Pharmacogenetics of Tamoxifen: Who Should Undergo CYP2D6 Genetic Testing?

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Abstract
Many women with hormone receptor–positive breast cancer will receive tamoxifen at some point in their treatment course. Tamoxifen is biotransformed to the potent antiestrogen endoxifen almost exclusively through the cytochrome P450 (CYP) 2D6 isof orm. Although prospective data are lacking, the balance of evidence available currently suggests that a single nucleotide polymorphism in the CYP2D6 gene, particularly the presence of 2 null alleles, predicts for reduced tamoxifen metabolism and possibly poorer outcome than expected in patients with a wild-type genotype. Studies evaluating the impact of genetic polymorphisms that result in CYP2D6 with reduced or no activity on long-term outcome have been mostly retrospective and conducted on archival tissues or those obtained previously in prospective studies of tamoxifen. Until data are available from retrospective examinations of the large prospective trials already conducted, or adequately powered prospective analyses, transforming this information into guidelines for individual patients remains challenging. The authors do not currently recommend routine testing for CYP2D6 genotype for making clinical decisions regarding tamoxifen. Use of concomitant strong or intermediate inhibitors of CYP2D6 should be avoided when alternate medications are available. Ongoing research is directed toward identifying other polymorphisms that may influence the efficacy and safety of tamoxifen, other hormonal agents, and chemotherapies used to treat breast cancer. The hope is that in the future, not only tumor-associated factors but also germ-line host genetics can be used to determine whether a woman should receive treatment, and with which specific agents, to prevent breast cancer recurrence or death or avoid drug-related toxicities. (JNCCN 2009;7:203–213)

Breast cancer is the most prevalent non–skin cancer diagnosed in women worldwide. Breast cancer–related mortality in the United States has declined recently because of significant advances in early detection and improved therapeutic treatments for the disease.1 As with many other tumors, knowledge of the molecular pathways involved in breast carcinogenesis is rapidly expanding. This explosion in molecular biology has resulted in the development of more effective targeted therapies. Response to treatment, however, varies greatly among patients, leading researchers to believe that efficacy and safety ofanticancer therapies may depend on not only tumor but also treatment and host characteristics.

Small variations in the germ-line DNA sequence (genotype) can lead to different expression of an encoded protein or expression of an altered protein. Genetic variants associated with clinically relevant functional changes can occur in noncoding (intron) regions of the genome or in exons that code for protein expression.2 These changes can lead to individual differences in drug metabolism, distribution, excretion, and activity, including benefit and toxicity.3,4 Sequencing of the human genome and new high throughput technologies have enabled greater appreciation of the role that pharmacogenetics and individual host factors may play in predicting response to treatment.

More than two thirds of breast cancers express estrogen receptors (ERs) or progesterone receptors (PRs) and
almost every woman with ER- or PR-positive tumors are offered hormonal interventions at some point during the disease course. The selective ER modulator tamoxifen has been used for more than 30 years to treat and, more recently, prevent breast cancer. Its efficacy and adverse effects are well described, and in the past several years the metabolic pathway involved in processing the drug has been elucidated.

This article summarizes the pharmacogenetics and drug interactions that may influence the metabolism, efficacy, and secondary benefits, as well as adverse events associated with tamoxifen. In addition, available evidence on the role of cytochrome P450 2D6 (CYP2D6) in predicting tamoxifen response and whether testing for variant CYP2D6 genotypes should be used in clinical practice are discussed.

Metabolism of Tamoxifen
Tamoxifen can be considered a prodrug. The parent drug itself binds weakly to ER, but it undergoes extensive biotransformation through phase I and II enzymes into both active and inactive metabolites. Several CYP450 enzymes, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5, are responsible for the in vivo conversion of tamoxifen into its metabolites (Figure 1).5 Using in vitro models of drug metabolism, researchers have identified the primary and secondary metabolic routes of tamoxifen and the role of each enzyme in catalyzing these reactions at clinically relevant concentrations.5 N-desmethyl-tamoxifen is the major primary metabolite formed by CYP3A4/5 (Figure 1), and is a weak antiestrogen similar to tamoxifen. In contrast, the potent antiestrogen 4-hydroxy-tamoxifen is a minor primary metabolite, the formation of which is catalyzed by multiple CYP450 enzymes, including CYP2D6. Other, minor primary metabolites are also formed, which then undergo further conversion. N-desmethyl-tamoxifen is metabolized into α-hydroxy-tamoxifen, N-didesmethyl-tamoxifen, and 4-hydroxy-N-desmethyl-tamoxifen (also known as endoxifen).

