhibitor use [41].
2025	Observational cohort	1,309	Multi-ethnic	U-shaped association observed: Both poor and ultrarapid metabolizers showed higher mortality compared with normal metabolizers [42].
2024–2025	Prospective-retrospective analysis	~1,200	Predominantly European ancestry	CYP2D6 genotype showed modest association with tamoxifen benefit after adjustment for prognostic variables, though not sufficient to support routine testing [48].

Table 3: Food and Drug Administration-approved HER2-targeted therapies and associated biomarkers in breast cancer [67-73]

Drug	Class	Target/Mechanism	Approved indication	Required biomarker
Trastuzumab	Monoclonal antibody	HER2 extracellular domain	Early and metastatic breast cancer	HER2-positive (IHC 3+or ISH+)
Pertuzumab	Monoclonal antibody	HER2 dimerization inhibitor	Metastatic and neoadjuvant	HER2-positive (IHC 3+or ISH+)
T-DM1 (Ado-trastuzumab emtansine)	Antibody–drug conjugate	HER2-directed cytotoxic delivery	Residual/metastatic disease	HER2-positive (IHC 3+or ISH+)
T-DXd (Trastuzumab deruxtecan)	Antibody–drug conjugate	HER2-directed topoisomerase I inhibitor	Metastatic disease	HER2-positive and HER2-low (IHC 1+or 2+/ISH−)
Tucatinib	Tyrosine kinase inhibitor	HER2-selective TKI	Advanced/metastatic disease	HER2-positive (IHC 3+or ISH+)
Lapatinib	Tyrosine kinase inhibitor	HER2/EGFR inhibition	Metastatic disease	HER2-positive (IHC 3+or ISH+)

HER2: Human epidermal growth factor receptor 2, IHC: Immunohistochemistry, ISH: *In situ* hybridization, EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor

Table 4: Summary of meta-analyses evaluating ABCB1 and CYP2C8 variants and taxane toxicity [104,105]

Gene	Variant	No. of studies (patients)	Main toxicity endpoint	Key conclusion
ABCB1	C3435T	20 (~6,000)	Neuropathy, neutropenia	No consistent association
CYP2C8	*3	12 (~3,500)	Neuropathy	Variable PK effect; no strong toxicity link

PGx OF HER2-TARGETED THERAPY

Nearly 15–20% of breast cancers overexpress HER2, an aggressive subtype driven by HER2 gene amplification or protein overexpression [63]. Trastuzumab, a monoclonal antibody targeting the HER2 extracellular domain, has revolutionized treatment by blocking signaling and triggering antibody-dependent cellular cytotoxicity (ADCC). Yet > 50% of patients develop primary or acquired resistance, highlighting the need to investigate pharmacogenomic and molecular mechanisms behind this treatment failure [64] (Table 3).

HER2 amplification testing as standard biomarkers

The Immunohistochemistry (IHC) and *in situ* hybridization (ISH) are used to determine the HER2 status of patients to ascertain trastuzumab eligibility [65]. Recent advancements of antibody-drug conjugates (ADCs), such as trastuzumab-deruxtecan (T-DXd) – have added HER2-ultra-low categories to HER2-low. These sophisticated testing requirements are better patient stratification and widen treatment choices in precision oncology [66].

Fc Gamma receptor (FCGR3A, FCGR2A) polymorphisms and ADCC

The efficacy of Trastuzumab partially depends on the immune effector functions that are mediated by Fc 4 receptors on the immune cells (ICs). FCGR3A (V158F) and FCGR2A (H131R) polymorphisms influence the strength of ADCC in response to trastuzumab and Fc domain binding and clinical outcomes. The genotyping of the variants may be of use in predicting response and personalizing therapy [74].

PGx considerations in Trastuzumab resistance

Resistance of trastuzumab arises through multiple mechanisms: Genetic mutations in ATM, RB1, TP53, etc., which disrupts cell-cycle control and apoptosis; structural alterations in HER2 (such as truncated p96HER2, splice variants, such as HER2Δ16, or epitope masking by MUC4/ECM); activation of alternative pathways (e.g., PI3L/AKT/mTOR via PIK3CA mutations or loss of PTEN); immune-microenvironment changes (immune evasion via altered ADCC, human leukocyte antigen (HLA)-G/KIR2DL4 signaling, immunosuppressive fibroblast and macrophages); and increased autophagy/lysosomal dysfunction, which impairs cytotoxic drug processing and ADC efficacy [75].

