Pharmacogenetics in Breast Cancer Therapy

Sing-Huang Tan, Soo-Chin Lee, Boon-Cher Goh, and John Wong

Abstract

Interindividual and interethnic variability of drug pharmacokinetics and pharmacodynamics may be contributed by commonly occurring genetic polymorphisms of drug-metabolizing enzymes and transporters. Polymorphisms of CYP2D6 in particular have been associated with effects on tamoxifen disposition and clinical efficacy, with interethnic differences in distribution of functional alleles that affect metabolizer phenotype. Other tamoxifen-related genetic variants of CYP3A4, CYP3A5, and sulfotransferase1A1 (SULT1A1) are also briefly reviewed here. Polymorphisms of CYP19A1 (aromatase gene) have been reported to correlate with clinical outcomes from aromatase inhibitors in small studies but require further confirmation. Many studies on chemotherapy are based on hypothesis-generating association studies and need to be validated through larger-scale cooperative group studies. For anthracyclines, polymorphisms in genes such as carbonyl reductase 3 (CBR3), ATP-binding cassette subfamily B, member 1 (ABCB1), glutathione-related transporter genes, and oxidative stress-related genes have been reported to correlate with clinical outcomes. The pharmacogenetics of taxanes has been extensively investigated, but associations of genetic polymorphisms in drug-metabolizing enzymes and transporters reported in earlier small studies have not been validated in a recent large clinical trial. Allelic variants associated with gemcitabine, capecitabine/5-fluorouracil, vinorelbine, and platinum disposition are reviewed. No pharmacogenetic studies have been published for targeted agents thus far, although several potential candidate genes warrant investigation. Future pharmacogenetic studies will need to focus on integration of multiple drug pathways to allow a more comprehensive analysis of genetic factors influencing drug efficacy and toxicity.

Background

Breast cancer is a global health problem with an estimated age-standardized incidence rate of 37.4 per 100,000 and age-standardized mortality rate of 13.2 per 100,000 women (1). Increasing interest in personalized medicine has led to in-depth research into genetic pathways of drug metabolism and the role of biomarkers to optimize therapeutic decisions for each individual patient (2, 3). Although the current armamentarium of breast cancer therapies is improving rapidly, it is often hindered by drug resistance and treatment-related toxicities. In this regard, interethnic and interpatient variability is observed but not fully understood; the study of pharmacogenetics is making great strides in revealing possible mechanisms. More than a decade ago, amonafide, a site-specific intercalating agent and topoisomerase II inhibitor, showed activity in advanced breast cancer (4). However, genetic polymorphisms in the N-acetyltransferase-2 gene causing varying acetylation rates, interethnic differences in drug clearance, and unpredictable toxicities have hampered its clinical development (5, 6). Nonetheless, it is one of the early examples of interethnic differences playing an important role in pharmacogenetics. Drugs such as warfarin also exhibit interethnic differences in dose requirements with a possible genetic basis (7). Both tumor genomic factors (3) as well as heritable genetic factors may affect interindividual responses to drug therapy. This review aims to provide an overview of heritable genetic factors that might predict drug response and toxicities of major classes of breast cancer therapy (Table 1): hormonal therapies [tamoxifen and aromatase inhibitors (AI)] chemotherapeutic agents (anthracyclines, taxanes, etc.), and biological targeted therapy (trastuzumab, lapatinib, and bevacizumab), including possible interethnic differences.

Potentially relevant studies and review articles were obtained from a PubMed search spanning the period from 1980 to 2008. Search terms included the following combined subject headings: pharmacogenetics, pharmacogenomics, genetic polymorphisms, single nucleotide polymorphisms, breast cancer, tamoxifen, AIs, fulvestrant, anthracyclines, taxanes, paclitaxel, docetaxel, gemcitabine, capecitabine, vinorelbine, platinum, trastuzumab, lapatinib, and bevacizumab. The citation lists of all retrieved articles were examined to identify other potentially relevant articles.

Hormonal Therapies

Tamoxifen. Tamoxifen is used in treating estrogen receptor (ER)–positive early and advanced breast cancers, ductal carcinoma in situ, and as primary chemoprevention in high-risk
Table 1. Summary of genetic polymorphisms that influence PK and/or PD of breast cancer therapeutics

<table>
<thead>
<tr>
<th>Genes/polymorphisms</th>
<th>In vitro activity</th>
<th>In vivo data clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine therapy</strong></td>
<td></td>
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<tr>
<td>Tamoxifen</td>
<td></td>
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<tr>
<td>Poor metabolizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>Nonfunctional</td>
<td>Homozygotes or heterozygotes had decreased plasma endoxifen concentrations after adjuvant tamoxifen for 4 mo (37).</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>Nonfunctional</td>
<td>Allele carriers had more recurrences and significantly worse DFS (16, 17). One negative study biased by inclusion of ER-negative patients (18). Two conflicting studies reported allele carriers to have decreased risk of breast cancer recurrence but had several confounding factors (19, 20).</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>Enzyme absent</td>
<td>Allele carriers had significantly worse EFS with adjuvant tamoxifen (17).</td>
</tr>
<tr>
<td>CYP2D6*6</td>
<td>Nonfunctional</td>
<td>Homozygotes or heterozygotes had decreased plasma endoxifen concentrations after adjuvant tamoxifen for 4 mo (37).</td>
</tr>
<tr>
<td>Intermediate metabolizers</td>
<td></td>
<td></td>
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<tr>
<td>CYP2D6*10</td>
<td>Reduced</td>
<td>Allele carriers had worse recurrence outcomes with adjuvant tamoxifen (17, 26, 29). Metastatic breast cancer patients had shorter TTP with tamoxifen (13).</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>Reduced</td>
<td>No established data in relation to breast cancer clinical outcomes.</td>
</tr>
<tr>
<td>CYP2D6*41</td>
<td>Reduced</td>
<td>Allele carriers had increased recurrences, decreased RFS, significantly worse EFS with adjuvant tamoxifen (17).</td>
</tr>
<tr>
<td>Ultrarapid metabolizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6*2xn</td>
<td>Increased</td>
<td>No established data in relation to breast cancer clinical outcomes.</td>
</tr>
<tr>
<td><strong>Clinical application:</strong> Food and Drug Administration – approved AmpliChip CYP450 Test commercially available. No consensus on testing or clinical algorithm for genotype-based treatment.</td>
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<tr>
<td>CYP3A4*1B</td>
<td>Reduced</td>
<td>Three-fold increased risk of endometrial cancer in tamoxifen-treated women (36). Several negative studies on tamoxifen metabolism (37, 38) or breast cancer outcomes (16), but one study reported significantly improved RFS in adjuvant tamoxifen-treated postmenopausal breast cancer (20).</td>
</tr>
<tr>
<td>CYP3A5*3</td>
<td>Reduced</td>
<td>Tamoxifen-treated homozygotes had three times the risk of death compared with heterozygotes or wild-type (39). Adjuvant tamoxifen-treated breast cancer patients with SULT1A1*2/<em>2 and either UGT2B15</em>1/<em>2 or UGT2B15</em>2/*2 had significantly decreased 5-y survival (18). Two negative studies with respect to tamoxifen PK (20, 37).</td>
</tr>
<tr>
<td>SULT1A1*2</td>
<td>Reduced</td>
<td></td>
</tr>
<tr>
<td>UGT1A4 Leu48Val</td>
<td>Increased</td>
<td>Glucuronidation of tamoxifen and 4-hydroxytamoxifen (40).</td>
</tr>
</tbody>
</table>

