

CYP2D6 Pharmacogenomics of Tamoxifen Treatment



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Executive Summary

Background

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor-positive breast cancer recurrence, as treatment of metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ (DCIS). The cytochrome P450 (CYP) metabolic enzyme CYP2D6 has a major role in tamoxifen metabolism. The CYP2D6 gene is polymorphic; variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on tamoxifen treatment efficacy.

Objective:

This Assessment evaluates the evidence for CYP2D6 genotyping, compared to no testing, to direct treatment regimen choices for patients at high risk for primary breast cancer or breast cancer recurrence, and improve survival outcomes.

Search Strategy

MEDLINE[®] was searched (via PubMed) using the search string “tamoxifen”[MeSH[®]] AND (“pharmacogenetics”[MeSH[®]] OR “cytochrome P450 enzyme system”[MeSH[®]]) through January 2008. Clinical trials, recent reviews (2004–2008), editorials, and letters related to the pharmacogenomics of tamoxifen were retrieved. In addition, text and reference lists of retrieved papers were examined for additional relevant articles.

Selection Criteria

Full-length, peer-reviewed papers reporting studies of postmenopausal women undergoing endocrine therapy whose treatment regimen selection is based on CYP2D6 genotyping versus usual selection methods, OR, studies of the association of CYP2D6 genotype with intermediate (e.g., tamoxifen active metabolite levels) or final outcomes (e.g., time to recurrence, survival) were selected for review.

Main Results

One U.S. Food and Drug Administration (FDA) -cleared test for CYP2D6 genotyping has consistent evidence of analytic validity (i.e., technical accuracy and reliability).

Evidence for clinical validity (i.e., association of CYP2D6 genotype with clinical outcomes) consists of the following elements grouped into the beginning of two possible evidence chains, A and B:



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A.

Association of genotype with plasma levels of active tamoxifen metabolite: Three prospective cohort studies of adjuvant tamoxifen treatment provide consistent evidence that CYP2D6 nonfunctional variant alleles that render patients intermediate (one variant allele) or poor (two variant alleles) metabolizers of tamoxifen (intermediate [IMs] and poor [PMs] metabolizers, respectively), are associated with significantly reduced plasma levels of endoxifen, the most bioavailable of tamoxifen active metabolites. However, endoxifen levels overlap across all genotypes, suggesting that CYP2D6 genetic variability does not explain all variability in endoxifen levels. One study suggests that reduced-function variant homozygotes, but not heterozygotes, also have significantly reduced circulating endoxifen. Co-administration of a potent CYP2D6 inhibitor to CYP2D6 homozygous wild-type patients (extensive metabolizers [EMs]) is associated with endoxifen levels near those of patients who are poor metabolizers.

AND

Association of in vivo endoxifen levels with clinical outcomes: The relationship between endoxifen plasma concentrations and clinical outcomes has not been established.

B.

Association of genotype with clinical outcomes: an ideal study would compare tamoxifen-treated women versus those not receiving tamoxifen, with stratification by CYP2D6 genotype to see if PMs derive less benefit from tamoxifen than EMs. One group¹ conducted such a study retrospectively, on archived samples from a randomized controlled trial of tamoxifen treatment. Paradoxically, they found that EMs treated with tamoxifen received no statistically significant clinical benefit compared to EMs not treated with tamoxifen, and that carriers of a CYP2D6*4 nonfunctional variant allele obtained significant benefit from tamoxifen treatment. There were several limitations to this study such that results are questionable. The other included studies enrolled only tamoxifen-treated women and evaluated outcomes by CYP2D6 genotype. Evidence from two higher-quality trials of adjuvant tamoxifen (Table) suggests that women who are CYP2D6 IMs or PMs, whether by genotype or by co-medication with CYP2D6 inhibitors, treated with tamoxifen have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to EMs in multivariate analyses adjusted for other parameters of disease prognosis. The strength of these associations was marginal and might be stronger and more convincing if PMs alone could be compared to EMs, but PM numbers were insufficient. Few variant alleles were typed in these studies, and samples negative for variant alleles were assumed to be wild-type EMs; more extensive genotyping and better categorization might also strengthen results. Three other studies were of lesser quality and provide conflicting evidence.

There is no direct evidence of clinical utility (whether use of CYP2D6 genotype testing for endocrine therapy regimen selection improves recurrence and survival outcomes). Two indirect evidence chains, A and B (above), can be constructed; the final element for both in postmenopausal women would be evidence that CYP2D6 PMs treated with aromatase inhibitors (AI) alone have outcomes at least as good as CYP2D6 EMs treated with AI alone or AI plus tamoxifen. In premenopausal women who are CYP2D6 PMs, ovarian ablation or suppression, which confers a significant benefit compared to no therapy, might be added to or might replace tamoxifen. Evidence chain A depends on demonstrating a significant association between in vivo endoxifen levels and clinical outcomes; this evidence does not exist. Evidence chain B depends on the association of genotype with clinical outcomes. As noted, there are several limitations to this evidence, and as a result it is judged insufficient to support clinical utility.

Author's Conclusions and Comments

The hypothesis examined in this Assessment is that CYP2D6 poorer metabolizers, whether by genotype or by co-administration of CYP2D6 inhibitory medication, have reduced tamoxifen metabolism and lower endoxifen levels compared to better metabolizers, and as a direct result have poorer clinical outcomes. This hypothesis is based on the assumption, not yet supported by evidence, that some level of endoxifen is sufficient and necessary for tamoxifen efficacy, and that this level is not achieved in genotypic and functional CYP2D6 PMs, and possibly not in some IMs.

¹ Wegman P, Vainikka L, Stal O et al. (2005). Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. *Breast Cancer Res*, 7(5):R284-90.

Table. Summary of Two Studies of CYP2D6 Genotype and Clinical Outcomes

Study	n	Study design, Patients	Results
Goetz et al. 2007	171	Retrospective analysis of archived samples from NCCTG RCT (89-30-52) of adjuvant TAM, TAM-only arm	Cox HR (adjusted for tumor size and nodal status), PM or IM vs. EM: TTR: HR=1.91; 95% CI: 1.05–3.45; p=0.034 RFS: HR=1.74; 95% CI: 1.10–2.74; p=0.017 OS: HR=1.34; 95% CI: 0.83–2.16; p=0.223 Cox unadjusted HR, PM (n=16) vs. EM: TTR: HR=3.20; 95% CI: 1.37–7.55; p=0.007 RFS: HR=2.69; 95% CI: 1.34–5.37; p=0.005 OS: HR=2.00; 95% CI: 0.92–4.17; p=0.077
Schroth et al. 2007	206	Retrospective cohort analysis of archived samples, Primary breast cancer patients taking adjuvant TAM alone	Cox adjusted (tumor size and nodal status) HR of TAM-treated patients with decreased vs. normal CYP2D6 activity: TTR: HR 2.24; 95% CI: 1.16–4.33; p=0.02 RFS: HR 1.89; 95% CI: 1.10–3.25; p=0.02 There were no significant associations with OS.

Abbreviations

TAM, tamoxifen; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; HR, hazard ratio; TTR, time to recurrence; RFS, recurrence-free survival; OS, overall survival; NCCTG, North Central Cancer Treatment Group

Goetz MP, Knox SK, Suman VJ et al. (2007). The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat*, 101(1):113-21.

Schroth W, Antoniadou L, Fritz P et al. (2007). Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol*, 25(33):5187-93.

It seems feasible to propose such a study in tamoxifen-treated populations of completed clinical trials, where appropriate specimens are available. The advantage of such a study is that the metabolite itself, rather than the activity of the enzyme producing it, would be directly measured in relation to clinical outcomes. Because tamoxifen metabolism is complex and CYP2D6 does not appear to account for all variability in endoxifen levels, it is conceivable that polymorphisms in other tamoxifen metabolic pathway enzymes may affect active metabolite levels, and direct measurement of the metabolite(s) itself may be the better predictor of benefit from tamoxifen treatment. However, since it takes 8 weeks for tamoxifen metabolites to reach steady-state concentrations, measuring metabolite levels is not practical for clinical applications outside of a retrospective study.

Additionally or alternatively, larger studies of the CYP2D6 genotype-clinical outcomes association are needed to expand and verify initial results, and to accurately identify the exact genotypes that have poorer outcomes and would best benefit from AI treatment alone, versus those that would best benefit from regimens including tamoxifen.

Multiple enzyme genotypes may be needed to confidently predict tamoxifen versus AI treatment benefit; however, there are little data at present to recommend any genotype combinations.

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for primary breast cancer or breast cancer recurrence meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The Roche AmpliChip CYP450 Test is cleared by the FDA to determine patients' CYP2D6 and CYP2C19 genotypes.

CYP2D6 genotyping assays are also available as laboratory-developed services. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. While the FDA has technical authority to regulate home-brew tests, to date there has been no active oversight with the possible exception of "in vitro diagnostic multivariate index assay" (IVDMIA) devices, for which a guidance document is currently in the draft stage.