Table 5: Ongoing pharmacogenomic clinical trials in breast cancer

Trial Name/ID	Gene(s)/ Variant(s) studied	Clinical question/intervention	Status/Notes	Primary outcome	Preliminary results
TARGET-1 (Phase II) —Tamura *et al*.	CYP2D6	Does *CYP2D6* genotype–guided dose escalation of tamoxifen improve outcomes? (20 mg→40 mg for reduced-function alleles)	Completed; randomized, open-label in hormone-receptor–positive metastatic breast cancer [119].	Endoxifen concentration; progression-free survival	Completed; genotype-guided escalation increased endoxifen levels without excess toxicity.
NCT03504631	CYP2D6	Genotyping and phenotyping of CYP2D6 in breast cancer patients to correlate genotype with tamoxifen response	Recruiting/ observational [120].	Association between CYP2D6 genotype and tamoxifen response	Recruiting; results pending
NCT07158164	DPYD	Validating DPYD-guided dose reduction strategies for fluoropyrimidine chemotherapy in real-world clinical practice	Ongoing; treatment-interventional study [121].	Incidence of severe fluoropyrimidine toxicity	Ongoing; early data support improved safety
PACIFIC-PGx	DPYD, UGT1A1	Prospective single-arm study of DPYD/UGT1A1 genotype–guided dosing for fluoropyrimidines (and irinotecan) to reduce toxicity	Published feasibility and safety data [122].	Reduction in grade≥3 toxicity	Published feasibility data show reduced severe toxicity and safe implementation
TAMENDOX — EudraCT 2016-000418-31/ NCT03931928	CYP2D6 (and phenotype)	Supplementing tamoxifen-treated breast cancer patients with low endoxifenlevels with exogenous endoxifen based on genotype/ phenotype	Ongoing/planned; trial aims to correct low metabolite concentrations [123].	Correction of subtherapeutic endoxifen levels	Ongoing; feasibility and pharmacokinetic outcomes awaited
CYP2D6 Genotyping in Indonesia — Maggadani *et al*.	CYP2D6	Real-world CYP2D6 genotyping in Indonesian breast cancer patients on tamoxifen; correlate genotype with metabolite levels	Single-arm, prospective study [124].	Endoxifen concentration by genotype	Completed; genotype strongly correlated with metabolite variability

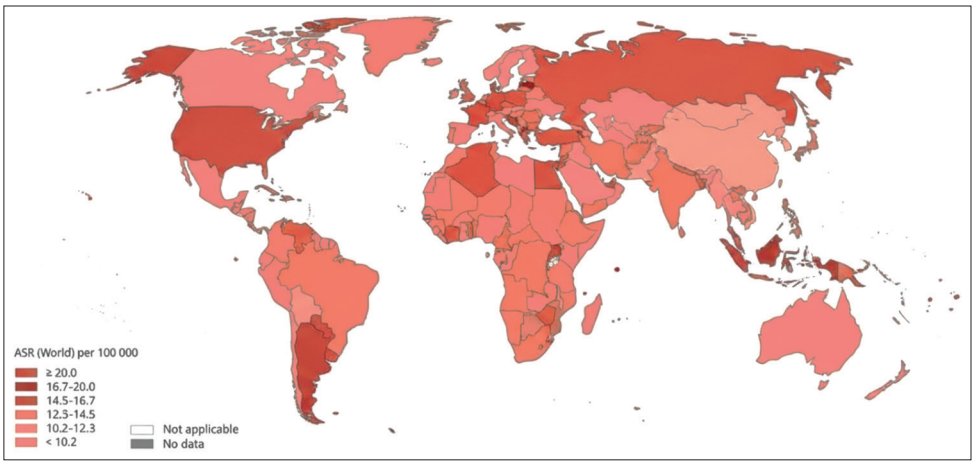

Fig. 1: Estimated mortality of breast cancer in 2022 globally (according to GLOBOCAN 2022) [2]

Emerging therapies: T-DXd, Margetuximab, and Pertuzumab

Novel therapies help overcome resistance and improve outcomes. T-DXd targets HER2-low and HER2-ultralow tumors and provides a strong bystander-killing effect [76]. Combination therapy with pertuzumab improves efficacy by binding a different HER2 epitope and limiting receptor dimerization. For patients with FcγR variants associated with weaker trastuzumab response, mergetuximab, engineered with an optimized Fc region, enhance FcγR activation and ADCC [77].

Classification of HER2-Low and HER2-Ultra: Precision treatment expansion

At present, HER2 expression is classified by IHC and ISH. HER2-low tumors are cases that are IHC 1+ or 2+ with negative ISH and HER2-ultralow cases were those showing faint, incomplete membrane staining in ≤10% of tumor cells (IHC 0 with minimal staining) and were ISH-negative [78]. These categories do not satisfy HER2 amplification criteria; however, they have relevant clinical significance as ADCs, especially T-DXd, demonstrated improved outcomes in those with HER2-low metastatic breast cancer. Proper categorization is therefore key for broadening the eligibility of precision medicine interventions and guiding treatment [79].