(Continued on the following page)
## Table 1. Summary of genetic polymorphisms that influence PK and/or PD of breast cancer therapeutics (Cont’d)

<table>
<thead>
<tr>
<th>Genes/polymorphisms</th>
<th>In vitro activity</th>
<th>In vivo data clinical application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UGT2B15*2</strong></td>
<td>Increased</td>
<td>Adjuvant tamoxifen-treated breast cancer patients with SULT1A1*2/<em>2 and either UGT2B15</em>1/<em>2 or UGT2B15</em>2/*2 had significantly decreased 5-y survival (18).</td>
</tr>
<tr>
<td><strong>ESR-Xba1/ESR2-02</strong> genotypes</td>
<td>—</td>
<td>ESR-Xba1 associated with tamoxifen-induced changes in triglycerides and HDL in premenopausal women (41). ESR1-Xba1 and ESR2-02 genotypes associated with tamoxifen-induced changes in total cholesterol and triglycerides, respectively, in postmenopausal women (41).</td>
</tr>
<tr>
<td><strong>AIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP19A1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3′-untranslated region variant (rs4646)</td>
<td>—</td>
<td>Increased complete response rate and TTP in postmenopausal metastatic breast cancer patients treated with letrozole (43).</td>
</tr>
<tr>
<td><strong>CYP19A1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cys&lt;sup&gt;364&lt;/sup&gt;, Thr&lt;sup&gt;364&lt;/sup&gt;, Arg&lt;sup&gt;39&lt;/sup&gt;Cys&lt;sup&gt;264&lt;/sup&gt;</td>
<td>Decreased enzyme activity. Relative resistance to letrozole with the Arg&lt;sup&gt;39&lt;/sup&gt;Cys&lt;sup&gt;264&lt;/sup&gt; allozyme (42)</td>
<td></td>
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<tr>
<td><strong>Fulvestrant</strong></td>
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<tr>
<td><strong>Chemotherapy</strong></td>
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<tr>
<td><strong>Anthracyclines</strong></td>
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<tr>
<td><strong>CBR3</strong></td>
<td>Reduced enzyme activity</td>
<td>Reduced conversion of doxorubicin to doxorubicinol, increased tumor reduction, and increased hematologic toxicities (48).</td>
</tr>
<tr>
<td><strong>CBR3 730G&gt;A</strong></td>
<td>Higher catalytic activity</td>
<td>Increased doxorubicin conversion to doxorubicinol (48). No significant correlation with doxorubicin PK or PD (49).</td>
</tr>
<tr>
<td><strong>CBR3 c.1236-2677-3435</strong></td>
<td></td>
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<tr>
<td><strong>CC-GG-CC</strong> haplotype</td>
<td>Associated with higher P-glycoprotein expression and lower drug exposure (51)</td>
<td>Associated with significantly lower doxorubicin exposure compared with CT-GT-CT and TT-TT-TT haplotypes (51).</td>
</tr>
<tr>
<td><strong>ABCB2</strong> (c.421C&gt;A)</td>
<td>Reduced protein expression and function</td>
<td>No correlation with doxorubicin PK (51).</td>
</tr>
<tr>
<td><strong>GSTM1 null genotype</strong></td>
<td>Reduced enzyme activity; reduced removal of chemotherapy-induced secondary oxidation products</td>
<td>Breast cancers patients (majority stages I and II) null for GSTM1 and GSTT1 had decreased mortality with chemotherapy (predominantly CAF; ref. 52).</td>
</tr>
<tr>
<td><strong>GSTT1 null genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MnSOD C allele (Ala (16))</td>
<td>C allele (Ala&lt;sup&gt;16&lt;/sup&gt;) has higher activity than the T allele (Val&lt;sup&gt;16&lt;/sup&gt;; ref. 53)</td>
<td>Nonsignificant decreased risk of death in chemotherapy-treated (primarily anthracycline treated) breast cancer patients (53). Combination of MnSOD CC and MPO GG genotypes had significantly 3-fold decrease in hazard of death (53).</td>
</tr>
<tr>
<td><strong>MPO -463G</strong></td>
<td>Higher transcriptional activity than the A allele and generates more reactive oxygen species</td>
<td>Better DFS in breast cancers treated with adjuvant CAF or CMF (54).</td>
</tr>
</tbody>
</table>

(Continued on the following page)
### Table 1. Summary of genetic polymorphisms that influence PK and/or PD of breast cancer therapeutics (Cont’d)