Both 4-hydroxy-tamoxifen and endoxifen have nearly a 100-fold higher affinity for ER than tamoxifen.6,7 In patients undergoing tamoxifen therapy, endoxifen is found at a 6- to 12-fold higher concentration compared with 4-hydroxy-tamoxifen and is associated with equivalent antiestrogenic potency.8 These observations suggest that endoxifen might be the most important metabolite required for tamoxifen activity. Every secondary tamoxifen metabolite except endoxifen is formed by CYP3A4/5. In contrast, endoxifen production is almost totally dependent on the enzymatic activity of CYP2D6 (Figure 1).9 The active metabolites of tamoxifen are converted to inactive, soluble products through sulphate conjugation and glucuronidation by phase II liver enzymes.10

Genetic Polymorphisms in CYP450 Enzymes Involved in Tamoxifen Metabolism
Many of the genes encoding for CYP450 enzymes involved in tamoxifen metabolism have known polymorphisms, which can affect the catalytic activity of the enzymes. Single nucleotide polymorphisms (SNPs) in CYP2C19 and CYP2D6 genes, for example,
can result in lack of enzymatic activity through the formation of truncated, inactive proteins.\textsuperscript{11} Observed variability in the concentrations of tamoxifen and its metabolites might be explained through genetic polymorphisms in genes encoding for CYP450 enzymes.

More than 100 allelic variants of CYP2D6 have been described, with incidence varying according to race and ethnicity.\textsuperscript{12} The wild-type allele is designated CYP2D6*1. Among Caucasians, the variant allele most commonly observed is the null allele CYP2D6*4, for which approximately 7% of this population are homozygous.\textsuperscript{13} The most common allele in Asians (allelic frequency > 50%) and thus perhaps the most common CYP2D6 allele in the world is CYP2D6*10, which leads to a reduction in enzyme activity.\textsuperscript{14} In African and African-American populations, the CYP2D6*17 allele is found with a frequency of 22% to 24% and is associated with substrate-specific effects.\textsuperscript{15,16} The CYP2D6*17 allele carries 3 nonsynonymous coding region SNPs. Phenotyping studies and in vitro data suggest that the metabolism of CYP2D6 substrates may be differentially decreased.\textsuperscript{17}

Other variant alleles can lead to the production of an enzyme that is active or hyperactive, or has reduced activity. In one commonly used classification of CYP2D6 activity, persons homozygous for alleles that produce enzymes with normal activity (e.g., the wild-type CYP2D6*1) are designated extensive metabolizers,\textsuperscript{18} and those who carry multiple copies of CYP2D6 alleles are associated with high enzyme activity and are termed ultra-rapid metabolizers.\textsuperscript{19} Individuals with 1 or 2 variant alleles with reduced or null activity are designated intermediate and poor metabolizers, respectively.

**Drugs That Inhibit CYP2D6**

CYP2D6 is responsible for metabolizing approximately 25% of all metabolized drugs, including tamoxifen, many β-blockers, antidepressants, antipsychotics, antiarrhythmics, and analgesics.\textsuperscript{20} Poor metabolizers are likely to experience decreased analgesic effect from codeine or tramadol, and potentially experience increased side effects, for example from β-blockers. Therefore, CYP2D6 testing may have a broad clinical efficacy that is beyond the scope of this article.

Paroxetine, fluoxetine, and bupropion are strong inhibitors of the CYP2D6 enzyme. Moderate inhibitors include sertraline, duloxetine, and diphenhydramine.\textsuperscript{21} Information about these and other drugs, potential interactions, and references can be found at www.drug-interactions.com. Regarding breast cancer, selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and fluoxetine, and selective serotonin-noradrenergic reuptake inhibitors are among the most effective drugs used to alleviate hot flashes\textsuperscript{22} and have therefore been prescribed commonly to women receiving tamoxifen.