Liquid biopsy and circulating tumor DNA (ctDNA) for monitoring HER2 mutations and resistance

Liquid biopsy, utilizing ctDNA, is an emerging method for real-time assessment of molecular alterations, such as HER2 mutations and therapy resistance in breast cancer [80]. In addition, it has been previously shown that ctDNA mirrors tumor load as well as the genetic diversity and dynamic treatment response of metastatic breast cancer, thereby providing an opportunity for non-invasive evaluation of

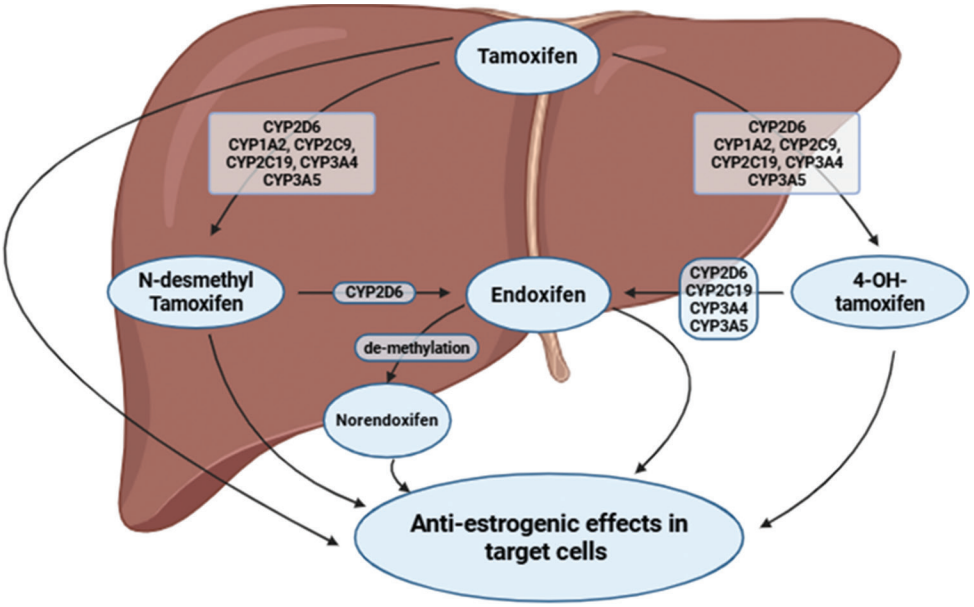

Fig. 2: Schematics of tamoxifen metabolism (CYP2D6 pathway). Tamoxifen is a substrate for hepatic cytochrome P450 enzymes. Tamoxifen is metabolized to N-desmethyltamoxifen by CYP3A4/5 and 4-hydroxytamoxifen by CYP2D6. N-desmethyltamoxifen is metabolised to endoxifen by CYP2D6, which acts as the major metabolite with the best affinity for estrogen receptor. Diminished activity of CYP2D6 can reduce endoxifen generation

development-based resistance against HER2-targeted therapy [81,82]. Clinical data have demonstrated that genomic alterations, including ERBB2 amplification and various targeted mutations, can be identified from patients at a time point before the appearance of radiographic progression, with implications for prompt management decisions. Despite remaining technical and sensitivity issues, monitoring with ctDNA offers the potential to guide adaptive HER2-directed therapies and improve outcomes for patient [83,84].

PGx IN IMMUNOTHERAPY

Checkpoint inhibitors in triple-negative breast cancer (TNBC)

TNBC does not express the hormonal receptors (ER) and PR, as well as HER2, and is resistant to hormonal and HER2-based treatments [85]. Immune checkpoint inhibitors (ICIs), in particular targeting the Programmed Death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis are a promising treatment, although a sub-group of patients with sustained benefit. To identify patients, preempt responsiveness, and restrict immune-related toxicity, reliable PGx biomarkers are desperately required [86].

PD-L1 expression testing

The main biomarker that is used to control ICI in TNBC is the expression of PD-L1, which is normally quantified through assays, such as Dako 22C3 (CPS), Ventana SP142, and SP263. The sensitivity and scoring systems differ greatly, which leads to a great variability in PD-L1 positivity. In clinical trials, such as KEYNOTE-355 and KEYNOTE-522, PD-L1-positive disease was based on CPS ≥10 and revealed an obvious pembrolizumab advantage. However, because of inter-assay variability and lack of predictive power, there is increasing evidence in support of multi-marker approaches combining PD-L1 with other genomic and immune biomarkers [85].