<table>
<thead>
<tr>
<th>Genes/polymorphisms</th>
<th><strong>In vitro activity</strong></th>
<th><strong>In vivo data clinical application</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taxanes</strong></td>
<td></td>
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</tr>
<tr>
<td>ABCB1, ABCC1, ABCC2, ABCG2, CYP1B1, CYP2CB, CYP3A4, CYP3A5, MAPT, TP53, CDKN1A</td>
<td>—</td>
<td>No clear correlation in ovarian cancer patients treated with a taxane (paclitaxel or docetaxel) and carboplatin (65).</td>
</tr>
<tr>
<td><strong>Gemcitabine</strong></td>
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<tr>
<td>RRM1 -37C and -524T</td>
<td>Increased transcriptional activity (2.29-fold; ref. 113)</td>
<td>Advanced breast cancer patients treated with carboplatin/gemcitabine had increased tumor response, PFS and OS (80).</td>
</tr>
<tr>
<td>RRM1 2455G-2464A</td>
<td>Cell lines with 2455A&gt;G and 2464G&gt;A variants exhibited similar sensitivity to gemcitabine compared with wild-type (79)</td>
<td>Associated with less neutropenia, granulocyte colony-stimulating factor requirements, poorer PFS and OS (79).</td>
</tr>
<tr>
<td>CDA*3 (208G&gt;A)</td>
<td>Decreased deamination activity</td>
<td>Decreased gemcitabine clearance, increased neutropenia when gemcitabine administered with platinums or 5-FU in Japanese cancer patients (81).</td>
</tr>
<tr>
<td>CDA 435C&gt;T</td>
<td>Synonymous variant</td>
<td>Decreased response rates and TTP in lung cancer patients treated with carboplatin/gemcitabine (84). Breast cancer data not available as yet.</td>
</tr>
<tr>
<td>SLC28A1 1561G&gt;A</td>
<td>Associated with increased uptake of the pyrimidine nucleoside, thymidine into cells (114)</td>
<td>Increased hematologic toxicity in lung cancer patients given carboplatin/gemcitabine (84). Breast cancer data not available as yet.</td>
</tr>
<tr>
<td><strong>Capcitabine/5-FU</strong></td>
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<tr>
<td>TS tandem repeat sequences (TSER<em>2, TSER</em>3, TSER<em>4, TSER</em>9)</td>
<td>Increases TS expression and leads to resistance</td>
<td>TSER<em>3/TSER</em>3 genotype has poorer response to 5-FU and shows no improvement in survival from adjuvant 5-FU compared with TSER<em>3/TSER</em>2 or TSER<em>2/TSER</em>2 genotype (86).</td>
</tr>
<tr>
<td>MTHFR 677C&gt;T</td>
<td>Decreased</td>
<td>No correlation with capcitabine toxicity (87).</td>
</tr>
<tr>
<td>MTHFR 1298A&gt;C</td>
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</tr>
<tr>
<td>DPYD*2A and other functional variants</td>
<td>Complete or partial deficiency</td>
<td>Severe 5-FU toxicity in 0.1% and 3-5% of people, respectively (88). Clinical application: rarity and heterogeneity of genetic variants has precluded routine clinical testing.</td>
</tr>
<tr>
<td><strong>Vinorelbine</strong></td>
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</tr>
<tr>
<td>ABCB1 1236T&gt;C</td>
<td>Synonymous variant</td>
<td>No association with vinorelbine clearance in cancer patients (91).</td>
</tr>
<tr>
<td>ABCB1 2677G&gt;T/A</td>
<td>Association with P-glycoprotein function or expression not certain. 2677T has been associated with increased digoxin efflux in vitro (59).</td>
<td></td>
</tr>
<tr>
<td>ABCB1 3435C&gt;T</td>
<td>Lower expression of P-glycoprotein and lower active efflux of drug affecting resistance</td>
<td></td>
</tr>
<tr>
<td><strong>Platinums</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCCC2, ABCG2, ERCC1, ERCC2, GSTP1, MPO, XRCC1</td>
<td>—</td>
<td>No clear correlation with clinical outcomes or toxicities in ovarian cancer patients treated with carboplatin and a taxane (paclitaxel or docetaxel; ref. 65).</td>
</tr>
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CYP2D6 is the key enzyme catalyzing N-desmethyl-tamoxifen to endoxifen. More than 80 allelic variants have been described in CYP2D6, many of which are associated with increased, decreased, or absent enzyme activity. These variants result in phenotypes with a tetramodal distribution of metabolic activity: poor, intermediate, extensive (“normal”), and ultrarapid. The nonfunctional variants CYP2D6*3 (2637delA), CYP2D6*4 (1934G>A), CYP2D6*5 (gene deletion), and CYP2D6*6 (1795delT) constitute the majority of poor metabolizer phenotypes (11, 12), with reportedly lower endoxifen concentrations compared with wild-type. Five percent to 10% of Caucasians are poor metabolizers, with the CYP2D6*4 allele being the predominant allele (70-90%; ref. 13). In contrast, CYP2D6*4 is extremely rare in Asians or Black Africans. CYP2D6 alleles resulting in the intermediate metabolizer phenotype include CYP2D6*10 that occurs in 38% to 70% of Asians (14) and CYP2D6*17 that occurs in 20% to 34% of Africans (14), both of which are rare in Caucasians. In contrast, ultrarapid metabolizers carry gene duplications or multiduplications of functional alleles resulting in increased enzyme activity. These genotypes are rare in Caucasians and Asians but are common in Ethiopians and Saudi Arabsians (Table 2; ref. 15).

In a study by Goetz et al. (16) on 190 postmenopausal breast cancer patients treated with adjuvant tamoxifen, CYP2D6*4 homozygotes (n = 13) had significantly worse relapse-free and disease-free survival (DFS) and lower incidence of hot flashes compared with women with either one or no CYP2D6*4 variant. This was confirmed by Schroth et al. (17) in a retrospective cohort of 486 patients who noted that tamoxifen-treated patients with the CYP2D6*4, CYP2D6*5, CYP2D6*10, and CYP2D6*41 alleles had significantly worse survival, whereas no association was found among the women. Substantial interindividual variation exists in steady-state levels of tamoxifen and its metabolites following standard dosing (8). The majority of patients with metastatic disease and a significant proportion of patients receiving adjuvant tamoxifen eventually relapse, suggesting that the benefit is not uniform. Emerging data on tamoxifen pharmacogenetics have clinical relevance, as AIs have proven efficacy in both early and advanced postmenopausal breast cancers and offer a viable alternative.

Tamoxifen undergoes metabolism via the cytochrome P450-mediated pathway to several primary and secondary metabolites that show variable potencies toward the ER. N-desmethyl-tamoxifen, resulting from CYP3A4/5-mediated metabolism, is the major primary metabolite, accounting for ~90% of primary tamoxifen oxidation, whereas 4-hydroxy-tamoxifen, mediated by CYP2D6 activity, is a minor metabolite. Both N-desmethyl-tamoxifen (via CYP2D6) and 4-hydroxy-tamoxifen (via CYP3A4/5) are secondarily metabolized to 4-hydroxy-N-desmethyl-tamoxifen (endoxifen). Both 4-hydroxy-tamoxifen and endoxifen are important active metabolites, exhibiting similar potency, although endoxifen plasma concentrations are up to 14-fold higher (9). Tamoxifen metabolites are inactivated via conjugation by sulfotransferases such as sulfotransferase1A1 (SULT1A1), or glucuronidation by the UDP-glucuronosyltransferases (UGT), including UGT1A8, UGT1A10, UGT2B7, UGT2B15, and UGT2B17. In addition, CYP1B1, CYP2B6, and CYP2C19 may be responsible for the isomerization of trans-4-hydroxy-tamoxifen to its weakly estrogenic cis-isomer form, a reaction that could be associated with drug-resistant phenotypes (Fig. 1; ref. 10). As many of the tamoxifen-metabolizing enzymes are polymorphic, genetic variations may account for interindividual or interethnic differences in tamoxifen-related outcomes.
untreated. Three studies reported conflicting results (18–20), although confounding factors such as heterogeneity in patient populations may explain this difference. In Asia, the CYP2D6*10 allele is a major polymorphism resulting in the intermediate metabolizer phenotype. The frequency of this allele is approximately 37% to 70%, 50%, and 40%, respectively, in Chinese (21, 22), Koreans (23, 24), and Japanese (25, 26) compared with only 2% in European Caucasians (11). Two early Southeast Asian studies reported the CYP2D6*1/CYP2D6*10 to be the most common genotype in Malays and Chinese in Malaysia (27, 28). A Korean study in metastatic breast cancer patients found that CYP2D6*10 homozygotes had lower plasma levels of tamoxifen metabolites and a correspondingly shorter time to progression (TTP) compared with other CYP2D6 genotypes (13). In the adjuvant setting, CYP2D6*10 homozygotes have also been found to have significantly higher incidence of recurrence compared with wild-type (26, 29).