A pilot study designed to evaluate the effects of the SSRI paroxetine on concentrations of tamoxifen and its metabolites found that women taking chronic tamoxifen who had genetic variants in CYP2D6 or were coprescribed paroxetine had very low serum concentrations of the active tamoxifen metabolite, endoxifen.\textsuperscript{23} These findings were confirmed in a later study of women with normal wild-type CYP2D6 who were taking concomitant drugs that were strong inhibitors of the enzyme and were found to have reductions in serum endoxifen concentrations similar to those seen in women with 2 null alleles (poor metabolizers).\textsuperscript{24} Unfortunately, concomitant inhibitor prescription use has been reported in only a minority of the currently available studies on the clinical interaction between tamoxifen and CYP2D6 genotype, and therefore the effects of this apparently important confounding bias are unclear.

**Results of Trials Correlating CYP2D6 Variants to Tamoxifen Efficacy**

Taken together, the results on the importance of endoxifen as an estrogen antagonist in preclinical studies coupled with the effects of CYP2D6 activity on generation of endoxifen suggest that this metabolite might be an important factor in tamoxifen’s activity against breast cancer. Furthermore, women with inactive CYP2D6, and thus presumably low endoxifen concentration, might have reduced benefit from this drug. Several reports have evaluated the potential interaction between CYP2D6 genotype and outcomes in women treated with tamoxifen therapy (Table 1).

In an initial report, investigators from the North Central Cancer Treatment Group (NCCTG)/Mayo Clinic and the Consortium on Breast Cancer Pharmacogenetics (COBRA) determined CYP2D6 genotype through extracting DNA from formalin-
### Table 1 Summary of Studies to Date Correlating CYP2D6 Variants With Clinical Outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Data Collection</th>
<th>Tamoxifen Dosing</th>
<th>CYP2D6 Variants</th>
<th>Other Genotypes</th>
<th>Patients</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Goetz et al.¹⁰</td>
<td>Adjuvant</td>
<td>Retrospective review of participants</td>
<td>20 mg/d x 5 y</td>
<td>CYP2D6*4,*6</td>
<td>CYP3A5*3</td>
<td>256</td>
<td>CYP2D6*4 vs. other: RFS HR, 1.85 (P = .176) DFS HR, 1.86 (P = .089)</td>
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<td>in a a prospective study</td>
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<td>No association found with CYP3A5*3</td>
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<tr>
<td>Goetz et al.¹⁰</td>
<td>Adjuvant</td>
<td>Retrospective; same cohort as Goetz et al.¹⁰</td>
<td>13 patients on inhibitors</td>
<td>CYP2D6*4,*6</td>
<td></td>
<td>190</td>
<td>PM vs. other: TTR HR, 1.91 (P = .034)</td>
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<tr>
<td>Wegman et al.¹⁶</td>
<td>Adjuvant</td>
<td>Retrospective review of participants</td>
<td>40 mg/d x 2 y</td>
<td>CYP2D6*4</td>
<td>SULT1A1*1,*2</td>
<td>226</td>
<td>CYP2D6*4 carrier: lower risk for recurrence (RR, 0.28; P = .0089)</td>
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<td>in a a prospective study</td>
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<td>SULT1A1*1,*2: no association found</td>
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<td>SULT1A1*1/*1: lower risk for recurrence (RR, 0.48; P = .0074)</td>
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<td>CYP2D6*4</td>
<td>SULT1A1*1/*1</td>
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<td>CYP2D6<em>4 and/or SULT1A1</em>1/*1: lower risk for distant recurrence (RR,</td>
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<td>0.38; P = .0014)</td>
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<td>CYP2D6<em>4 vs. CYP2D6</em>1 or SULT1A1*1/*1: improved DFS (P = 0.04 and .05)</td>
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<td>CYP2D6<em>4, SULT1A1</em>1/<em>2, and UGT2B15</em>1/<em>2: no association found CYP2D6</em>4</td>
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<td>CYP2D6*4 or other in Tam-treated HRs: OS, 0.77 (95% CI, 0.32–1.81)</td>
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<td>Nowell et al.¹⁰</td>
<td>Adjuvant</td>
<td>Retrospective</td>
<td>Details not provided</td>
<td>CYP2D6*4</td>
<td>SULT1A1*1/*2</td>
<td>337</td>
<td>CYP2D6*4 vs. Tam pre- and postmenopausal HR+</td>
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<td>UGT2B15*1/*2</td>
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<td>175 no Tam</td>
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<td>Schroth et al.¹⁷</td>
<td>Adjuvant</td>
<td>Retrospective</td>
<td>Details not provided</td>
<td>CYP2D6*4,</td>
<td>CYP2C19*2,*3,*17</td>
<td>486</td>
<td>Tam-treated PM vs. other RFS HR, 2.24; P = .02 EFSR HR, 1.89; P = .02</td>
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<td>CYP2C9*2,*3</td>
<td>CYP3A5*3</td>
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<td>CYP2C9*17 vs. other CPYCT19 alleles: HR for RFT, 0.45 (95% CI, 0.21–0.92;</td>
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fixed paraffin-embedded archival tumor specimens of patients participating in a prospective, phase III trial \((n = 190)\).\(^{24}\) They reported that the CYP2D6*4 variant allele was an independent predictor of higher risk for relapse.\(^{25}\) Notably, patients in this study did not undergo chemotherapy or other antineoplastic therapy, but the study did not include an untreated control group. A follow-up study by the same investigators...
subsequently reported that concomitant CYP2D6-inhibiting medications contributed as an independent predictor of worse outcome in this same patient population. A recent update with an extended follow-up and a more comprehensive genotype analysis of these original patients showed a hazard ratio of 4.0 in relapse-free time among poor metabolizers relative to extensive metabolizers (P ≤ .001).