PD-L1 assay in breast cancer: Clinical validation and variability

Several IHC assays are available to analyze PD-L1 expression in breast cancer with variations in antibody clones, scoring criteria, and clinical validation. The Dako 22C3 test utilizes the CPS and is a clinically proven test for pembrolizumab in TNBC, as seen in the KEYNOTE-355 study [87]. The Ventana SP142 test assesses tumor-infiltrating (ICs ≥1%) expressing PD-L1 on the cell membrane, which was approved for atezolizumab in TNBC based IMpassion130 data [88]. The analytical concordance of the Ventana SP263 assay with 22C3 is higher, but there is no prospective, consistent validation of treatment selection for breast cancer [89]. Such assay-specific discrepancies add to patient classification variability and serve as a reminder to deploy companion diagnostic-matched assays in clinical scenarios.

Tumor mutational burden (TMB) and microsatellite instability (MSI)

MSI and TMB are new immunotherapy response biomarkers of TNBC. MSI-high status is an uncommon occurrence in breast cancer, but pembrolizumab has tissue-agnostic clinical activity in MSI-high or mismatch repair-deficient tumors of any origin [90]. Similarly, TMB-high tumors have also demonstrated a better response to the ICIs, which have elicited a regulatory approval of pembrolizumab to TMB-high solid tumors, including select TNBC cases [91]. Nonetheless, the prevalence is low and non-standardized cutoffs in the current state restrict regular clinical applications in breast cancer [92].

Germline variants and immune gene signatures influencing response

Germline variants in HLA, CTLA4, and PDCD1 (PD-1) influence both response to ICIs and risk of immune-related adverse events (irAEs); some alleles predispose to autoimmunity, while HLA heterozygosity may enhance tumor antigen recognition. Polygenic risk scores (PRS) are being explored to predict ICI efficacy and toxicity. In addition, tumor immune gene signatures – including cytotoxic T-cell markers, interferon-γ-response genes, and multigene panels, such as the 27-gene classifier – improve prediction of TNBC response by complementing PD-L1 and TMB assessments [93].

Germline HLA and CTLA4 variants: Current evidences and clinical limitations

Substantial evidence is emerging to indicate that germline variations in HLA genes could affect the accounts of ICIs and the chance of irAEs, with preliminary investigations having analyzeda CTLA4-related genetic variation in terms of immunotherapy reaction [94]. The available evidence to data is, however, mostly associative and based on small cohorts or retrospective studies, which have not been prospectively validated and no germline HLA or CTLA4 mutation is in routine clinical