In addition to genetic variants, concomitant administration of CYP2D6 inhibitors may affect tamoxifen-related breast cancer outcomes by converting an extensive metabolizer to a phenotypic poor metabolizer and should be avoided. Potent CYP2D6 inhibitors include antidepressants such as fluoxetine and paroxetine, whereas moderate/weak inhibitors include cimetidine, amiodarone, ticlopidine, and haloperidol (30). These interactions were elegantly shown by Borges et al. (31)
that it may be clinically rational to carry out pharmaco-}

dynamics (PD). Hartman and Helft (33) have suggested
active metabolites that collectively account for tamoxifen phar-
is likely because CYP2D6 influences the exposure to several
establish the predictive importance of these measurements; this
correlated has not been shown to be informative; the studies that
higher dose. Measuring plasma levels of tamoxifen metabolites
metabolizers should avoid tamoxifen altogether or receive a
switching to AI (30).

A Food and Drug Administration–approved microarray-
based pharmacogenetic CYP2D6 test (Amplichip CYP450 Test)
is currently available detecting 27 CYP2D6 variants, including
nonfunctional variants (CYP2D6*3, CYP2D6*4, CYP2D6*5, and
CYP2D6*6), deficient variants commonly found in Asians
and Black Africans (CYP2D6*10 and CYP2D6*17), and
ultrarapid variants (CYP2D6*2XN in Middle Easterns and Ethiopians). A label change has been proposed to discuss the
option of CYP2D6 testing before tamoxifen use, although Food and Drug Administration has yet to reach a consensus to
recommend testing. There is currently no established treatment
algorithm based on CYP2D6 genotype, and it is unclear
whether women who are intermediate or poor CYP2D6
metabolizers are likely to benefit from longer tamoxifen use (up to 4-5 years) before
switching to AI (30).

Other genetic variants responsible for tamoxifen metabolism
have been studied. A CYP3A4 promoter variant, CYP3A4*1B (392A>G) has been associated with cancer phenotype and has
an allele frequency of 35% to 67% in African-Americans, 2% to
9% in Caucasians, and 0% in Taiwanese and Chinese (34, 35). No studies to date have linked CYP3A4*1B with altered
tamoxifen metabolism, although it has been reported to confer
a 3-fold increased risk of endometrial cancer for tamoxifen-
treated women (36). A CYP3A5 genetic polymorphism,
CYP3A5*3 (6986A>G), results in severely decreased CYP3A5
activity, although several studies have failed to show its
association with tamoxifen metabolism (37, 38) or breast cancer
outcomes (16). However, in a recent study, postmenopausal
patients treated with adjuvant tamoxifen, who were homozygous
for the CYP3A5*3C variant, displayed significantly improved
recurrence-free survival (RFS; ref. 20). These conflicting findings
underscore the complexity of tamoxifen metabolism and
resistance mechanisms and suggest that the evaluation of
variants representing different interacting mechanisms may be
more informative than evaluating single variants.

The enzymes responsible for elimination and inactivation of
tamoxifen and its metabolites through conjugation with either
a sulfate or a glucuronide may also have important genetic
variation. A polymorphism of the UGT2B15 gene, UGT2B15*2
variant (638G>A, Arg211His) encodes for a protein with
reduced activity. However, two studies exploring its association
with tamoxifen pharmacokinetics (PK) were negative (20, 37),
whereas a third study reported conflicting results of greater risk
of death in tamoxifen-treated patients (n = 160; ref. 39). In vitro
studies suggested a UGT1A4 variant (Leu48Val) to show
increased glucuronidation activity against tamoxifen and its
metabolites, although the clinical significance is still unex-
plored (40). A nonsynonymous polymorphism in UGT2B15
(UGT2B15*2; 253G>T) in a putative substrate binding domain
has been assessed (18); adjuvant tamoxifen-treated breast
cancer patients possessing UGT1A1*2/*2 and either
UGT2B15*1/*2 or UGT2B15*2/*2 had significantly reduced
5-year survival (18). This novel finding requires further
confirmation. In addition to drug-metabolizing enzymes, a
recent study reports that ER genotypes ESR-XbaI and ESR-02

<table>
<thead>
<tr>
<th>Genetic variant</th>
<th>Allele frequencies (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Caucasians</td>
</tr>
<tr>
<td>CYP2D6*3 (11)</td>
<td>1-2</td>
</tr>
<tr>
<td>CYP2D6*4 (11)</td>
<td>12-30 (median, 20%)</td>
</tr>
<tr>
<td>CYP2D6*5 (11)</td>
<td>2-7</td>
</tr>
<tr>
<td>CYP2D6*6 (11)</td>
<td>1</td>
</tr>
<tr>
<td>CYP2D6*10 (11)</td>
<td>1-2</td>
</tr>
<tr>
<td>CYP2D6*17 (11)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CYP2D6*41 (30)</td>
<td>8-10</td>
</tr>
<tr>
<td>CYP2D6*2Xn (115)</td>
<td>1-5</td>
</tr>
<tr>
<td>CYP3A4*1B (71)</td>
<td>2-9.6</td>
</tr>
<tr>
<td>CYP3A5*3C (116)</td>
<td>88</td>
</tr>
<tr>
<td>SULT1A1*2 (117, 118)</td>
<td>33</td>
</tr>
</tbody>
</table>

*Ethiopians and Saudi Arabs have allele frequencies ranging from 10% to 16%.
may be associated with tamoxifen-induced lipid changes and may further contribute to interindividual variability to tamoxifen benefits (41).