In contrast to the findings of the Mayo study, Swedish Trialists found that patients with at least 1 CYP2D6*4 allele treated with 2 years of tamoxifen, 40 mg daily, had better outcomes than those not treated with tamoxifen, which was an unexpected conclusion. The results of a second retrospective study by the same investigators in a different and larger cohort again showed that ER-positive patients who were homozygous for CYP2D6*4 had significantly improved disease-free survival compared with those with wild-type CYP2D6. However, these women may have received tamoxifen, 20 or 40 mg/d, for a variable length of time (2 vs. 5 years).

These findings were further supported by a group of investigators who reported a trend toward better overall survival in patients with CYP2D6*4 treated with tamoxifen either alone or in conjunction with chemotherapy and radiation. Because patients underwent varying lengths of treatment or may have undergone additional therapies, and because hormone receptor status was not centrally tested, comparing these and the Mayo study is difficult. As a possible explanation of the seemingly contradictory results, it is helpful to note that in the Mayo trial, the outcomes of women who were likely to have intermediate concentrations of endoxifen, as represented by the heterozygous CYP2D6*4, were no different from those of women carrying 2 wild-type CYP2D6 alleles. Together, these studies suggest that the clinical effect of tamoxifen is probably because of multiple metabolites, and that worse outcomes would be expected only if women carry 2 null CYP2D6 alleles, corresponding to the CYP2D6 poor metabolizer phenotype.

Several other researchers have reported similar results to those of the Mayo report. In a nonrandomized cohort study, Schrot et al. genotyped an extended number of variants of the CYP2D6 gene and found shorter relapse-free survival intervals in women treated with tamoxifen who were carriers of a variant allele, compared with those with functional alleles. Three studies from Asia examined the relationship between CYP2D6*10 and outcomes of patients treated with tamoxifen. In patients with metastatic disease, investigators found that individuals treated with tamoxifen who had 2 variant CYP2D6 alleles had a shorter time to progression than those with 1 variant allele.