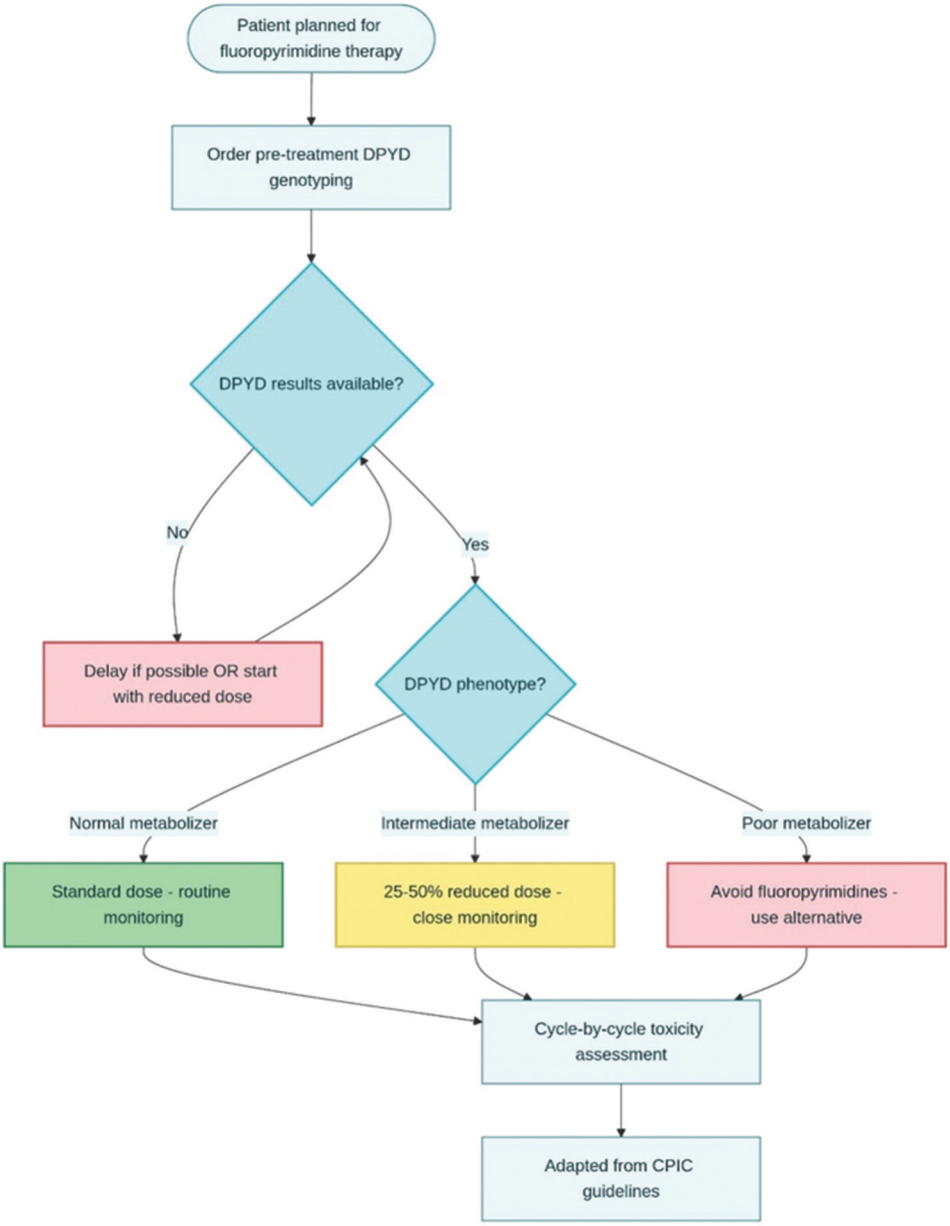

Fig. 3: Illustration of a practical pathway for DPYD-guided fluoropyrimidine dosing

use in immunotherapy. As a result, their predictive and prognostic power is still investigational and needs to be conducted in large and prospective multi-ethnic studies before it can be implemented in clinical practice [95].

PGx of irAEs

A significant disadvantage of ICI therapy is irAEs. Certain HLA alleles (e.g., HLA-DRB1*11:01) and immune-regulatory variants (PTPN22, CTLA4) have been connected by germline PGx studies to organ-specific irAEs, such as pneumonitis, thyroiditis, and colitis. Severe irAEs are more likely to occur in patients with higher autoimmune PRS. These results imply that pre-emptive risk assessment and monitoring techniques during immunotherapy may soon be guided by host genetic profiling [96].

Combination therapies and PGx implications

Combining ICIs with chemotherapy or targeted therapies improves efficacy by enhancing antigen release and modulating immune suppression. In the KEYNOTE-522 trial, neoadjuvant pembrolizumab plus chemotherapy significantly increased pathogenic complete response and event-free survival, regardless of PD-L1 status [97,98]. Immune-active gene signatures and BRCA1/2 mutations are associated with better responses, while germline variants in CYP2C8 and ABCB1 may alter chemotherapy pharmacokinetics and indirectly affect ICI toxicity. As combinations with ADCs (e.g., Sacituzumab govitecan) expand, integrated PGx profiling will be crucial to optimize efficacy and manage overlapping toxicities [99].

PGx AND CHEMOTHERAPY TOXICITY

Taxanes (Paclitaxel, Decetaxel)

Although taxanes (paclitaxel and docetaxel) are commonly used to treat breast cancer, they often result in dose-limiting peripheral neuropathy and neutropenia.

Key genes involved:

- ABCB1 (P-glycoprotein): One of the most important transporters of drugs in taxane disposition. There are a large number of candidate-gene studies that have compared common variants of ABCB1 (C3435T and G2677T/A) to paclitaxel and docetaxel-induced toxicity

(especially peripheral neuropathy and neutropenia). Nevertheless, the findings of meta-analyses and systematic reviews indicate non-homogeneous and moderate-sized associations, which have small effect sizes and large inter-study variabilities and limit their predictive potential. Ethnicity differences, different treatment regimens, and the definition of toxicity also add to the discrepancy in the results, and existing evidence does not justify regular clinical testing [100,101].

- CYP2C8: One of the main enzymes that metabolizes paclitaxel. Pharmacokinetic investigations have identified reduced-function alleles like CYP2C83 to be associated with reduced paclitaxel clearance and exposure. Some of these pooled analyses indicate the potential interdependence between CYP2C8 variants and a higher risk of toxicity; however, the meta-analyses' results are inconclusive, and there are inconsistent corrections between genotyping, drug exposure, and adverse effects that are of clinical relevance. Therefore, the CYP2C8 genotyping is not an option that is recommended in determining the dosing of taxanes in standard practice [102] (Table 4).
- CYP3A4/CYP3A5: These enzymes metabolize taxanes, but evidence on whether common CYP3A variants predict neuropathy is inconsistent. While some sequencing studies identified rare CYP3A mutations linked to severe neuropathy, large population analyses show little to no significant effect [103].