The FDA has been considering updating the product labeling for tamoxifen with information or recommendations regarding CYP2D6 genotyping and impact on tamoxifen efficacy. On October 18, 2006, the FDA held an Advisory Committee meeting to answer specific questions regarding the evidence and recommendations for the label update; the members of the Advisory Committee recommended including information on CYP2D6 genotypes and potential effect on patient outcomes, and information on CYP2D6 genotyping tests. The members did not reach a consensus as to whether testing should be recommended or considered as an option. Since the Advisory Committee meeting, AstraZeneca, the brand name (Nolvadex[®]) manufacturer, has ceased producing tamoxifen and is no longer maintaining the prescribing information. As of the date of this Assessment, no direction has come from the FDA regarding revised labeling of generic versions of tamoxifen to include CYP2D6 genotyping information.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There is no direct evidence of clinical utility. Two indirect evidence chains can be constructed. One depends on demonstrating a significant association between endoxifen and clinical outcomes; this evidence does not exist. The other depends on the association of genotype with clinical outcomes; there are several limitations to this evidence, and, as a result, it is judged insufficient to support clinical utility.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

There is insufficient evidence to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer.

5. The improvement must be attainable outside the investigational settings.

Whether or not the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer improves health outcomes has not been demonstrated in the investigational setting.

Based on the above, CYP2D6 genotyping does not meet the TEC criteria for directing endocrine therapy regimen selection for women at high risk for primary breast cancer or breast cancer recurrence.

Contents

Assessment Objective	6	Review of Evidence	14
Background	6	Discussion	26
Methods	12	Summary of Application of the Technology Evaluation Criteria	27
Formulation of the Assessment	12	References	29

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Assessment Objective

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor-positive breast cancer recurrence, as treatment of metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ (DCIS). The cytochrome P450 (CYP450) metabolic enzyme CYP2D6 has a major role in tamoxifen metabolism. The CYP2D6 gene is polymorphic; variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on tamoxifen treatment efficacy.

This Assessment will evaluate the evidence for CYP2D6 genotyping, compared to no testing, to direct treatment choices for patients at high risk for or with breast cancer, and improve survival outcomes.

Background

Tamoxifen Metabolism

Tamoxifen metabolites, rather than tamoxifen itself, are likely the primary effectors of tamoxifen benefit. Tamoxifen undergoes extensive primary and secondary metabolism, and the plasma concentrations of tamoxifen and its metabolites vary widely. 4-Hydroxytamoxifen (4-OH tamoxifen) has demonstrated 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent in vitro cell proliferation when compared with the parent drug (summarized in Goetz et al. 2008). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has identical properties and potency compared with 4-OH tamoxifen in terms of its binding affinity to estrogen receptors, suppression of in vitro estrogen-receptor-dependent cell proliferation, and gene expression of progesterone receptors, a marker of estrogenic effect (Stearns et al. 2003; Johnson et al. 2004; Lim et al. 2005; 2006). Because 4-OH tamoxifen represents less than 20% of the product of tamoxifen primary metabolism (Fabian et al. 1981) and steady-state plasma endoxifen concentrations are, on average, 5- to 10-fold higher than 4-OH tamoxifen (Stearns et al. 2003), although the variability among individuals may be high (2- to 25-fold; Jin et al. 2005), it has been assumed that endoxifen is the major active metabolite of tamoxifen.

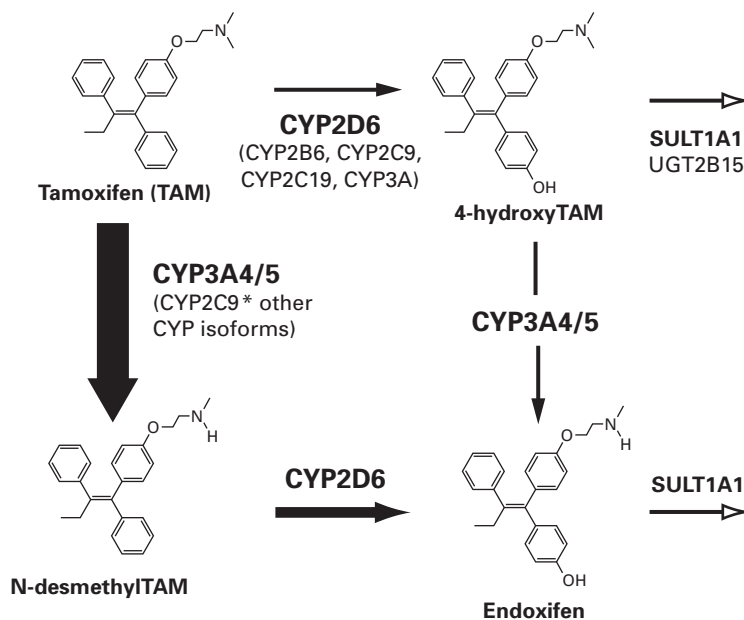
The metabolism of tamoxifen to 4-OH tamoxifen is catalyzed by multiple enzymes. However, endoxifen is formed predominantly by the CYP2D6-mediated oxidation of N-desmethyl tamoxifen, which is the most abundant tamoxifen primary metabolite and which has activity no greater than the parent drug (Figure 1). The plasma concentration of endoxifen exhibits high interindividual variability, as described in breast cancer patients (Stearns et al. 2003). The CYP2D6 enzyme has known inter-individual variability in activity and therefore has been of great interest in investigating tamoxifen metabolism and variation in circulating active metabolite levels.

Metabolic Enzyme Genotypes

The CYP2D6 gene exhibits a high degree of polymorphism, with more than 75 allelic variants identified (Bernard et al. 2006). While the most prevalent CYP2D6 *1 and *2 alleles (both termed “wild-type” for this Assessment) produce an enzyme with normal activity, there are several variant (V) alleles that result in enzymes with no activity or reduced activity (Table 1). Because individuals have two CYP2D6 alleles, various combinations of the possible alleles result in a spectrum of CYP2D6 function; these have been categorized as extensive metabolizers (EM or “normal”), intermediate metabolizers (IM), and poor metabolizers (PM), based originally on pharmacokinetic studies of CYP2D6-dependent probe drugs prior to the discovery of the genetic basis of variable function. An additional, rare category of ultra-rapid metabolizers (UM) is defined by the possession of three or more functional alleles due to gene duplication. UMs have greater functional activity than EM genotypes because of additional expression of enzyme from the extra gene(s).

Griese et al. (1998) studied the correlation of CYP2D6 functional categories, determined by metabolic capacity using a probe drug, with genotypes in 195 Caucasian individuals in Germany. While all poor metabolizers were “unambiguously identified as carriers of two nonfunctional alleles...the most frequent functional genotypes extensively overlapped.” The authors concluded that except for PMs, genotype was not a useful predictor of function. Thus, fully functional homozygous wild-type genotypes are consistently assigned to the EM category and homozygous inactive variant genotypes are consistently assigned to the PM category in pharmacogenomic studies. However,

Figure 1. Biotransformation of Tamoxifen; Major Metabolic Pathways Leading to the Production of High Activity Tamoxifen Metabolites



Modified slightly from Jin et al. (2005). CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*, 97(1):30-9. Reproduced with permission of Oxford University Press.

assignment of other genotypes with function in between these two is inconsistent among authors and requires standardization so that results may be better compared across studies (Beverage et al. 2007).

The prevalence of CYP2D6 PMs, defined either by metabolic function or by the detection of 2 nonfunctional alleles, has been estimated in various ethnic populations in several studies, summarized by Bernard et al. (2006). The PM prevalence is approximately 7–10% in Caucasians of Northern European descent, 1.9–7.3% in African Americans, and about 1% or less in most Asian populations studied. The PM phenotype in whites is largely accounted for by CYP2D6*3 and *4 nonfunctional variants (Table 1). In African-American and Asian populations, the nonfunctional *5 variant allele is present in at most 6–7%, but homozygous genotypes would be relatively rare. However, some PMs may reflect the combination of a nonfunctional and a reduced function allele. Among reduced function variants, *17, *10 and *8 are the most important in African-Americans, Asians, and Caucasians, respectively. Few studies have investigated the frequency of CYP2D6 variant alleles or of PMs in the Hispanic population (Bernard et al. 2006).

As shown in Figure 1, several other enzymes are involved in the metabolism of tamoxifen to the active metabolite 4-OH tamoxifen (CYP2B6, CYP2C9, CYP2C19, CYP3A). CYP3A is also primarily responsible for the conversion of tamoxifen to N-desmethyl tamoxifen, the precursor of endoxifen. Other enzymes are involved in the elimination of active metabolites (SULT1A1, UGT2B15). Polymorphisms in the genes for these enzymes have been found that have an impact on enzyme activity and could have an effect on overall tamoxifen efficacy. Research regarding the effect of variant alleles for these enzymes is in an earlier, discovery stage compared to the research on CYP2D6 and will not be further discussed in this Assessment.

Genetic Variability and Endocrine Therapy Regimens

Because a small, but significant, proportion of most ethnic populations have markedly reduced CYP2D6 metabolic capacity, there is concern that similar proportions of patients treated with tamoxifen may have poorer outcomes than patients with relatively normal CYP2D6 activity. Some have recommended that patients who are to be prescribed tamoxifen be genotyped for CYP2D6, and that those patients

Table 1. Frequencies of the Most Prevalent CYP2D6 Alleles Across Ethnic Groups

Allele Type	CYP2D6 Allele	Caucasian (%)	African-American (%)	Asian (%)
Functional	*1	33–40	28–50	23–42
	*2	22–34	11–78	9–20
Reduced function	*9	0–2.9	0	3.3
	*10	1.9–8	3.1–8.6	38–70
	*17	0.1–0.3	9–34	0.5
	*41	8	—	—
Nonfunctional	*3	1–3.9	0–0.5	0.8–1
	*4	12–23	1.2–7	0–2.8
	*5	1.6–7.3	0.6–6.1	4.5–6.1
	*6	0.7–1	0	—
	*8	(rare)	(rare)	(rare)
Duplication	*1x2	0.2–0.5	3.3	0.5
	*2x2	0.7–1.6	1.6–2.5	0–1
	*4x2	0.1–0.2	0.9	—

Reproduced from Beverage et al. CYP2D6 polymorphisms and the impact on tamoxifen therapy. *J Pharm Sci*, 2007; 96(9):2224-31; Copyright © 2007 American Pharmacists Association; Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. Modified with information on *8 from Sachse et al. (1997); Kubota et al. (2000); Ji et al. (2002); Griese et al. (1999)

found to be PMs be treated with alternative therapy, if possible.