A second group measured tamoxifen and 4-hydroxy-tamoxifen concentrations in 37 women with breast cancer who were undergoing adjuvant tamoxifen treatment. Serum 4-hydroxy-tamoxifen concentrations were significantly lower in women homozygous for CYP2D6*10 than in those with the homozygous wild-type genotype (P = .04). The association between CYP2D6*10 genotype and survival was then determined in a cohort of 293 women with breast cancer who either received tamoxifen or did not. Women treated with tamoxifen with 2 variant alleles had significantly worse disease-free survival than those who were homozygous for the wild-type or had 1 variant allele.

The third Asian study echoed the findings of the previous 2, showing a significantly higher incidence of recurrence in patients receiving adjuvant tamoxifen who were homozygous for the CYP2D6*10 allele than in those with 2 wild-type alleles.

Recently, Newman et al. correlated CYP2D6 genotype, concomitant use of CYP2D6 inhibitors, and outcome of 113 BRCA1 or 2 carriers treated with adjuvant tamoxifen, and found that time to tumor recurrence, disease-free survival, and overall survival were worse in the poor metabolizer group. The differences were significant in the BRCA2 group, whose cancers were more likely to be ER-positive, but not in the BRCA1 group. BRCA2 carriers with low CYP2D6 activity had a median overall survival of 6.9 years versus 28.1 years in those with normal activity (P = .008; adjusted hazard ratio, 9.7). In a very small case-control study reported as a letter to the editor, homozygous variant CYP2D6 genotype seemed to be associated with development of a new breast cancer in high-risk but previously unaffected women treated with tamoxifen as a chemopreventive agent.

Investigators from the Mayo Clinic and the Austrian Breast Cancer Study Group (ABCSG) recently genotyped CYP2D6 in tumor sections obtained from participants in ABCSG Trial 8 in which women received tamoxifen for 2 to 5 years followed by an aromatase inhibitor for 2 to 5 years, or an aromatase inhibitor for 5 years. Although results are not yet...
available, preliminary reports suggest that poor metabolizers who received 5 years of tamoxifen therapy had a significantly increased relative risk for breast cancer–related events compared with extensive metabolizers undergoing the same therapy.

In summary, data on the clinical effect of CYP2D6 genotype are highly variable. Although most select studies suggest that poor metabolizers of CYP2D6 have a worse outcome than wild-type patients when treated with tamoxifen in either the preventive, adjuvant, or advanced disease settings, not all studies have provided consistent results, and at least 2 suggest the opposite. Overall, results from retrospective analyses of specimens collected through clinical trials support the concept that select women considering tamoxifen therapy and for whom an alternative therapy is less appealing might wish to be tested to help decide which therapeutic agent to use.

**Other Pharmacogenetic Determinants of Tamoxifen Activity**

The variability in clinical results suggests that CYP2D6 is not the only determinant of tamoxifen activity. Of course, somatic differences in tumoral ER expression have been shown for decades to be the single most important determinant of antiestrogenic (or “endocrine”) response. Some studies on CYP2D6 and tamoxifen included patients with either unknown or negative ER status. Furthermore, substantial evidence has suggested other somatic factors that may modulate ER function, even if it is expressed, such as PR, human epidermal growth factor receptor 2 (HER2), ERβ, insulin-like growth factor 1, and coactivators and repressors of ER. Unexamined differences in these factors will certainly confound small retrospective studies.

In addition to somatic differences in expression, germ-line genetic variants in ERα and β (ESR1 and ESR2, respectively) have been associated with tamoxifen resistance or tamoxifen-stimulated growth. Only preliminary studies have evaluated the role of germ-line variants in ESR1/2 and outcomes or other effects in tamoxifen-treated women. Furthermore, variations in serum endoxifen concentrations are probably at least partly related to variants in genes other than CYP2D6 that may affect metabolism of tamoxifen and its downstream metabolites or the estrogen activity pathway. For example, elimination of endoxifen and 4-hydroxy-tamoxifen from the serum is dependant on enzymes, including UDP-glucuronosyltransferase (UGT) and sulfotransferase 1A1 (SULT1A1). A twofold lower enzyme activity has been shown among women with polymorphism in the gene coding for SULT1A1, designated SULT1A1*2, and a higher hazard ratio for death among homozygous carriers of SULT1A1*2 who were treated with tamoxifen. Other studies suggested that CYP2C19*17 variants may correlate with lower risk for relapse. Again, data are conflicting and discussion of their clinical relevance is beyond the scope of this article.