Clinical implications

PGx profiling – especially when used with clinical risk factors, such as diabetes – can pinpoint patients at higher risk for taxane toxicity, enabling closer monitoring or tailored doses. However, genetic testing for common pharmacokinetic variants is not yet standard practice, due to inconsistent associations across studies and populations [106].

Fluoropyrimidines (Capecitabine, 5-fluorouracil)

Patients with reduced DPYD/DPD activity are at high risk for severe toxicity (e.g., diarrhea, mucositis, myelosuppression, hand-foot syndrome) when treated with fluoropyrimidines. Variants, such as DPYD *2A, 13, c.2846A>T, and HapB3 are strongly linked to decreased DPD function. Screening for these can guide genotype-based dose reductions (typically 20-50%) per CPIC and DPWG guidelines (Fig. 3). Pre-treated testing is now recommended by European guidelines, and real-world data show that PGx-guided dosing reduces serious adverse events [107].

Clinical implications

The most obvious example of how pre-emptive PGx testing enhances safety in oncology is DPYD genotyping (with phenotyping when necessary), which is becoming more and more advised in practice [108].

Anthracyclines (Doxorubicin, Epirubicin)

The genetic predisposition to cardiotoxicity caused by anthracyclines has been most consistently reported in pediatric cancer groups, in which variations in RARG, SLC28A3, UGT1A6, and ABCC1 have been reported to hold constant relationships with cardiac dysfunction in the long run [109,110]. Conversely, the evidence in the cohort of breast cancer in adulthood is still limited and less consistent with a smaller body of evidence indicating that variants in CBR3, NAD(P)H oxidase-related genes, and oxidative stress pathways may have a role. Variations in cumulative dose, cardiac reserve and adulthood, comorbidities, and years of follow-up are likely to be cause of variation between pediatric and adult results [111,112]. As a result, although pediatric data are of value regarding the mechanistic understanding, there is no genetic marker that is anticipated to be used as a routine anthracycline cardiotoxicity risk-stratifying in adult patients with breast cancer, which highlights the necessity of large, prospective trails of adult-specific validation [113].

Clinical implications

Genotyping for the risk of anthracycline cardiotoxicity is a field of present research; when high-risk alleles are found (particularly in conjugation with clinical risk factors), physicians may decide to limit cumulative anthracycline dosage, pick different regimens, or improve cardiac surveillance. However, until there are more extensive prospective validations, routine pre-treatment testing is not yet generally advised [114].

Importance of toxicity prediction for personalization

PGx-based toxicity prediction enhances chemotherapy safety by reducing preventable severe adverse reactions, enabling risk-adapted monitoring, and guiding individualized starting dose. These methods also aid in the prevention of unnecessary hospitalization and interruption of treatment, as well as dose intensity, where feasible. Among present applications, DPYD genotyping is the most firmly established with guideline-supported dosing algorithms. Growing evidence indicates that broader PGx panels – capturing key pharmacokinetic and cardiotoxicity loci – may further optimize taxane and anthracycline use, particularly when integrated with clinical risk factors and validated in prospective studies [115].

Practical recommendations

- DPYD testing: When resources permit, suggest pre-treatment genotyping for common high-risk DPYD alleles; use CPIC/DPWG dose algorithms (25–50% reductions depending on genotype)
- Taxane PGx: When unexplained severe toxicity occurs or in clinical trials, take into account PGx data (ABCB1, CYP2C8, CYP3A4/5, and transporters); routine testing is not yet conventional
- Anthracyclines: Recognize UGT2B7, SLC28A3, RARG, and other potential variations associated with toxicity; make a decision based on genetic data, clinical risk factors, and echocardiographic surveillance. Before widespread pre-treatment testing, more prospective trials are required [116].

TRANSLATIONAL IMPLEMENTATION

Clinical guidelines and regulatory biomarker label

Translational PGx relies on biomarker information from drug labels and evidence-based clinical guidelines. The CPIC provides peer-reviewed prescribing recommendations that translate genotype results into actionable treatment decisions. Regulatory agencies also include PGx markers in drug labels; for example, the U. S. FDA maintains an updated Table of PGx Biomarkers in Drug Labeling that highlights drugs with relevant genetic information. National authorities (EMA, Health Canada, PMDA) further guide local implementation through complementary scientific advice [117].