Tamoxifen has several prescribing indications: chemoprevention of invasive breast cancer in high-risk women without current disease or with ductal carcinoma in situ; adjuvant treatment of primary breast cancer; and treatment of metastatic disease. In women with breast cancer, endocrine-receptor-positive disease predicts likely benefit from tamoxifen treatment.

Tamoxifen is the only adjuvant treatment approved for preventing breast cancer in women with ductal carcinoma in situ (about 20% of all new breast cancer, American Cancer Society 2008), and for preventing disease in pre- or perimenopausal women at high risk. Thus, pharmacogenomic evaluation would not change treatment in these women.

Tamoxifen is currently the most commonly prescribed adjuvant treatment to prevent recurrence of endocrine-receptor-positive breast cancer in pre- or perimenopausal women. Pharmacogenomic evaluation could

direct consideration of ovarian ablation or suppression in those found to be CYP2D6 PMs. In pre- or perimenopausal women with hormone-receptor-positive tumors, ovarian ablation is an effective treatment compared to no adjuvant therapy (Adjuvant Breast Cancer Trials Collaborative Group [ABCTCG] 2007), but may be accompanied by acute and chronic adverse effects, e.g., hot flashes, sweats, and sleep disturbance. Ovarian ablation does not appear to add benefit to adjuvant chemotherapy (ABCTCG 2007). Similarly, functional ovarian suppression with gonadotropin-releasing-factor analogs in women with hormone-receptor-positive tumors confers benefits comparable to chemotherapy. National Comprehensive Cancer Network (NCCN) breast cancer guidelines (2008) indicate ovarian ablation/suppression is an option in combination with endocrine therapy for premenopausal women who have invasive or recurrent disease, and is recommended for premenopausal women with systemic disease. The optimal use of ovarian ablation/suppression and tamoxifen in premenopausal women is currently under study (Lonning 2007).

For prevention of cancer in postmenopausal women, who make up the majority of patients with breast cancer, raloxifene is an alternative treatment option, with equal efficacy and markedly reduced risk of endometrial hyperplasia. Raloxifene is currently not indicated for the treatment of invasive breast cancer, reduction of the risk of recurrence of breast cancer, or reduction of risk of noninvasive breast cancer (see full prescribing information at <http://pi.lilly.com/us/evista-pi.pdf>).

The pharmacogenomics of tamoxifen have been most often studied in postmenopausal women with endocrine-receptor-positive tumors who require endocrine therapy to prevent recurrence. For this population, the NCCN breast cancer guidelines make no preferential treatment recommendations among the following choices:

- aromatase inhibitors (AI) for 5 years
- tamoxifen for 2–3 years, followed by AI to complete 5 years or longer
- tamoxifen to 4.5–6 years, followed by AI for 5 years
- tamoxifen for 5 years in women with contraindications to AI treatment, who decline AI treatment, or who are intolerant of AI treatment.

In clinical practice, AIs may eventually replace tamoxifen because of fewer adverse effects and equal or better efficacy. For example, in the multicenter, double-blind Adjuvant Treatment of Breast Cancer in Postmenopausal Women trial (ATAC), adjuvant treatment with anastrozole at 1 mg daily was compared with tamoxifen at 20 mg daily. Recurrence-free survival at about 8 years was improved in the anastrozole arm compared to the tamoxifen arm: hazard ratio (HR) = 0.85, 95% CI: 0.76–0.94, $p=0.003$ (ATAC Trialists' Group 2008); there was no significant effect on overall survival. Table 2 shows results for prespecified adverse events in the ATAC trial at a median follow-up of almost 3 years; in particular, patients receiving anastrozole had a statistically significant decrease in hot flashes, vaginal bleeding, vaginal discharge, endometrial cancer, venous thromboembolic events (including deep venous thrombosis) and ischemic cerebrovascular events compared with patients receiving tamoxifen (shaded areas of Table 2). However, after about 8 years of follow-up, there were no significant differences in risk of cardiovascular morbidity or mortality; fracture rates were higher in patients treated with anastrozole versus tamoxifen

during active treatment, but not after treatment completion (ATAC Trialists' Group 2008).

Early results from the BIG 1-98 trial, designed to compare AI alone to sequential AI plus tamoxifen and to tamoxifen alone indicate that AI alone results in significantly fewer early relapses than tamoxifen (Mauriac et al. 2007). However, it is not yet clear that AI treatment alone maintains or improves long-term outcomes compared to sequential use of tamoxifen and AI (Lin and Winer 2007). Nor is there evidence as yet to support AI use in premenopausal women. Finally, tamoxifen is important in the treatment of metastatic cancer, where either tamoxifen or AI resistance may develop. Therefore the use of pharmacogenomics to improve the likelihood of tamoxifen benefit is of current interest.

The impact of CYP2D6 genotype and phenotype is the most extensively studied pharmacogenomic influence on tamoxifen treatment, and for that reason is the sole topic for this Assessment. As mentioned (see “Background: Metabolic Enzyme Genotypes”), genotypic variation in other enzymes mediating tamoxifen metabolism and metabolite elimination may also affect tamoxifen metabolite levels and potentially tamoxifen efficacy, and has undergone limited study to date. In addition, other pharmacogenomic contributors to the efficacy of endocrine therapy are under study. These include variability in estrogen receptor genes (Ntukidem et al. 2007), variability in aromatase genes and in AI metabolism (e.g., CYP2A6 and letrozole; Minami et al. 2007), and polymorphisms in coactivators and corepressors for the estrogen receptor (Flockhart 2005).

Several trials listed in ClinicalTrials.gov include analysis of aromatase gene polymorphisms (e.g., ClinicalTrials.gov Identifier NCT00228956 and NCT00244959), analysis of aromatase inhibitor metabolizing enzyme polymorphisms (e.g., ClinicalTrials.gov Identifier NCT00237198), or otherwise unspecified genetic influences on the outcomes of AI treatment (e.g., ClinicalTrials.gov Identifier NCT00263913).

Pharmacologic Inhibitors of Metabolic Enzymes

CYP2D6 activity may be affected not only by genotype, but also by co-administration of drugs that inhibit the metabolic activity of CYP2D6. For example, in healthy volunteers found to be EM phenotype, CYP2D6 activity has

Table 2. Number (%) of Patients with Prespecified Adverse Events in the ATAC Trial*

	Anastrozole n=3,092 (%)	Tamoxifen n=3,093 (%)	Odds Ratio	95% CI
All fractures	224 (7)	145 (5)	1.59	1.28–1.97
Fractures of spine, hip, wrist	89 (3)	62 (2)	1.45	1.04–2.04
Musculoskeletal disorders**	940 (30)	737 (24)	1.41	1.28–1.55
Ischemic cardiovascular disease	92 (3)	74 (2)	1.25	0.91–1.72
Asthenia	513 (17)	491 (16)	1.05	0.93–1.20
Nausea and vomiting	348 (11)	342 (11)	1.02	0.88–1.19
Mood disturbances	521 (17)	511 (17)	1.02	0.90–1.16
Cataracts	128 (4)	140 (5)	0.91	0.71–1.17
Hot flashes	1,082 (35)	1,246 (40)	0.80	0.73–0.87
Deep venous thromboembolic events	40 (1)	60 (2)	0.66	0.43–1.00
Venous thromboembolic events	73 (2)	120(4)	0.60	0.44–0.81
Ischemic cerebrovascular event	40 (1)	74 (2)	0.53	0.35–0.80
Vaginal bleeding	147 (5)	270 (9)	0.52	0.42–0.64
Vaginal discharge	94 (3)	378 (12)	0.23	0.18–0.28
Endometrial cancer	3 (0.1)	15 (0.5)	0.20	0.04–0.70

* Reproduced from FDA-approved label at <http://www.fda.gov/cder/foi/label/2002/20541s10lbl.pdf>

** Refers to joint symptoms, including arthritis, arthrosis, and arthralgia.

been determined by measuring the metabolic products of CYP2D6-dependent probe drugs before and after administration of potential CYP2D6 inhibitory medications. Studies of selective serotonin reuptake inhibitors (SSRIs) in particular have shown that fluoxetine and paroxetine, but not sertraline, fluvoxamine, or venlafaxine, are potent CYP2D6 inhibitors (Alfaro et al. 1999; 2000; Lam et al. 2002). Some individuals treated with fluoxetine or paroxetine changed from EM phenotype to PM (Alfaro et al. 1999). The degree of inhibition may depend upon the SSRI dose; for example, sertraline may be weakly, if at all, inhibitory at 50 mg but can become a potent inhibitor at higher doses (Sproule et al. 1997).