Aromatase inhibitors. AIs have proven efficacy in both advanced and early postmenopausal hormone receptor–positive breast cancers. Pharmacogenetic associations pertaining to their efficacy and toxicities have not been well described, although efforts are ongoing to elucidate these mechanisms. The target of AIs is the cytochrome P450 enzyme aromatase, which is encoded by the CYP19A1 or aromatase gene. Ma et al. (42) detected 88 CYP19 polymorphisms resulting in 44 haplotypes in 60 patients from each of four ethnic groups, Caucasian Americans, African-Americans, Han Chinese Americans, and Mexican Americans, and found wide interethnic variation in genotype distribution. Functional characterization showed the Cys264 and double variant Arg39Cys264 allozymes to show decreased activity compared with wild-type; the Arg39Cys264 allozyme also displayed a significant increase in inhibitor constant for letrozole, suggesting relative resistance. Interestingly, the Arg39 variant is present in 6.7% Han Chinese Americans but very rare in the other three ethnic groups, whereas the Cys264 variants occurred at higher frequencies in Han Chinese Americans and African-Americans (11.7% and 22.5%) than Caucasian Americans or Mexican Americans (2.5% and 5%). These findings suggest that patients with an aromatase enzyme with lower activity may derive less benefit from an AI and that interethnic differences in Al responses could exist, although confirmation in clinical studies is required. More recently, a small Spanish study (n = 67) described the association of a common CYP19A1 3’-untranslated region variant (rs4646) with higher complete response rate and improved TTP in postmenopausal, hormone receptor–positive, metastatic breast cancers treated with letrozole (43). Although the mechanism by which the variant affected letrozole activity was not directly addressed, possible mechanisms postulated included increased enzyme activity through mRNA stabilization or enhanced transcription. Another Spanish study (n = 94) evaluated 13 CYP19A1 polymorphisms in women receiving neoadjuvant letrozole and derived a predictive model comprising eight most informative polymorphisms, including rs4646, which could predict letrozole response at 4 months with 86% accuracy (44). These promising data warrant validation before clinical application.

Other CYP enzymes may also affect the PK of AIs. For example, anastrozole inhibits CYP1A2, CYP2C9, and CYP3A4; letrozole is metabolized by CYP2A6 and CYP2C19; and exemestane is metabolized by CYP3A4. Genetic polymorphisms in these enzymes could affect their efficacy or resistance.

To determine the clinical significance of genetic influence on AIs, several large studies are being carried out under the auspices of the Pharmacogenetics Research Network (45), including a study on single nucleotide polymorphisms and intragene haplotypes in adjuvant anastrozole PK and estrogen PD pathways (45). Further research into the genetic polymorphisms affecting specific subtypes of AIs is needed before they can be used to guide clinical decisions and provide further insight into therapy selection for the individual patient.

Fulvestrant. Fulvestrant is a pure antiestrogen that antagonizes the hormone-dependent activation of ERs. It is glucuronidated by UGT1A1, UGT1A3, UGT1A4, and UGT1A8 (46). There have been no studies to date about the clinical outcomes of UGT polymorphisms and fulvestrant and there is room for more research in this area.

Chemotherapeutic Agents

Anthracyclines. Anthracyclines (doxorubicin and epirubicin) have wide interindividual variation in PK and PD. A prospective study had suggested interethnic variations, noting Chinese breast cancer patients to experience more profound neutropenia from adjuvant doxorubicin/cyclophosphamide than Caucasians (47). Anthracyclines have complex disposition pathways involving various metabolizing enzymes and transporters that may contribute to interindividual variability. Doxorubicin and epirubicin undergo phase I reduction reactions to doxorubicinol and epirubicinol by carbonyl reductases (CBR1 and CBR3) and aldo-ketoreductases (AKR1A1 and AKR1C2); efflux out of cells is mediated by transporters including ABCB1, ABCC1, ABCC2, and ABCC9, whereas inactivation is by the cytochrome P450 enzymes (CYP3A4 and CYP3A5). Epirubicin also undergoes phase II reactions by conjugation, mainly by UGT2B7. The orphan nuclear receptors regulate transcription of multiple cytochrome P450 enzymes and transporters and may further contribute to the variability.

A recent prospective study on CBR1 and CBR3 in Asian breast cancer patients treated with single-agent doxorubicin (n = 101) revealed two common CBR3 variants to affect doxorubicin PK and/or PD (48). The CBR3 11G>A variant was associated with lower conversion of doxorubicin to doxorubicinol, greater tumor reduction, and hematologic toxicities, whereas the CBR3 730G>A variant was associated with increased conversion of doxorubicin to doxorubicinol but did not correlate with hematologic toxicity. The CBR3 11A variant was more common in Chinese than Caucasians (57% versus 36%) and may contribute to the greater doxorubicin-induced myelosuppression observed in Chinese, although this hypothesis requires validation in larger cohorts. Comprehensive analysis of three orphan nuclear receptors (PXR, CAR, and HNF4α) and CYP3A5*3C in the same cohort of patients revealed no significant correlation between these genotypes and doxorubicin PK or PD (49).

Among the ATP-binding cassette transporters, the ABCB1 gene, which encodes P-glycoprotein implicated in drug resistance, is one of the most studied. Common ABCB1 variants (1236C>T, 2677G>T/A, and 3435C>T) that show linkage and seem to impair ABCB1 substrate transport have been extensively studied with respect to their influence on drug disposition. Kafka et al. (50) reported significant correlation between the 3435T variant and better clinical response to anthracyclines with or without taxanes in locally advanced breast cancer patients (n = 68). Another retrospective study in Asian breast cancer patients (n = 62) receiving adjuvant doxorubicin-based chemotherapy reported the ABCB1 c.1236-2677-3435 CC-GG-CC haplotype to be associated with significantly lower doxorubicin exposure than the CT-GT-CT and TT-11T11 haplotypes, although effects on doxorubicin toxicities
were not reported (51). A variant (c.421C>A) in another transporter, ABCG2, did not correlate with doxorubicin PK in the same study.

In addition to genes that encode for metabolizing enzymes or transporters, genetic variants that may affect anthracycline-mediated tumor cell kill have been investigated. The glutathione S-transferases (GST) catalyze the reduction of secondary organic oxidation products produced by chemotherapy that contribute to further cellular damage, and individuals lacking or deficient in these enzymes may have better treatment outcome. In a retrospective study on 251 breast cancer women who predominantly received doxorubicin-based combination chemotherapy, women with null GSTM1 or GSTT1 genotypes had reduced mortality (52). Ambrosone et al. (53) studied variants in genes related to oxidative stress, including *manganese superoxide dismutase* (*MnSOD*), *catalase* (*CAT*), and *myeloperoxidase* (*MPO*), in radiotherapy- and/or chemotherapy-treated (including doxorubicin combinations) breast cancer survivors, and found those with genotypes associated with higher levels of reactive oxygen species [*MnSOD* C ( Ala19)] and *MPO-463G* variants] to have better survival. Concordant findings were reported in a preliminary Southwest Oncology Group study, which described association of the *MPO-463G* allele with better DFS in breast cancer women given adjuvantCAF [cyclophosphamide, doxorubicin, 5-fluorouracil (5-FU)] or CMF (cyclophosphamide, methotrexate, 5-FU) but not in untreated women (54).