Role of PharmGKB and ClinVar in breast cancer PGx

The translational pipeline revolves around two public resources. Clinicians and researchers frequently utilize PharmGKB to analyze PGx results and map evidence levels for gene-drug combinations. PharmGKB curates clinical annotations, dosage instructions, and evidence summaries that relate variations to treatment responses. Acrucial step for uniform reporting and the integration of PGx into electronic health records (EHRs), ClinVar offers a central repository for variant assertions (pathogenicity/clinical significance) and has been developing to better support germline and somatic variant classification pertinent to therapy decisions. When combined, these materials enable clinical decision support (CDS) technologies, minimize redundancy, and standardize variant interpretation [105].

Current genotype-guided and implementation trials

From 2020–2025, several large-scale trials and implementation studies have evaluated genotype-guided chemotherapy dosing and preventive PGx screening. Examples include PACIFIC-PGx, which tests UGT1A1- and DPYD-guided dosing across multiple centers, national programs showing reduced fluoropyrimidine toxicity with pre-treatment DPYD genotyping, and ongoing CYP2D6-tamoxifen studies assessing endoxifen-guided strategies. Collectively, these efforts demonstrate a shift from hypothesis-based research toward system-level clinical implementation of pharmacogenomics (Table 5). [118].

Practical implementation considerations and research gaps

Although this is increasingly proving to be true, practical barriers continue to hamper clinical application of PGx in breast cancer. Financial limitations of testing and reimbursement due to recourse constraints, especially in resource-constrained environments limits routine uptake [125]. Treatment decisions may be delayed because of turnaround time unless pre-emptive testing in present [126]. Moreover, insufficient clinician training and apprehension of intermittent adaptation of PGx findings to EHRs and decision-support tools are impediments to real-time practice in oncology [127].

To make use of PGx in routine oncology, a number of co-ordinated factors must be involved. First, the standardized testing panels and consistent alleles-to-phenotype reporting are necessary such that the labs generate harmonized results that can be used in CDS systems. Furthermore, crucial is a quick turnaround with smooth integration of HER functionality that enables the use of genotype information to guide treatment until treatment is commenced [128]. Broader adoption also depends on reimbursement and aligned national policies, which are often guided by the FDA biomarker table and regional regulatory recommendations. Ensuring equity is critical, since allele frequencies and variant effects differ across populations; implementation must be supported by multiethnic validation to avoid widening disparities. Finally, although DPYD testing offers a successful model, additional large pragmatic and randomized trials across drug classes and diverse clinical settings are needed to strengthen evidence, demonstrate clinical benefit, and refine cost-effectiveness [129].

CHALLENGES, LIMITATIONS, AND CONTROVERSIES

Conflicting evidence (Especially CYP2D6-tamoxifen)

One of the issues with tamoxifen therapy is the difference in CYP2D6 activity; genotype effects and clinical evidence are discussed in detail in the "Tamoxifen and CYP2D6" Section.

Need of multi-ethnic PGx evidence and equity considerations

Multi-ethnic biorepositories and PGx studies in the underrepresented populations are urgently needed to facilitate equitable translation of the results to clinical practice. The relationships between alleles frequencies and genotype-phenotypes of the most common PGx variants vary significantly between populations, and restrict the external validity of evidence based on many cohorts of European ancestry [130,131]. Devoted multi-ethnic research is necessary to prevent complicating the inequality in health and contribute to worldwide useable evidence-based PGx recommendations [132].

Inter-ethics genetic variability

PGx variant frequencies differ widely across populations, and functional alleles, such as CYP2D6*10 and CYP2D6*17 occur far more in Asian and African groups than in Caucasians. This diversity limits the generalized of many PGx studies, which frequently lack adequate multi-ethnic representation. A recent global systematic review of PGx research in Indigenous and underrepresented populations highlighted that incomplete diversity can restrict clinical applicability and risks widening – rather than reducing – health disparities if implementation proceeds without proper validation [133].

Lack of standardization in testing

Another major shortcoming is the lack of a standard procedure of pharmacogenetic testing in cancer. Variations occur in the alleles which are assayed, in the methods used to reduce genotype to phenotype (e.g., by using an activity rating), in reporting of results and in the speed of results returned. A 2024 narrative evaluation found that the standards of testing and reporting processes varied greatly between laboratory reports and guideline papers worldwide, undermining the credibility of cross-institutional comparison and harmonized application. Without uniformity, the results interpretation, CDS, and systematic adaptation are all affected [134].

Integration barriers in clinical oncology (Cost, infrastructure, regulatory hurdles)

There is widespread adoption in the real world, even in cases where evidence has suggested the use of actionable PGx testing. The barriers are show genotyping turnaround, inadequate HER-integrated decision support, and less expertise in clinicians. A 2024 qualitative study of health-informatics leaders identified inadequate data infrastructure, unclear institutional protocols, and reimbursement uncertainty as major obstacles. Although cost-effectiveness analyses often favor tests, such as DPYD genotyping in high-income settings, upfront implementation costs, and variable regulatory or reimbursement policies continue to restrict broader uptake [135].