SSRIs are often prescribed to alleviate hot flashes, which can be an adverse effect of tamoxifen therapy. However, research has suggested that hot flashes accompanying tamoxifen treatment predict a lower likelihood of breast cancer recurrence (Mortimer et al. 2007). Reduction in hot flashes with SSRI

co-administration may reflect CYP2D6 inhibition, reduction of tamoxifen metabolism, and reduced levels of active tamoxifen metabolites, resulting in poorer outcomes. Contrasting with this hypothesis are results from a study showing that venlafaxine, at doses previously shown not to inhibit CYP2D6 activity, can also reduce hot flashes during tamoxifen treatment (Loprinzi et al. 2000).

Currently, the NCCN breast cancer guidelines (2008) state that “Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.” Nevertheless, CYP2D6 inhibitors have the potential to change the CYP2D6 phenotype, and therefore, studies of CYP2D6 genotype and tamoxifen treatment outcomes should account for the use of CYP2D6 inhibitors in assigning CYP2D6 functional status.²

² CYP2D6 is not considered to be an inducible enzyme in vivo (Ingelman-Sundberg 2005; Lynch and Price 2007).

Regulatory Status

The Roche AmpliChip CYP450 Test is cleared by the U.S. Food and Drug Administration (FDA) and is “intended to identify a patient’s CYP2D6 and CYP2C19 genotype from genomic DNA extracted from a whole blood sample. Information about CYP2D6 and CYP2C19 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized by the CYP2D6 or CYP2C19 gene product” (product insert, available at http://www.amplichip.us/documents/CYP450_P.I._US-IVD_Sept_15_2006.pdf).

CYP2D6 genotyping assays are also available as laboratory-developed services. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. While the FDA has technical authority to regulate home-brew

tests, to date there has been no active oversight with the possible exception of “in vitro diagnostic multivariate index assay” (IVDMIA) devices, for which a guidance document is currently in the draft stage.

The FDA has been considering updating the label for tamoxifen (brand and generics) with information or recommendations regarding CYP2D6 genotyping and impact on tamoxifen efficacy. On October 18, 2006, the FDA held an Advisory Committee meeting to answer specific questions regarding the evidence and recommendations for the label update; the questions and a summary of the Advisory Committee responses are presented in Table 3. Since the Advisory Committee meeting, AstraZeneca, the brand name (Nolvadex[®]) manufacturer, has ceased producing tamoxifen and is no longer maintaining the prescribing information. As of the date of this Assessment, no direction has come from the FDA regarding revised labeling of generic versions of tamoxifen to include CYP2D6 genotyping information.

Table 3. Questions (Q) Submitted to the FDA Advisory Committee for Pharmaceutical Science, Clinical Pharmacology Subcommittee (October 18, 2006) and Summaries of Subcommittee Answers (A) from the Final Minutes of the Advisory Committee Meeting (<http://www.fda.gov/ohrms/dockets/ac/cder06.html>)

Q1: The scientific evidence on the metabolism of tamoxifen demonstrates that CYP2D6 is an important pathway in the formation of endoxifen.	A: No disagreement.
Q2: The pharmacologic and clinical evidence are sufficient to demonstrate that endoxifen significantly contributes to the pharmacologic (anti-estrogenic) effect of tamoxifen.	A: While the Subcommittee felt that CYP2D6 contributed clinically to the level of endoxifen in in vitro data, there was no direct concentration/response information to indicate that endoxifen is a major contributor to the clinical effect of tamoxifen.
Q3: Does the clinical evidence demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizers (by genotype or drug interaction) are at increased risk for breast cancer recurrence? If yes, should the tamoxifen label include information about increased risk for breast cancer recurrence in CYP2D6 poor metabolizers prescribed tamoxifen?	A: The label should be updated to reflect the increased risk for breast cancer along with the mechanistic data presented.
Q4: Is there sufficient scientific and clinical evidence to support revisions of the tamoxifen label that recommends CYP2D6 genotype testing for postmenopausal patients before they are prescribed tamoxifen for adjuvant treatment?	A: The Subcommittee did not reach consensus on this question. Some members felt that the genetic test should be RECOMMENDED while others felt that it should be mentioned in the label as an OPTION for discussion between the health care provider and patient. However, the majority indicated that it should be included in an appropriate section of the package insert.

Clinical Trials of CYP2D6 Pharmacogenomics and Tamoxifen in Progress

An editorial by Hartman and Helft (2007) stated that “The Breast Intergroup has tentatively approved a randomized study to further evaluate the role of CYP2D6 status and treatment with an AI upfront versus tamoxifen followed by an AI in postmenopausal women.” However, no additional information regarding this proposed trial could be found.

On October 22, 2007, Medco Health Solutions, Inc. and Laboratory Corporation of America announced a strategic research agreement to study the pharmacogenomics of tamoxifen. No details of the study were provided.

Only one ongoing trial was found in the ClinicalTrials.gov database, which was a continuation of Lim et al. (2007, see Review of Evidence; ClinicalTrials.gov Identifier NCT00532454).

Methods

Search Methods

MEDLINE® was searched (via PubMed) using the search string “tamoxifen”[MeSH®] AND (“pharmacogenetics”[MeSH®] OR “cytochrome P450 enzyme system”[MeSH®]) through January 2008. Clinical trials, recent reviews (2004–2008), editorials, and letters related to the pharmacogenomics of tamoxifen were retrieved. In addition, text and reference lists of retrieved papers were examined for additional relevant articles.

Study Selection

Full-length, peer-reviewed papers reporting studies of postmenopausal women undergoing endocrine therapy whose treatment regimen selection is based on CYP2D6 genotyping versus usual selection methods; OR, studies of the association of CYP2D6 genotype with intermediate (tamoxifen active metabolite levels) or final outcomes (time to recurrence, survival) were selected for review. Study quality was evaluated by considering consistency of patient populations, tumor characteristics, and treatment and/or incorporation of confounders into analysis of results; as well as considering possible sources of bias.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on February 12, 2008.

In order to maintain the timeliness of the scientific information in this Special Report, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate.

Formulation of the Assessment

Patient Indications

Indications for CYP2D6 pharmacogenomic testing include patients who are to be treated with tamoxifen (alone or prior to treatment with an aromatase inhibitor) for prevention of breast cancer in high-risk women or women with DCIS, for adjuvant treatment to prevent breast cancer recurrence, or for treatment of metastatic disease, and who have no contraindications to treatment with aromatase inhibitors (for treatment of existing disease) or raloxifene (for prevention of disease). Postmenopausal patients determined to be CYP2D6 poor metabolizers could avoid tamoxifen therapy and be treated with aromatase inhibitors alone. Premenopausal patients determined to be CYP2D6 poor metabolizers could consider ovarian ablation or suppression in place of or in addition to tamoxifen treatment. All indications of tamoxifen use will be considered in this Assessment, as the biologic effects of tamoxifen treatment should not differ by treatment indication. For any indication, co-administration of drugs that inhibit CYP2D6 activity should be taken into account.

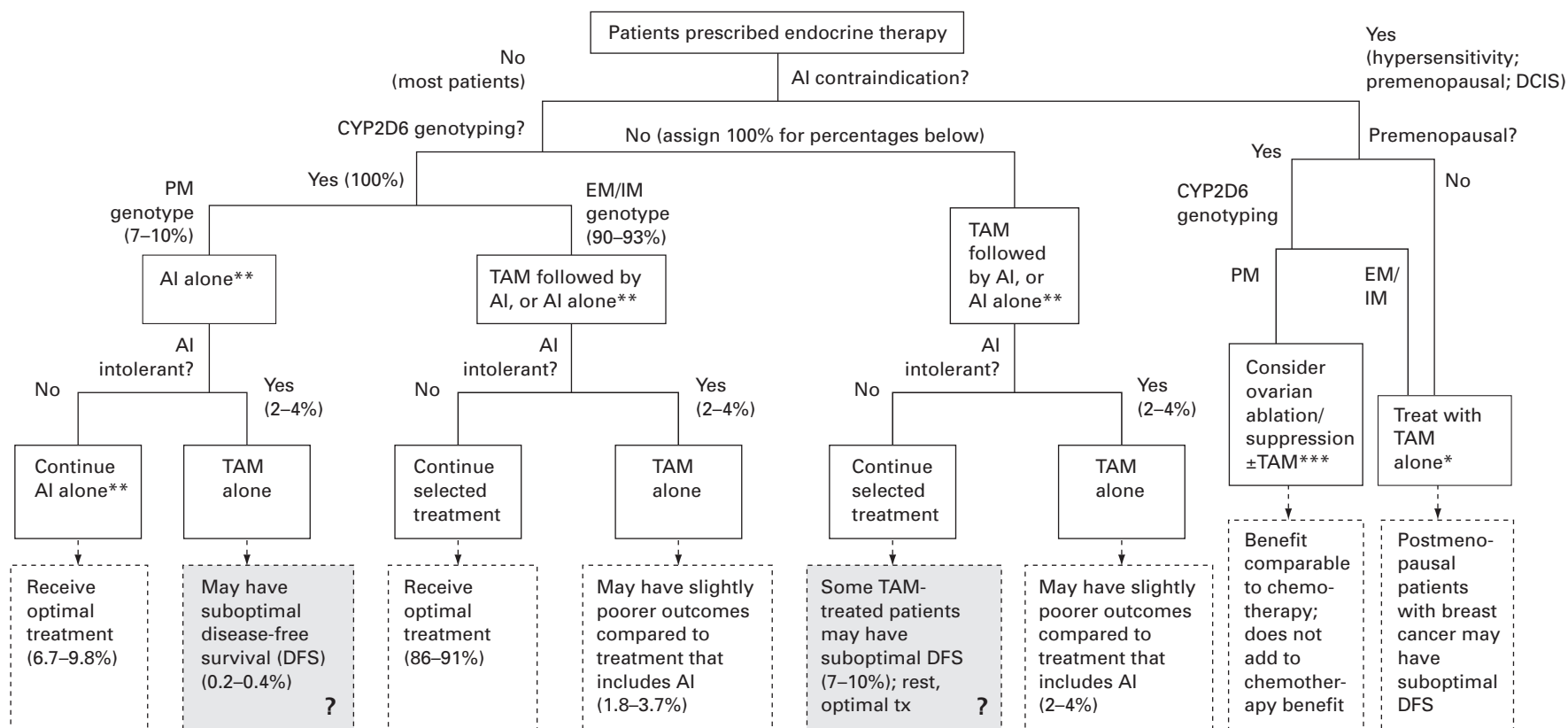
Technologies to Be Compared

CYP2D6 testing and consequent alteration of treatment regimen in CYP2D6 poor metabolizers is compared to no testing and no alteration of decision to treat with tamoxifen. A decision tree for the use of CYP2D6 testing to direct subsequent treatment decisions is presented in Figure 2.