Although anthracyclines have been used for decades, the mechanisms underlying their interindividual variability remain unclear. Although several prospective candidate genes and polymorphisms have been studied, most reports are retrospective, were confounded by the concurrent administration of other chemotherapeutic agents, and did not incorporate drug PK or report direct drug PD effects such as tumor responses or toxicities, making it difficult to derive clear correlations between genotype and anthracycline effects. Larger prospective studies incorporating both PK and PD end points, preferably in between genotype and anthracycline effects. Larger prospective studies incorporating both PK and PD end points, preferably in women (54).

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Functional CYP2C8 polymorphisms include CYP2C8*2 (Phe268Ile) and CYP2C8*3 (Lys183Arg), which have impaired intrinsic clearance for paclitaxel in vitro; however, no clinically significant associations have been found with paclitaxel clearance in vivo (70). Possibly, CYP metabolism of xenobiotics has evolved considerable redundant pathways, often including CYP3A4, which could be activated to compensate for dysfunction of the main metabolic pathway. CYP3A4 and CYP3A5 polymorphisms have also been studied in correlation with taxane disposition. CYP3A4*1B is a promoter polymorphism frequently found in African-Americans (45%) and Caucasians (2% to 9.6%) but rare in Southeast Asians and has been associated with increased CYP3A4 transcriptional activity (71). CYP3A5*3C is an intron 3 splicing variant that results in protein truncation. In Caucasian breast cancer patients receiving paclitaxel, doxorubicin, and cyclophosphamide, ABCB1 (1236G>T, 2677G>T/A), ABCG2 (421C>A), CYP1B1*3, CYP3A4*1B, CYP3A5*3C, CYP2C8*3, and CYP2C8*4 genotypes were not correlated with paclitaxel clearance, although homozygotes of CYP1B1*3 had significantly longer progression-free survival (PFS) (64). Alone, CYP3A5*3C was not associated with doxorubicin clearance in other studies (63). In a recent study in Caucasian patients, subjects harboring simultaneous CYP3A4*1B and CYP3A5*1A alleles had 64% higher doxorubicin clearance than those without (68). However, given the rarity of CYP3A4*1B in Asians, the finding is likely ethnic specific.

**Taxanes.** Together with anthracyclines, taxanes are the most active cytotoxic agents in breast cancer treatment. Both paclitaxel and docetaxel are good substrates of P-glycoprotein located at the biliary canalicular membrane and bind to tubulin residues to stabilize microtubules (55). Docetaxel is predominantly metabolized by CYP3A4/5, whereas paclitaxel is metabolized by CYP2C8/CYP3A4 to inactive hydroxylated metabolites (55). The hepatic influx protein transporter OATP1B3 has been shown to mediate transport of paclitaxel and docetaxel into the hepatocytes at the basolateral membrane (56). Given these potential candidate genes that have well-described polymorphisms, much effort has been put into correlating genetic variants with taxane PK and PD. This is particularly pertinent given that both taxanes have highly variable PK and unpredictable toxicities.

Pharmacogenetics will only be useful clinically if there is validated and mechanistic evidence for the influence of allelic variants on one or more specific PD end points. Taxanes present challenges in validation because of their schedule dependence, necessitating evaluation of genetic variants on PD at different regimens and doses. Furthermore, paclitaxel shows saturable distribution kinetics, and exposure time above threshold concentrations is better correlated with PD than area under the curve or maximum concentrations, complicating interpretation of any genotype-phenotype relationships.

As noted for anthracyclines, ABCB1 polymorphisms may affect the activity of P-glycoprotein, thereby potentially perturbing the disposition of taxanes (57–59). Although some studies have found ABCB1 genotype and haplotypes to correlate with taxane PK and toxicities (60–62), there have been many others that have not shown any correlation (63–65). For example, in Japanese patients with ovarian cancer, variant alleles at ABCB1 129T>C, 1236T>C, and 2677G>A/T were associated with lower paclitaxel area under the curve (60). For docetaxel, C1236T homozygotes had significantly lower clearance in a study of 92 patients (61), and the 3435TT genotype was associated with greater neutropenia in 58 patients (66). A previous report found that patients with the 2677TT-3435TT diplotype had significantly worse nadir neutropenia secondary to docetaxel treatment (67). On the other hand, several larger studies have not shown any effect of ABCB1 polymorphisms on taxane PK or PD (64, 65). No associations have been found between the genotype of membrane transporters MRP2, *breast cancer resistance protein* (BCRP), and OATP1B3 with paclitaxel or docetaxel PK or PD (68, 69).

Functional CYP2C8 polymorphisms include CYP2C8*2 (Phe268Ile) and CYP2C8*3 (Lys183Arg), which have impaired intrinsic clearance for paclitaxel in vitro; however, no clinically significant associations have been found with paclitaxel clearance in vivo (70). Possibly, CYP metabolism of xenobiotics has evolved considerable redundant pathways, often including CYP3A4, which could be activated to compensate for dysfunction of the main metabolic pathway. CYP3A4 and CYP3A5 polymorphisms have also been studied in correlation with taxane disposition. CYP3A4*1B is a promoter polymorphism frequently found in African-Americans (45%) and Caucasians (2% to 9.6%) but rare in Southeast Asians and has been associated with increased CYP3A4 transcriptional activity (71). CYP3A5*3C is an intron 3 splicing variant that results in protein truncation. In Caucasian breast cancer patients receiving paclitaxel, doxorubicin, and cyclophosphamide, ABCB1 (1236G>T, 2677G>T/A), ABCG2 (421C>A), CYP1B1*3, CYP3A4*1B, CYP3A5*3C, CYP2C8*3, and CYP2C8*4 genotypes were not correlated with paclitaxel clearance, although homozygotes of CYP1B1*3 had significantly longer progression-free survival (PFS) (64). Alone, CYP3A5*3C was not associated with doxorubicin clearance in other studies (63). In a recent study in Caucasian patients, subjects harboring simultaneous CYP3A4*1B and CYP3A5*1A alleles had 64% higher doxorubicin clearance than those without (68). However, given the rarity of CYP3A4*1B in Asians, the finding is likely ethnic specific.
are activated by ligand binding (49, 72, 73). Incorporating common polymorphisms of PXR, CAR, and HNF4α and CYP3A5*3C with other covariates in a nonlinear mixed effect model (NONMEM) for docetaxel clearance showed no significant contribution from these polymorphisms in explaining variability of clearance (74).