**Tamoxifen Secondary Benefits and Side Effects**

Much of the data presented suggest that women treated with tamoxifen who have CYP2D6 null alleles metabolize tamoxifen poorly and may experience worse outcomes than those with 1 or 2 normal alleles (intermediate and extensive metabolizers). A corollary of these data is that extensive metabolizers may be more likely to experience the adverse effects of antiestrogenic therapy, such as hot flashes, as a result of higher circulating endoxifen concentrations. In the original Mayo report of CYP2D6 and tamoxifen outcomes, women with normal CYP2D6 genotype were more likely to report hot flashes than those who are intermediate or poor metabolizers (intermediate/poor metabolizers). Supporting this hypothesis, COBRA reported in a prospective cohort study of women taking tamoxifen that those who were extensive metabolizers were more likely to discontinue tamoxifen during the first year of treatment compared with those who were either intermediate or extensive metabolizers. In a recent prospective investigation, CYP2D6 activity was a modest predictive factor for tamoxifen-induced hot flashes suggesting that the presence or absence of hot flashes should not be used to determine tamoxifen’s efficacy.

However, CYP2D6 activity is probably not the only determinant of tamoxifen activity. COBRA investigators have also reported that variants in ESR1 and ESR2 may also predict tamoxifen-induced hot flashes, bone mineral density, and circulating lipid levels. Overall, although intriguing, the data on pharmacogenetic effects and tamoxifen-associated
secondary effects and side effects are hypothesis-generating and require validation.

Who Should be Tested?

Do these accumulated considerations suggest that all women should be tested for CYP2D6 before initiating endocrine treatment for ER-positive breast cancer? Although prospective data are lacking, the balance of evidence currently available suggests that polymorphisms in CYP2D6, particularly the presence of 2 null alleles, predicts for altered tamoxifen metabolism and possibly poorer outcomes than that expected in extensive metabolizers. The heterogeneity of the reported trials limits their combined interpretation; some included patients who were treated in the adjuvant setting without account of menopausal status, ER status, or chemotherapy given, whereas others included mixed populations of individuals with metastatic disease. Perhaps the highest level of available evidence comes from the Mayo/Cobra study, which included only postmenopausal women with centrally determined hormone receptor positivity who received just tamoxifen.

The challenge is to transform this information into guidelines for an individual patient. Although endoxifen concentrations are low in poor metabolizers, tamoxifen and 4-hydroxy-tamoxifen are present and expected to occupy and modulate the ER, although a recent preliminary report suggested that endoxifen, but not 4-hydroxy tamoxifen, is associated with degradation of the ER. A reasonable number of studies suggest that poor metabolizers may have reduced benefit from tamoxifen compared with intermediate or extensive metabolizers.

However, one cannot ignore the 2 large studies conducted retrospectively using archived specimens from prospectively conducted trials that suggest that women with homozygous variant CYP2D6 genotypes actually did better when treated with tamoxifen. Moreover, no studies have clearly shown that a poor metabolizer will obtain no benefit from the drug. For example, as noted, the Mayo/Cobra trial had no untreated control population, and thus whether women with CYP2D6 would have fared even worse if they had not received tamoxifen cannot be determined. It is reassuring that, in the study by Schroth et al., CYP2D6 genotype was not associated with outcome in 280 patients who were not treated with tamoxifen, suggesting that CYP2D6 status is predictive of response to tamoxifen but not an independent prognostic factor.

Although the data and hypothesis are intriguing, these authors do not currently recommend withholding tamoxifen from patients who have ER-positive breast cancer and who do not have alternate approved therapies in any setting based on CYP2D6 genotype or phenotype.

Perhaps, however, a setting exists in which CYP2D6 could be reasonably used, such as for postmenopausal women with ER-positive breast cancer. Several prospective, randomized clinical trials have shown that specific aromatase inhibitors are at least as effective as tamoxifen, if not more, in unselected women with ER-positive breast cancer in the metastatic and adjuvant settings. These results led a panel of experts, convened by ASCO, to recommend that “optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer includes an aromatase inhibitor as initial therapy or after treatment with tamoxifen. Women with breast cancer and their physicians must weigh the risks and benefits of all therapeutic options.”