Health Outcomes

The main health outcomes are disease prevention, improved time to recurrence, recurrence-free, and/or overall survival for patients whose treatment decisions are altered by CYP2D6 testing. Intermediate outcomes, such as tamoxifen active metabolite levels (endoxifen, 4-hydroxytamoxifen) do not provide sufficient evidence unless linked to evidence of main health outcomes.

Figure 2. Decision Tree for Using CYP2D6 Genotyping to Determine Endocrine Therapy Regimen



Shaded outcomes depend on evidence review.

* Or raloxifene for disease prevention in high-risk, non-diseased patients.

** Long term outcomes of AI alone vs. TAM followed by AI are not known. Based on current evidence, either AI alone or TAM followed by AI are considered optimal treatment (NCCN guidelines 2008).

*** The optimal use of estrogen suppression (ovarian ablation with or without aromatase inhibition) and tamoxifen (administered sequentially or in concert with ovarian ablation) in premenopausal women has yet to be defined.

Specific Assessment Questions

1. Are CYP2D6 genotyping assays accurate and reliable (i.e., analytic validity)?
2. In women who need endocrine therapy, are CYP2D6 variant genotypes significantly associated with (i.e., do they predict) intermediate and/or main health outcomes (i.e., clinical validity)?
3. In women who need endocrine therapy, does use of CYP2D6 genotype testing result in selecting endocrine therapy regimens that improve health outcomes compared to selection of endocrine therapy regimens without testing (i.e., clinical utility)?

Review of Evidence

1. Are CYP2D6 genotyping assays accurate and reliable (i.e., analytic validity)?

The Roche AmpliChip CYP450 Test (for detecting variants in CYP2D6 and CYP2C19 enzymes) has been fully validated for analytic validity; a summary of the results submitted for FDA clearance is provided in the product insert (available at http://www.amplichip.us/documents/CYP450_P.I._US-IVD_Sept_15_2006.pdf). Compared to sequencing (gold standard), the specificity of the AmpliChip CYP450 Test for detection of wild-type samples (n=100; 3 different wild-type alleles) was 100%; sensitivity for 22 different variant alleles in 492 alleles tested was 99.2% with no mis-calls, and 4 no-calls. Reproducibility (99.9%) and other measures of assay robustness indicate highly reliable performance. The AmpliChip kit contains positive and negative quality control samples that must yield specified results for an assay run to be valid.

While comparable information on the analytic validity of laboratory-developed tests is usually not available, in an experienced laboratory and with validation of in-house results compared to either sequencing or to AmpliChip, accurate and reliable performance should be achievable. For example, Heller et al. (2006) compared their in-house method to AmpliChip and achieved 95.6% agreement; 7 discordant samples contained CYP2D6 gene amplifications not detected by the in-house method (discordant results were verified by sequencing).

2. In women who need endocrine therapy, are CYP2D6 variant genotypes significantly associated with (i.e., do they predict) intermediate and/or main health outcomes (i.e., clinical validity)?

Association of Genotype with Tamoxifen Active Metabolite Concentrations

Four studies evaluated the association of CYP2D6 genotypes with circulating 4-OH tamoxifen and/or endoxifen levels (Table 4). All were prospective cohort studies of adjuvant treatment; tamoxifen was administered at the standard dose of 20 mg/day (or dose was not reported). Metabolite levels were determined at a minimum of 4 weeks from the start of tamoxifen treatment.

In three studies, the presence of a nonfunctional variant allele was associated with significantly reduced endoxifen levels (Stearns et al. 2003; Jin et al. 2005; Borges et al. 2006). There was an apparent allele dose effect in that two variant alleles were associated with lower endoxifen levels than one variant allele, which is associated with lower endoxifen levels than two wild-type alleles (Jin et al. 2005; Borges et al. 2006). In a fourth study of Korean women, the presence of two, but not one, reduced-function alleles (homozygous, nonfunctional variant alleles are rare in Asian populations, see Background, Tamoxifen Metabolism) was also associated with significantly reduced endoxifen levels (Lim et al. 2007).

While mean endoxifen levels for each genotype group differed significantly, individual patient data points for all groups overlapped considerably where shown in two studies (Jin et al. 2005; Borges et al. 2006); an example is shown in Figure 3. Thus, CYP2D6 variant alleles account for some but not all variability in endoxifen concentrations. Two studies also reported 4-OH tamoxifen levels by CYP2D6 genotype, finding nonsignificant differences in one (Jin et al. 2005), and significant differences in another (Lim et al. 2007). Because the production of 4-OH tamoxifen can be effected by several different CYP450 enzymes, major differences by CYP2D6 genotype would not be expected.

Table 4. Association of Tamoxifen Active Metabolite Levels with Clinical Outcomes

Study	n	Study Design, Patients	– TAM Use – Dose and Duration – before Evaluation	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison	Results		
Stearns et al. 2003	12	Prospective cohort	– Adjuvant	Yes	CYP2D6 (*4, *6, *8)	wt/V or V/V vs. wt/wt	Baseline endoxifen concentrations were lower in V carriers (p=0.002)		
		Breast cancer pts taking TAM and taking paroxetine (SSRI) for hot flashes	– 20 mg/day – ≥4 weeks	(Patients taking other CYP2D6 inhibitors excluded)			<p>Pre- vs. post-SSRI decrease in endoxifen</p> <p>CYP2D6 genotype</p> <p>wt/wt (n=7) 64%</p> <p>wt/V or V/V (n=5) 24%</p> <p>p-value 0.03</p>		
Jin et al. 2005	80	Prospective cohort	– Adjuvant – (Dose not reported) – 4 mos.	No	CYP2D6 (*1,*3, *4, *5,*6)	wt/wt vs. wt/V vs. V/V	Mean concentration after 4 mo:		
		Newly diagnosed, post-surgery breast cancer pts starting TAM					<p>Genotype (n) Endoxifen 95% CI 4-OH TAM 95% CI</p> <p>wt/wt (48) 78.0 nM 65.9–90.1 9.5 8.4–10.6</p> <p>wt/V (29) 43.1 33.3–52.9 8.3 6.7–9.9</p> <p>V/V (3) 20.0 11.1–28.9 7.1 1.2–13.0</p> <p>p-value <0.001 0.86</p>		
				Yes	No CYP2D6 inhibitor vs. CYP2D6 inhibitor by genotype	<p>Genotype+ inhibitor (n)</p> <p>wt/wt – inhib. (34)</p> <p>wt/wt + inhib. (13)</p> <p>wt/V – inhib. (17)</p> <p>wt/V + inhib. (11)</p> <p>V/V – inhib. (3)</p> <p>V/V + inhib. (0)</p>	<p>Mean endoxifen level (nM)</p> <p>91.4</p> <p>38.6</p> <p>51.7</p> <p>31.0</p> <p>20.0</p> <p>—</p>	<p>% Decrease</p> <p>57.8</p> <p>40.0</p> <p>20.0</p> <p>—</p>	<p>p-value</p> <p>0.0025</p> <p>0.08</p> <p>—</p>

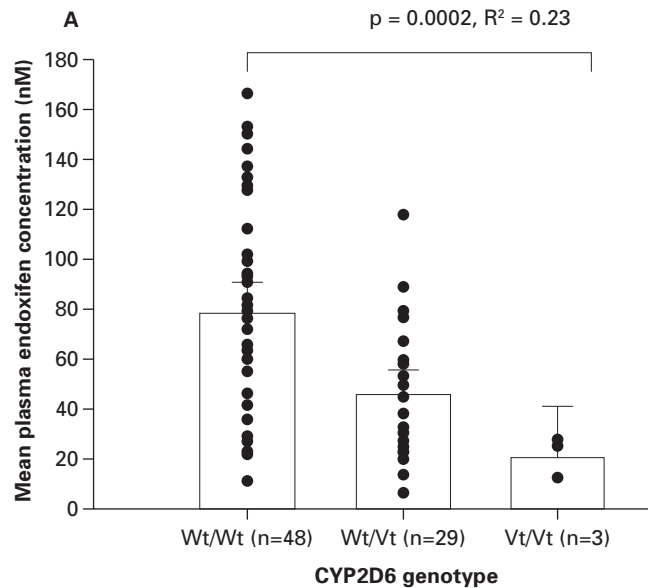
Note: distribution of individual patient results shows overlap among all groups