In summary, the contribution of pharmacogenetics to individualizing taxane therapy in breast cancer has been limited. To emphasize this issue, a large study, the Scottish Ovarian Cancer Study, showed that toxicities of paclitaxel or docetaxel and carboplatin did not correlate with known polymorphisms involved in the taxane disposition pathway (65). In this study carried out without PK, toxicities of the taxanes (paclitaxel/docetaxel) and platinum were studied in association with 27 polymorphisms of 16 genes in 914 patients, allowing application of a test set and a validation set, which gives more robust statistical conclusions than single- arm studies involving small patient numbers that could at best be considered exploratory. Possible reasons for discrepency apart from statistical chance may include less patient or physician bias, different schedules or combinations, or ethnic makeup of patients. Yet, other questions remain unresolved; for example, interethnic differences in docetaxel PK and toxicities have been described, with Chinese and Indians experiencing more frequent hematologic toxicity compared with Malays (49). However, no explanations for this have thus far been elucidated, warranting more studies.

**Other Chemotherapy Agents**

Chemotherapy agents, such as gemcitabine, capecitabine, vinorelbine, and platinum, are used widely, alone or in combination with other drugs, beyond first-line therapy in metastatic breast cancer. The pharmacogenetic effects of these drugs, however, are likely to be confounded by combination regimens and prior treatments resulting in relative tumor resistance and greater toxicities.

**Gemcitabine.** Gemcitabine is transported into cells by nucleoside transporters (SLC28 and SLC29; 75, 76), phosphorylated by deoxycytidine kinase (DCK) to its active monophosphate form, and subsequently by nucleotide kinases to gemcitabine triphosphate, and finally incorporated into DNA, inhibiting its repair and synthesis. Gemcitabine and gemcitabine monophosphate are inactivated by cytidine deaminase (CDA) and deoxycytidylylate deaminase, respectively (77, 78). Gemcitabine also inhibits thymidylate synthase (TS) and ribonucleotide reductases (RRM1 and RRM2) involved in DNA repair.

An RRM1 haplotype 2455G-2464A correlated with less neutropenia, granulocyte colony-stimulating factor requirements, and poorer PFS and OS in a prospective study of 74 Korean breast cancer patients treated with single-agent gemcitabine (79). In a retrospective study in advanced breast cancers treated with gemcitabine/carboplatin (n = 41), two RRM1 promoter region alleles (-37C and -524T) predicted for better tumor response, PFS and OS (80). A prospective study (n = 256) in Japanese reported patients with the CDA 208G>A (Ala70Thr) variant to have decreased gemcitabine clearance and greater hematologic toxicities following gemcitabine coadministered with fluorouracil or platinum (81); the variant is more common in Africans than in Japanese or Europeans (13% versus 4.3% versus 0%; refs. 82, 83). A synonymous variant CDA 435G>T (Thr145Thr) was associated with lower response rates and shorter TTP in Asian lung cancer patients receiving carboplatin/gemcitabine (84). In the same study, SLC28A1 1561G>A was related to increased hematologic toxicity (84) and showed interethnric differences in frequencies (Caucasians, 73%; Chinese, 12%; Malays, 30%; Indians, 35%) and warrants further evaluation (84). Ethnic differences have been observed in DCK with Asians showing a higher frequency of promoter variants -C360G/C201T than Caucasians, which may predispose to greater gemcitabine toxicities (85).

**Capecitabine and 5-FU.** Capecitabine is an oral prodrug of 5-FU. TS, the target of 5-FU, methylenetetrahydrofolate reductase (MTHFR), a key regulatory enzyme in folate metabolism, and dihydroxpyrimidine dehydrogenase (DPD), the catabolizing enzyme of 5-FU, are potential targets that could contribute to interindividual variability to 5-FU–based therapy. In the TS enhancer region, varying copies of 28-bp tandem repeated sequences (TSER*2, TSER*3, TSER*4, and TSER*9) have been described that increase TS expression and portend a worse response (86). MTHFR polymorphisms, 677C>T and 1298A>C, are associated with low enzyme activity but did not correlate with capecitabine toxicities (87). Complete or partial DPD deficiency resulting in severe 5-FU toxicities occurs in approximately 0.1% and 3% to 5% of individuals, and at least 20 functional DYPD variants have been described, with the DYPD*2A splice site variant being the most common. Unfortunately, the rarity and heterogeneity of DYPD mutations has precluded the routine use of DPD testing (88).

**Vinorelbine.** Vinorelbine is a Vinca alkaloid that prevents microtubule assembly, thereby inhibiting DNA replication. Studies relating to vinorelbine pharmacogenetics are limited. Metabolism is principally by CYP3A4 enzymes (89), whereas resistance has been said to be mediated by ABCB1 (90). However, in a prospective study involving 41 Caucasian cancer patients, including 10 breast cancers, no association was found between vinorelbine clearance and ABCB1 1236T>C, 2677G>T/A, and 3435C>T (91).

**Platinum.** Platinums cause interstrand DNA cross-linking leading to cessation of DNA synthesis and apoptosis, and toxicity due to platinums is modulated by proteins involved in DNA repair (ERCC1, ERCC2, and XRCC1). DNA detoxification (GSTP1 and MPO), and transport (SLC31A1, ABC2C, and ABCG2; ref. 65). However, there are no genetic polymorphisms that are ready for clinical application. In the large Scottish randomized trial of carboplatin and a taxane in ovarian cancer patients, genetic polymorphisms of genes relevant to the platinum pathway (ABCC2, ABCG2, ERCC1, ERCC2, GSTP1, MPO, and XRCC1) were not significantly associated with clinical outcomes or toxicity (65).

Heritable genetic factors may increase breast cancer risk; susceptibility loci include high-penetration genes that are rare (e.g., BRCA1/2) and low-penetration genes that are common. Understanding of these susceptibility loci has led to the elucidation of the biological mechanisms of breast cancer.
(92). For example, ~80% of BRCA1-related breast cancer are triple negative and basal-like by microarray, a phenotype for which no target exists for tailored therapy (93). However, BRCA1/2 mutations have been reported to confer differing tumor chemosensitivities. For example, tumors with BRCA1 mutations may be associated with taxane resistance (94), and those with BRCA1/2 mutations are unable to carry out DNA repair by homologous recombination, rendering them susceptible to platinum agents and poly(ADP-ribose) polymerase inhibitors (94–97). Perhaps one of the most recent illuminating findings in the arena of platinum agents and breast cancer is the discovery of secondary intragenic mutations that restore the open reading frame of BRCA2, resulting in cells that are now competent in homologous recombination, leading to resistance to platinum and poly(ADP-ribose) polymerase inhibitors (98, 99). These novel findings warrant further evaluation and confirmation from clinical trials.