Similar recommendations were proposed by the NCCN Task Force and members of the St. Gallen International expert consensus meeting. Therefore, if an aromatase inhibitor might be considered for this group of patients instead of, or in sequence with, tamoxifen anyway, testing CYP2D6 status might be rational if tamoxifen is being considered but an aromatase inhibitor is an equal option. For example, if a postmenopausal woman has suboptimal bone density, and therefore is at increased risk for osteoporosis while undergoing aromatase inhibitor therapy, and is an extensive metabolizer, her physician could feel comfortable prescribing tamoxifen, whereas an aromatase inhibitor and bisphosphonate therapy may be a better choice for an intermediate or poor metabolizer. The CYP2D6 enzyme does not interfere with aromatase inhibitor metabolism and no evidence suggests that a poor metabolizer of tamoxifen would experience a lesser response to an aromatase inhibitor.

Drawing from the data in 2 earlier studies, Punglia et al. recently designed a model to estimate whether women with wild-type CYP2D6 might have superior outcomes if prescribed tamoxifen rather than an aromatase inhibitor. They applied the model to results from the Breast International Group (BIG 1-98)
Ongoing studies in premenopausal women with breast cancer were prospectively randomized to treatment with either tamoxifen or the aromatase inhibitor letrozole. These investigators concluded that women carrying 2 wild-type CYP2D6 genes (extensive metabolizers) potentially would have had lower rates of relapse if treated with tamoxifen. Although the data are certainly exciting and deserve further confirmation, routine adoption of this model for standard clinical decisions is premature, considering the heterogeneous results among studies.

In contrast, the decision to use an alternative endocrine therapy to tamoxifen in premenopausal women with ER-positive breast cancer is complicated. Although ovarian ablation has been proven effective as adjuvant endocrine treatment in premenopausal women, tamoxifen has been the principal adjuvant hormonal therapy for those with functioning ovaries or men with breast cancer. Ongoing studies in premenopausal women are evaluating the role of ovarian suppression and tamoxifen or an aromatase inhibitor, compared with tamoxifen alone. A recently reported study suggested that premenopausal women treated with adjuvant ovarian suppression and tamoxifen had equivalent outcomes to those who received ovarian suppression and anastrozole, but a tamoxifen-only arm was not included. Furthermore, complete estrogen ablation with ovarian function suppression or ovariec- tomy and an aromatase inhibitor is likely to have substantial adverse effects on health and quality of life and should not be taken lightly. Currently, tamoxifen is the preferred agent in premenopausal women, and the use of alternative endocrine strategies based on CYP2D6 genotyping seems premature.

Conclusions
Studies to determine the clinical efficacy of CYP2D6 pharmacogenetic testing have not yet incorporated specimens collected from adequately powered prospective trials to assess whether knowledge of the genotype truly predicts outcome for patients being treated with tamoxifen. The authors believe the available retrospective studies are too variable to justify this approach in routine clinical practice. The field of pharmacogenetics is rapidly expanding, but many questions remain and confusion persists regarding conflicting trial results. While awaiting data from retrospective examinations of large prospective trials already conducted or from adequately powered prospective analyses, routine CYP2D6 genotyping cannot be recommended. In select situations in which premenopausal women with ER-positive breast cancer are considered for tamoxifen versus an aromatase inhibitor, and guided by judicious interpretation of available evidence, testing may be useful. However, the authors strongly recommend clinicians avoid known CYP2D6 inhibitors for women who are taking tamoxifen, because equally effective alternative options that do not inhibit CYP2D6 are available for most indications (http://medicine.iupui.edu/clinpharm/COBRA/ TamoxifenGuide.pdf), such as treatment of hot flashes or depression. The results of ongoing investigations into CYP2D6 polymorphisms and other genetic variants that may influence the efficacy and safety of many hormonal and chemotherapies used to treat breast cancer are eagerly awaited.

References
Pharmacogenetics of Tamoxifen