Table 4. Association of Tamoxifen Active Metabolite Levels with Clinical Outcomes (cont'd)

Study	n	Study Design, Patients	– TAM Use – Dose and Duration before Evaluation	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison	Results
Lim et al. 2007	202	Prospective cohort Korean women with early or metastatic breast cancer taking TAM	– Adjuvant or treatment of metastatic disease – 20 mg/day – >8 weeks	Yes (patients using CYP2D6 inhibitors excluded)	CYP2D6 (*2xN, *5, *10)	*10/*10 vs. wt/wt or wt/*10	<p>Genotype (n) wt/wt (64) or wt/*10 (89) vs. *10/*10 (49)</p> <p>endoxifen 19.9 ng/mL 18.1 7.9 (p<0.0001)</p> <p>4-OH TAM 2.8 ng/mL 2.5 1.5 (p<0.0001)</p> <p>Results were similar if *10 and *5 were combined as variant alleles; *5 allele frequency was 5%</p>

Abbreviations

TAM, tamoxifen; 4-OH TAM, 4-hydroxytamoxifen; chemo, chemotherapy; V, variant; wt, wild type (*1 or *2); EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; SSRI, selective serotonin reuptake inhibitor

Figure 3. Individual Patient and Mean Endoxifen Concentrations, by Genotype

Reproduced from Jin et al. (2005). CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst*, 97(1):30-9 with permission of Oxford University Press.

Consistently reduced plasma endoxifen levels were associated with CYP2D6 variant alleles whether (Stearns et al. 2003) or not (Jin et al. 2005) the concomitant use of CYP2D6 inhibitors was taken into account. When examined, co-administration of a CYP2D6 inhibitor medication to homozygous wild-type (EM) patients resulted in endoxifen levels close to those of homozygous nonfunctional genotype (PM) patients (Jin et al. 2005; Borges et al. 2006). After co-administration of a potent CYP2D6 inhibitor (the SSRIs paroxetine or fluoxetine), patients with homozygous wild-type alleles show a greater proportional decrease in endoxifen levels than carriers of one or two nonfunctional variant alleles (Stearns et al. 2003; Jin et al. 2005). Co-administration of a weak CYP2D6 inhibitor (various, e.g., the SSRIs sertraline or citalopram; celecoxib) was not associated with decreased endoxifen in one study (Borges et al. 2006). The SSRI venlafaxine, which does not affect CYP2D6 activity, was examined separately and had no effect on endoxifen plasma concentration (Borges et al. 2006). Thus, the use of potent CYP2D6 inhibitors, which includes some SSRIs that may be prescribed to ameliorate hot flashes, significantly reduces endoxifen levels; genotypic EMs treated with inhibitors appear to function like PMs. Thus, where inhibitor medication was not taken into account in comparing

endoxifen levels by genotype, the results represent the weakest case, as some genotypic EMs may have been functional PMs.

Summary. Three prospective cohort studies of adjuvant tamoxifen treatment provide consistent evidence that CYP2D6 nonfunctional variant alleles that render patients intermediate (one variant allele) or poor (two variant alleles) metabolizers, are associated with significantly reduced plasma endoxifen levels. However, endoxifen levels overlap across all genotypes, suggesting that CYP2D6 genetic variability does not explain all variability in endoxifen levels. One study suggests that reduced-function variant homozygotes, but not heterozygotes, also have significantly reduced circulating endoxifen. Co-administration of a potent CYP2D6 inhibitor to CYP2D6 homozygous wild-type patients (EMs) is associated with endoxifen levels near those of patients who are poor metabolizers.

Association of Tamoxifen Active Metabolite Levels with Clinical Outcomes

Whether reduced levels of endoxifen, either because of genotype or use of CYP2D6 inhibitor medication, result in poorer outcomes after tamoxifen treatment is not known (Desta and Flockhart 2007; see also Table 3).

Summary. The relationship between endoxifen (or 4-OH tamoxifen) plasma concentrations and clinical outcomes has not been established.

Association of Genotype with Clinical Outcomes

Seven studies evaluated the association between CYP2D6 genotype and clinical outcomes in women treated with tamoxifen (Table 5). Six were studies of adjuvant tamoxifen treatment; one (Lim et al. 2007) studied 21 patients with metastatic disease. Studies either enrolled all postmenopausal patients, or a mixture of pre- and postmenopausal patients without subgroup analysis.

We searched for data that evaluated CYP2D6 genotype as a prognostic marker, to ensure that a prognostic association would not confound the evaluation of the effect of genotype on tamoxifen outcomes in the studies included as evidence. Three of the studies (Nowell et al. 2005; Schroth et al. 2007; Wegman et al. 2005) evaluated outcomes stratified by genotype for women not treated with tamoxifen. While there were limitations in study quality or reporting, none of the studies found that outcome varied by CYP2D6 genotype. Therefore, this review assumed that CYP2D6 genotype was not a confounding factor in the evaluation of evidence.

An ideal way to evaluate the association of genotype with tamoxifen response is to compare tamoxifen-treated women versus those not receiving tamoxifen, with stratification by CYP2D6 genotype to see if PMs derive less benefit from tamoxifen than EMs. Wegman et al. (2005) conducted such a study retrospectively, on archived samples from a randomized, controlled trial of tamoxifen treatment. Paradoxically, they found that EMs treated with tamoxifen received no statistically significant clinical benefit compared to EMs not treated with tamoxifen, and that carriers of a CYP2D6*4 nonfunctional variant allele obtained significant benefit from tamoxifen treatment. There were several limitations to this study: tissue samples were available for only 33% of originally enrolled patients; only 47 patients carried a *4 allele (of these, only 4 were homozygous PMs); tamoxifen dose was 40 mg/day instead of the recommended 20 mg/day and was administered for only 2 years instead of the recommended 5 years. In addition, analysis of results did not take variable chemotherapy use or CYP2D6 inhibitors into account. Because of these limitations, the study results are questionable.

The other 6 studies studied only tamoxifen-treated women and evaluated outcomes by CYP2D6 genotype. The best evidence for whether CYP2D6 genotype predicts outcomes of tamoxifen treatment comes from Goetz et al. (2007) and Schroth et al. (2007). Both studies retrospectively enrolled relatively homogeneous populations of patients who were estrogen-receptor positive, were node positive in 63–64% and grade 1–2 in 78–91% of women, and for the primary analyses had been treated with tamoxifen alone (no chemotherapy) following resection of the tumor. Target treatment duration was 5 years in Goetz et al. (2007) but was not reported in Schroth et al. (2007). The studies differed in that Goetz et al. (2007) only genotyped for the CYP2D6*4 nonfunctional variant (most common), whereas Schroth et al. (2007) also tested for the *5 nonfunctional variant, and for the *10 and *41 reduced function variants. In both studies, negative results for the tested variants were assumed to represent wild-type genotypes. Schroth et al. (2007) also adjusted p values of risk estimates for multiple comparisons.

Goetz et al. (2007) reported a reanalysis of Goetz et al. (2005), incorporating information on CYP2D6 inhibitor medication use (6% of patients) and assigning CYP2D6 metabolizer status based on both genotype and use of inhibitor medications (Table 5). Due to lack of medication documentation, only 171 of the original 225 genotyped patients were included in this analysis. Cox proportional hazards (PH) analysis of survival outcomes by age, surgery (mastectomy vs. lumpectomy), quantitative ER (high vs. low), nodal status, tumor size, grade, and HER2 demonstrated that only tumor size greater than 3 cm and positive nodes were significant. Cox PH analyses of the effect of CYP2D6 metabolizer status (PM or IM vs. EM) on survival outcomes were adjusted for tumor size and nodal status, with statistically significant results for time to recurrence (TTR) and RFS, but not for OS:

- TTR: HR=1.91; 95% CI: 1.05–3.45; p=0.034
- RFS: HR=1.74; 95% CI: 1.10–2.74; p=0.017
- OS: HR=1.34; 95% CI: 0.83–2.16; p=0.223.

The population attributable risks (PAR), or the approximate proportions of outcomes accounted for by PM/IM status (calculated from the study PM/IM prevalence of 33% and hazard ratios) were 23%, 20%, and 10% for TTR, RFS, and OS, respectively.