**Targeted Therapy**

Targeted therapy such as anti-HER2 (trastuzumab and lapatinib) and antiangiogenesis agents [bevacizumab directed against vascular endothelial growth factor (VEGF)] are now approved treatments for advanced breast cancers and have entered clinical trials for early-stage breast cancer. No pharmacogenetic studies have been published for these agents, although several potential candidate genes warrant evaluation. No polymorphisms have been found to affect trastuzumab metabolism, efficacy, or toxicity thus far (100). However, binding of trastuzumab to its target at the extracellular domain of ERBB2 may be affected by differential amino acid expression, and functional polymorphism in this region may influence individual drug responses. CYP2C19, CYP3A4/5, P-glycoprotein, and BCRP are involved in the metabolism and transport of lapatinib, and polymorphisms in genes encoding these proteins may affect lapatinib disposition (101). Several polymorphisms have been described in genes that code for proteins or receptors involved in the VEGF pathway, including VEGF (102–105), VEGF-R2 (KDR; ref. 106), and HIF1α (107–109), which regulates transcription of VEGF. Some of these polymorphisms have functional activity in vitro, affecting VEGF production, VEGF-R2 expression, or downstream effects, and may potentially influence individual responses to anti-VEGF therapy. More research is eagerly awaited in this field for better selection of patients to improve cost-effectiveness in this area of treatment where the expense is often prohibitive.

**Future Directions**

In addition to single nucleotide polymorphisms, copy number variations may alter the expression levels and possibly the activity of a given gene. For example, copy number variations have been reported in PXR, CBR1, and ESR1 (110–112) and may well influence the response to commonly used chemotherapeutic agents or hormonal therapy in breast cancer.
cancer, warranting investigation. Furthermore, as drugs are inevitably involved in complex metabolic and transport pathways, individual genetic polymorphisms are likely to be less predictive than a panel of polymorphisms. The availability of high-throughput gene chips that allow simultaneous analysis of multiple prospective polymorphisms and copy number variations would facilitate research in these fields. The integration of multiple drug pathways into future trials would also be critical.

### Table 3. Summary of selected genetic polymorphisms that show differences in interethnic frequency distribution that may have influence on breast cancer therapeutics

<table>
<thead>
<tr>
<th>Genetic polymorphisms</th>
<th>Drug</th>
<th>Interethnic genetic variation</th>
<th>Clinical relevance to interethnic differences in drug disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Tamoxifen</td>
<td>Poor metabolizer phenotype more common in Caucasians than Asians or Black Africans. Lower levels of enzyme activity in Asians and Black Africans compared with Caucasians in the extensive metabolizer phenotype group (119). Clinical relevance of this interethnic variation is unclear.</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>Tamoxifen, taxanes</td>
<td>Commonest in Black Africans. Rare in Asians. Has been associated with increased transcriptional activity but clinical association unclear.</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td></td>
<td>Most common in Asians. Rare in Caucasians. Association unclear</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td></td>
<td>More common in Black Africans. Rare in Asians and Caucasians. More common in Ethiopians and Saudi Arabsians. Rare in Caucasians, Asians, and Black Africans.</td>
<td></td>
</tr>
<tr>
<td>CYP2D6*2xn</td>
<td>Tamoxifen</td>
<td>Most common in Asians followed by Blacks. Rare in Caucasians. Association unclear</td>
<td></td>
</tr>
<tr>
<td>CYP3A4*1B</td>
<td>Tamoxifen, taxanes</td>
<td>Commonest in Black Africans. Has been associated with increased transcriptional activity but clinical association unclear.</td>
<td></td>
</tr>
<tr>
<td>CYP3A5*3C</td>
<td>Tamoxifen</td>
<td>More common in Black Africans followed by Asians. Rare in Caucasians. Association unclear</td>
<td></td>
</tr>
<tr>
<td>CYP19A1 Arg&lt;sup&gt;39&lt;/sup&gt; variant</td>
<td>AIs</td>
<td>Present in 6.7% Han Chinese Americans (42). Rare in African-Americans, Caucasian Americans, and Mexican Americans (42). Association unclear</td>
<td></td>
</tr>
<tr>
<td>CYP19A1 Cys&lt;sup&gt;264&lt;/sup&gt; variant</td>
<td>Tamoxifen, taxanes</td>
<td>More common in African-Americans (22.5%) and Han-Chinese (11.7%) compared with Mexican Americans (5%) or Caucasian Americans (2.5%; ref. 42)</td>
<td></td>
</tr>
<tr>
<td>CBR3 11G&gt;A</td>
<td>Doxorubicin</td>
<td>Frequency of the A allele is 36% in Europeans, 47.5-57% in Chinese, and 27.3% in African-Americans (48, 120). Associated with lower conversion of doxorubicin to doxorubicinol (48). Greater doxorubicin-induced myelosuppression has been observed in Chinese compared with Caucasians (47), although direct evidence of link with this polymorphism is still lacking.</td>
<td></td>
</tr>
<tr>
<td>CDA 208G&gt;A (Ala&lt;sup&gt;70&lt;/sup&gt;Thr)</td>
<td>Gemcitabine</td>
<td>More common in Africans (13%) compared with Japanese (4.3%) or Europeans (0%; refs. 82, 83). Association unclear</td>
<td></td>
</tr>
<tr>
<td>SLC28A1 1561G&gt;A</td>
<td>Gemcitabine</td>
<td>More common in Caucasians (73%) compared with Chinese (12%), Malays (30%), or Indians (35%; ref. 84). Association unclear</td>
<td></td>
</tr>
<tr>
<td>DCK</td>
<td>Gemcitabine</td>
<td>Asians have a higher allele frequency (15.6%) of this linked promoter polymorphism compared with Caucasians (2%; ref. 85). Might predispose Asians to gemcitabine-associated toxicity but clinical association currently lacking.</td>
<td></td>
</tr>
</tbody>
</table>

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**Table continued on next page...**
to allow more comprehensive analysis of genetic factors that could influence drug efficacy and toxicity.

**Conclusion**

It seems promising that pharmacogenetics may, in the future, be used in conjunction with tumor genomics and clinical disease/tumor characteristics to better tailor our treatment of each individual (Fig. 2). However, despite the slew of exciting data generated over the years, there has been a lack of validation studies. Clinical application of pretreatment pharmacogenetic testing to determine drug response and toxicity is still limited in oncology, with CYP2D6 testing representing one of the first examples that may become more widely clinically applicable. Although some studies had suggested interesting interethnic differences in drug disposition and/or genetic distribution that may have correlations, such as CYP2D6 and tamoxifen, CYP19A1 and AIs, CBR3 and anthracyclines, CYP3A4 and tamoxifen and taxanes, and CYP3A5 and gemcitabine (Table 3), more work is required to compare drug efficacy and toxicity across different ethnic groups, where host-genotype interactions may be significant. These gaps emphasize the importance of prospective collection of germline DNA from early-phase clinical trials as well as for the concept of global consortia to accelerate the momentum in this area of research. With rapid biotechnology advances, personalized treatment based on genotype may hopefully be available in the future.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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