FUTURE PERSPECTIVES

Multi-omics integration: Beyond single-gene PGx

Future PGx research in breast cancer is shifting from single-gene analysis toward multi-omics integration, combining genomic, transcriptomic, proteomic, and metabolomic data to better capture mechanisms of drug response and resistance. Studies from 2020 to 2025 show that models incorporating multi-omics markers outperform genomics alone in predicting endocrine resistance and chemotherapy response. Large resources, such as TCGA and METABRIC have become essential for validating PGx pathways and identifying composite biomarkers with stronger clinical relevance [136].

Multi-omics is not only a progression of genomics but also includes transcriptomics and proteomic data to further narrow down prediction in therapeutic use. As an example, proteomic studies have reported that an altered HER2 signaling complex, loss of PTEN, and PI3K/AKT pathway indicate trastuzumab resistance, despite the presence of HER2 [137]. These kinds of integrative methods can enhance better patient stratification compared to single-gene biomarkers.

Polygenic risk and PGx score (PRS/PGx-scores)

PRS and PGx scores (PGx-scores) combine multiple variants into a single predictor of treatment response or toxicity. Integrated PRS models incorporating CYP2D6, CYP3A5, ESR1, and transporter genes have improved prediction of tamoxifen outcomes, while similar multi-gene models are being developed for taxane-induced neuropathy and anthracycline cardiotoxicity [138]. Although promising, PRS/PGx-scores require broad validation and standardized computational methods before clinical adoption [139].

Artificial Intelligence (AI) and Machine Learning (ML) in drug response prediction

Large-scale PGx and multi-omic datasets are now being harnessed by AI and ML to predict treatment outcomes, toxicity, and resistance. These models can capture complex, non-linear interactions across genetic, transcriptomics, and clinical data. Recent work (2023–2025) shows deep-learning frameworks accurately forecast chemotherapy toxicity and endocrine resistance, and ML models trained on real-world data can identify patients who will benefit most from agents, such as CDK4/6 or PARP inhibitors or suggest optimal combination strategies [140].

AI and ML are used to systematically introduce precision oncology based on the combination of genomic and clinical data. Watson Oncology has demonstrated high concurrence with oncology tumor board recommendations with regard to breast cancer treatment planning [141,145]. On the same note, the Tempus platform applies AI multimodal integration of data to facilitate guideline-based biomarker testing and patient stratification in breast cancer treatment [143].

Expanding PGx to novel and targeted therapies

PGx is increasingly relevant for CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) and PARP inhibitors (olaparib and talazoparib). Genetic variants in BRCA1/2, PARP1, and other DNA-repair genes may influence PARP inhibitor response, while polymorphisms in ABCB1, CYP3A4, and SULT2A1 are linked to CDK4/6 metabolism and toxicity [144]. New agents will also introduce new agents, and with new

agents, PGx biomarkers will be important to inform sequencing, dosing, and combination strategies [145].

Precision oncology trials and global implementation

Multi-omics and clinical integration are changing precision oncology to direct therapy. Studies, such as NCI-MATCH, CANCER-PREDICT, and PANGEA-PGx are transforming the paradigm shift to an organ-based to genotype-driven treatment [146]. Consortia, such as ICPerMed and GA4GH, are moving toward standardization, ethical models, population allele data, and low-cost testing across the globe to create equitable access [152].

CONCLUSION

PGx is transforming the treatment of breast cancer by explaining the disparities in responses of patients receiving endocrine therapy, targeted agents, immunotherapy, and chemotherapy. CYP2D6 is the most examined biomarker of tamoxifen because the variants of its functional functioning determine the endoxifen formation and treatment outcomes. New innovations in HER2-based PGx and immunogenomics are also enhancing the resistance prediction and identification of probable responders to ICIs, particularly in TNBC.

In general, approved genomic biomarkers are progressively improving treatment individualization by supporting the choice of drugs, improving dosage, and decreasing adverse effects. However, there are still obstacles, such as a lack of consistent evidence that some of the markers can be measured, ethnic diversity in research, and inconsistent testing platforms and clinical recommendations.

The way forward involves massive multiethnic prospective studies, multi-ome integration, poly-genetic risk models, and AI predictive tools to be incorporated. As scientific and regulatory progress, full-fledged individualized treatment of breast cancer is an ever-growing possibility.

AUTHOR CONTRIBUTIONS

Conceptualization, Formal analysis, Investigation, resources, data curation, writing original draft by Mr. Tejas D. Pimple. Data collection, writing, and editing by Ms. Pooja P. Hulke. Review by Dr. Manish P. Deshmukh and supervision by Dr. Ujwal B. Vyas.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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