Table 5. Association of Genotype with Clinical Outcome

Study	n	Study Design, Patients	– TAM Use – Dose – Duration – Median patient follow-up	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison (n)	Results
Goetz et al. 2005	223	Retrospective analysis of archived samples from NCCTG RCT (89-30-52), TAM-only arm (no chemo); all patients postmenopausal	– Adjuvant – 20 mg/day – 5 years – 11.4 (5.7–14.1) years	No	CYP2D6 (*4,*6)	*4/*4 (13) vs. wt/*4 (40) or wt/wt (137) (no *6 alleles detected)	Cox hazard ratio (HR) adjusted for nodal status and tumor size: RFS: HR 1.85, 95% CI: 0.76–4.52 p=0.176 RFS: HR 1.86, 95% CI: 0.91–3.82 p=0.089 OS: HR 1.12, 0.50–2.50 p=0.78 Note: Unadjusted RFS and RFS results were significant. Moderate/severe hot flashes in *4/*4 vs. *4/wt or wt/wt: 0% vs. 20%, p=0.064
Wegman et al. 2005	226	Retrospective analysis of archived samples from a TAM RCT, ± chemo or radiotherapy Post-surgery, postmenopausal breast cancer patients with positive nodes or tumor >30mm for whom tissue was available	– Adjuvant – 40 mg/day – 2 years – 10.7 (0.24–18.6) years	No	CYP2D6 (*4)	TAM-treated vs. no TAM, stratified by *4/*4 (4) or *4/wt (43) and wt/wt (109)	RFS of ER-positive and ER-negative women (?no TAM) were not significantly different by genotype; authors concluded that CYP2D6*4 has no prognostic value Recurrence rate ratio (RR) for ER-positive patients, TAM-treated vs. no TAM, adjusted for age, tumor size, and lymph node status: wt/wt: RR=0.91, 95% CI: 0.53–1.57, p=0.75 *4 carrier: RR=0.28, 95% CI: 0.11–0.74, p=0.009 Note: authors report selection bias could not be excluded.

Table 5. Association of Genotype with Clinical Outcome (cont'd)

Study	n	Study Design, Patients	– TAM Use – Dose – Duration – Median patient follow-up	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison (n)	Results																						
Nowell et al. 2005	162	Retrospective cohort, pre- and postmenopausal	– Adjuvant – (Dose not reported)	No	CYP2D6 (*3,*4,*6)	*4/*4 or wt/*4 (+TAM, 49; -TAM, 46) vs. wt/wt (+TAM, 112; -TAM, 120)	Survival of patients with at least one *4 allele (*3 and *6 alleles were rare) compared to wt/wt evaluated using Cox modeling, adjusting for age, race, stage, ER and PR status.																						
		Primary breast cancer pts taking TAM, ± chemo or radiotx	– (Duration not reported)																										
	175	Primary breast cancer pts not taking TAM, ± chemo, radiotx	– 5.4 years				<table border="1"> <thead> <tr> <th></th> <th></th> <th>HR</th> <th>95% CI</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td rowspan="2">TAM</td> <td>RFS</td> <td>0.67</td> <td>0.33–1.35</td> <td>0.19</td> </tr> <tr> <td>OS</td> <td>0.77</td> <td>0.32–1.81</td> <td>0.51</td> </tr> <tr> <td rowspan="2">No TAM</td> <td>RFS</td> <td>0.69</td> <td>0.40–1.18</td> <td>0.19</td> </tr> <tr> <td>OS</td> <td>0.79</td> <td>0.42–1.26</td> <td>0.26</td> </tr> </tbody> </table>			HR	95% CI	p value	TAM	RFS	0.67	0.33–1.35	0.19	OS	0.77	0.32–1.81	0.51	No TAM	RFS	0.69	0.40–1.18	0.19	OS	0.79	0.42–1.26
		HR	95% CI	p value																									
TAM	RFS	0.67	0.33–1.35	0.19																									
	OS	0.77	0.32–1.81	0.51																									
No TAM	RFS	0.69	0.40–1.18	0.19																									
	OS	0.79	0.42–1.26	0.26																									
Wegman et al. 2007	677	Retrospective analysis of archived samples, Postmenopausal ER+ breast cancer patients with stage II or III disease (238 randomized to 2 vs. 5 years TAM)	– Adjuvant – 20 or 40 mg/day – 2 or 5 years – 7.1 (0.04–18) years	No (SSRIs “rarely used in study population”)	CYP2D6 (*4)	*4/*4 (35) or wt/*4 (186) vs. wt/wt (475)	<p>In analysis of all patients, *4 homozygotes (p=0.05) and heterozygotes (p=0.04) were significantly associated with improved RFS but results were not significant in multivariate analysis (p=0.055).</p> <p>Multivariate analysis (controlled for tumor stage and size, lymph node status) of each randomized subgroup was not significant for a difference in RFS, comparing *4 carriers to homozygous wt.</p> <p>Note: only 2 events occurred in 35 *4/*4 patients</p>																						

Table 5. Association of Genotype with Clinical Outcome (cont'd)

Study	n	Study Design, Patients	– TAM Use – Dose – Duration – Median patient follow-up	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison (n)	Results
Schroth et al. 2007	206 280	Retrospective cohort analysis of archived samples from pre- and postmenopausal patients Primary breast cancer patients taking TAM alone Control breast cancer patients not taking TAM; ± chemo	– Adjuvant – (Dose not reported) – (Duration not reported) – 5.9 (0.7–19) years	No	CYP2D6 (*4,*5,*10,*41)	V/V (30) or wt/*4 or wt/*5 (49) vs. wt/wt or wt/*10 or wt/*41 (118)	Cox adjusted (tumor size and nodal status) HR of TAM-treated patients with decreased vs. normal CYP2D6 activity: TTR: HR 2.24; 95% CI: 1.16–4.33; p=0.02 RFS: HR 1.89; 95% CI: 1.10–3.25; p=0.02 There were no significant associations with OS. There were no significant associations between genotype and outcomes in patients not treated with TAM (?chemo not accounted for). Note: p values of risk estimates were adjusted for multiple comparisons
Lim et al. 2007	21	Retrospective cohort Korean pre-and postmenopausal women with metastatic breast cancer taking TAM ± prior chemo and/or AI	– Treatment of metastatic disease – 20 mg/day – Median 9 (2–23+) mos. – Median 1.6 (0.6–4.5) years	Yes	CYP2D6 (*5,*10)	*10/*10 (12) vs. wt/wt or wt/*10 (n=9)	Patients experiencing complete or partial response, or stable disease at ≥24 mos.: wt/wt or wt/*10 patients: 9 of 9 (100%) *10/*10 patients: 6 of 12 (50%) Median time to progression: wt/wt or wt/*10 patients: 21.8 mo *10/*10 patients: 5.03 (p=0.0032) In multivariate analysis, CYP2D6 genotype and number of disease sites remained significant (p=0.016 and 0.012).

Table 5. Association of Genotype with Clinical Outcome (cont'd)

Study	n	Study Design, Patients	– TAM Use – Dose – Duration – Median patient follow-up	Study accounted for CYP2D6 inhibitors?	Gene (typed variants)	Comparison (n)	Results
Goetz et al. 2007 (re-analysis of Goetz et al. 2005)	171	Retrospective analysis of archived samples from NCCTG RCT (89-30-52), TAM-only arm (no chemo); all patients postmenopausal	– Adjuvant – 20 mg/day – 5 years – Mean 11.4 (5.7–14.1) years	Yes 171 of original 223 CYP2D6*4 genotyped patients had medication information; of these, 6% were co-administered a CYP2D6 inhibitor for 2-3 years	CYP2D6 (*4)	PM (n=16) [*4/*4 or *4/wt + weak/mod. inhibitor or wt/wt + potent inhibitor] or IM (n=40) [*4/wt or wt/wt + weak/mod. inhibitor] vs. EM (n=115) [wt/wt]	Cox HR (adjusted for tumor size and nodal status), PM or IM vs. EM: TTR: HR = 1.91; 95% CI: 1.05–3.45; p=0.034 RFS: HR = 1.74; 95% CI: 1.10–2.74; p=0.017 OS: HR = 1.34; 95% CI: 0.83–2.16; p=0.223 Cox unadjusted HR, PM vs. EM: TTR: HR = 3.20; 95% CI: 1.37–7.55; p=0.007 RFS: HR = 2.69; 95% CI: 1.34–5.37; p=0.005 OS: HR = 2.00; 95% CI: 92–4.17; p=0.077 Cox unadjusted HR, IM vs. EM: TTR: HR = 1.40; 95% CI: 0.68–3.05; p=0.337 RFS: HR = 1.63; 95% CI: 0.95–2.78; p=0.075 OS: HR = 1.40; 95% CI: 0.80–2.43; p=0.240

Abbreviations

TAM, tamoxifen; chemo, chemotherapy; AI, aromatase inhibitor; V, variant; wt, wild type (*1 or *2); EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; HR, hazard ratio; TTR, time to recurrence; RFS, recurrence-free survival; OS, overall survival; SSRI, selective serotonin reuptake inhibitor; NCCTG, North Central Cancer Treatment Group

The results represent a potentially weaker effect than might otherwise have been found, because IMs are included in the decreased CYP2D6 activity group. When PMs alone were compared to EMs alone in univariate analyses, the results were highly significant for TTR (HR=3.20; 95% CI: 1.37–7.55; $p=0.007$) and RFS (HR=2.69; 95% CI: 1.34–5.37; $p=0.005$), although not for OS. In absolute terms, at 10 years after randomization, about 35% of PMs, 48% of IMs, and 72% of EMs were free of recurrence ($p=0.009$); 43% of PMs, 61% of IMs, and 73% of EMs were alive ($p=0.145$). Multivariate analyses for PM versus EM were not reported, likely because the number of PMs ($n=16$) was insufficient. At such low numbers, confounders such as tumor characteristics could significantly and unpredictably bias results. Study results may also be affected by the incorrect assignment of less common variants (that were not genotyped) to the EM category, which could bias the results toward the null.

Schroth et al. (2007) conducted a retrospective cohort analysis of patients diagnosed with primary invasive breast cancer between 1986 and 2000 at a single center. Women with clinical follow-up information and specimens of noncancerous breast tissue sufficient for genotyping were included if they were ER-positive and had received adjuvant tamoxifen alone. The authors also combined all homozygous variants with heterozygous nonfunctional variant genotypes (decreased metabolizers) and compared them to the combined group of homozygous wild type or heterozygous reduced function variant genotypes (extensive metabolizers). Only tumor size and nodal status were significantly correlated to RFS; these parameters were used to adjust for confounding effects in multivariate analyses of genotype-outcome associations. The adjusted Cox HRs and PARs for TTR and RFS of tamoxifen-treated decreased metabolizers compared to extensive metabolizers were significantly poorer:

- TTR: HR=2.24; 95% CI: 1.16–4.33; $p=0.02$; PAR=33%
- RFS: HR=1.89; 95% CI: 1.10–3.25; $p=0.02$; PAR=26%.

As with the Goetz et al. (2007) study, these results were potentially biased toward the null by inclusion of heterozygous wild-type/non-functional variants in the decreased CYP2D6 activity group. In this study, the assignment of patients to the functional CYP2D6 category did not take CYP2D6 inhibitor co-medication into

account (medication histories were incomplete); the association might be stronger if a significant proportion of EM patients had been taking potent CYP2D6 inhibitors and could have been correctly classified as functional PMs rather than EMs. It should also be noted that the authors corrected their p values for multiple comparisons. Considering all these points, the results likely represent the minimum strength of association between genotype and outcomes.

Of the remaining three studies, two reported poorer recurrence-free survival (Nowell et al. 2005) and time to progression (Lim et al. 2007) for carriers of nonfunctional variants or reduced function variant homozygotes, respectively. Only one of these was statistically significant (Lim et al. 2007). Wegman et al. (2007) reported no predictive significance of CYP2D6 genotyping on outcomes. Two studies were of adjuvant tamoxifen, while Lim et al. (2007) studied a small number ($n=21$) of metastatic patients treated with tamoxifen.

Wegman et al. (2007) enrolled patients treated with tamoxifen at either 20 or 40 mg/day; tamoxifen dose was not reported in the two studies reporting poorer outcomes for CYP2D6 variants (Lim et al. 2007 and Nowell et al. 2005, respectively). Others have speculated that at 40 mg/day, tamoxifen active metabolites are within the plateau of the concentration-response curve, whereas at 20 mg/day, they are within the rapidly changing section of the curve, where CYP2D6 genotype might be more likely to have a significant effect (Lim et al. 2007). No evidence supports this interpretation, however.

None of these three studies accounted for varying treatments other than tamoxifen described in their patient populations, in their patient selection, or analyses. Lim et al. (2007) and Nowell et al. (2005) did not adjust for chemotherapy use in multivariate analyses. Wegman et al. (2007) did not report whether patients received treatment other than tamoxifen. Wegman et al. (2007) and Nowell et al. (2005) did not account for CYP2D6 inhibitor medication. Wegman et al. (2007) stated in their Discussion that selective serotonin reuptake inhibitors were “rarely used in the current study population” but there is no indication that this was based on chart review. As noted, lack of adjustment for CYP2D6 inhibitors would likely bias results toward the null rather than otherwise.

Genotype grouping was similar (wt/V patients with V/V patients) in the two studies that examined the effect of nonfunctional variants (Nowell et al. 2005; Wegman et al. 2007). Lim et al. (2007) grouped wt/reduced function variant patients with wt/wt patients. Differences in patient grouping, however, do not correlate with differences in results.

Summary. Evidence from two higher-quality trials of adjuvant tamoxifen in relatively homogeneous patient populations suggests that women who are functional poor or intermediate CYP2D6 metabolizers, whether by genotype or by co-medication with CYP2D6 inhibitors, treated with tamoxifen have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to EMs in multivariate analyses adjusted for other parameters of disease prognosis. The significance levels were marginal, although in one study were corrected for multiple comparisons. The strength of these associations might be stronger and more convincing if PMs alone could be compared to EMs, but numbers of PMs were insufficient. Few variant alleles were typed in these studies, and samples negative for variant alleles were assumed to be wild-type EMs; more extensive genotyping and better categorization might also strengthen results. Four other studies provide conflicting evidence; results were not sufficiently adjusted for variable treatment and tamoxifen dose.

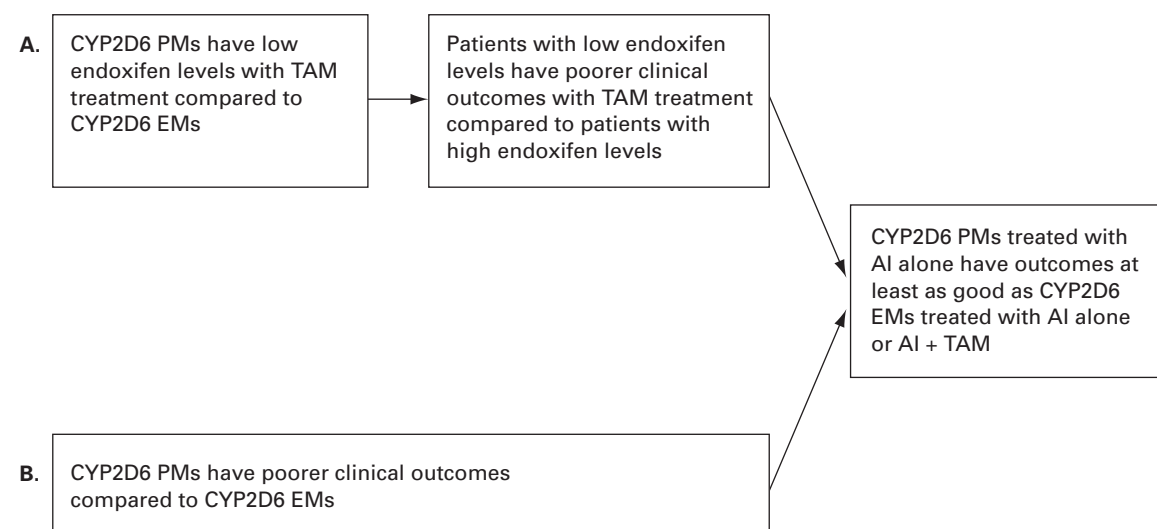
3. In women who need endocrine therapy, does use of CYP2D6 genotype testing result in selecting endocrine therapy regimens that improve health outcomes compared to selection of endocrine therapy regimens without testing (i.e., clinical utility)?

No clinical trials have been conducted that would provide direct evidence of clinical utility. Such a trial might prospectively enroll patients who would be prescribed endocrine therapy including tamoxifen, but who would also be eligible for AI treatment. Patients would be randomized to usual methods of treatment selection or to CYP2D6 genotyping after which poor metabolizers would receive AI treatment alone (see Figure 4).

In the absence of direct evidence, a chain of indirect evidence can be constructed. There are two possible ways to do this, outlined in Figure 4 and for simplicity comparing only CYP2D6 PMs and EMs in postmenopausal women.

Indirect Evidence Chain A. Consistent evidence shows that poorer metabolizers have lower levels of endoxifen, the major active metabolite of tamoxifen. However, there is no evidence to support the second part of the chain; no evidence directly links tamoxifen metabolite levels in patients to clinical outcomes.

Figure 4. Two Possible Indirect Chains of Evidence for Clinical Utility of CYP2D6 Genotyping for Selecting Endocrine Therapy Regimen



Boxed text describes evidence that would be needed to complete each section of the chain

Indirect Evidence Chain B. This indirect chain of evidence depends on the CYP2D6 genotype-clinical outcomes associations evaluated for clinical validity (Key Question 2). There are several limitations to this evidence:

- Studies are retrospective and, as such, more prone to bias.
- Only two studies enrolled relatively homogeneous populations of women given the same treatment and adjusted for the most significant confounders of the genotype-outcome association.
- To demonstrate the strongest effect, PMs should be compared to EMs; because there were small numbers of PMs and of events in PMs, an adjusted analysis was not possible (Goetz et al.: 9 events in 16 patients for RFS; Schroth et al.: 10 events in 30 patients⁵ for RFS). Addition of IMs to the PM group and comparison with EMs resulted in adjusted associations that were statistically significant, but not compelling.
- There was no effect on overall survival; larger studies would be needed to determine effect.
- Most studies are of Caucasian patients; with the exception of one study in a Korean population, relevant CYP2D6 variant alleles in relation to tamoxifen treatment have not been studied in other ethnic groups.

Regarding the final set of evidence needed to complete both indirect chains, there is no direct evidence on outcomes of subpopulations of patients with CYP2D6 variant alleles treated with AI versus tamoxifen. However, none of the FDA-approved aromatase inhibitors is metabolized by CYP2D6 (Reddy 1998; Grimm et al. 1997; and prescribing information for letrozole, anastrozole, and exemestane) and therefore treatment outcomes would not be expected to vary by this parameter. Given current trial evidence, outcomes for CYP2D6 PMs treated with AI alone should be as good as outcomes for EMs treated with AI plus tamoxifen (see Background, Genetic Variability and Endocrine Therapy Regimens).

Summary. There is no direct evidence of clinical utility. Two indirect evidence chains can be constructed. One depends on demonstrating a significant association between in vivo endoxifen levels and clinical outcomes; this evidence does not exist. The other depends

on the association of genotype with clinical outcomes, summarized for clinical validity in Key Question 2. There are several limitations to this evidence, and as a result it is judged insufficient to support clinical utility.

Discussion

The hypothesis examined in this Assessment is that CYP2D6 poorer metabolizers, whether by genotype or by co-administration of CYP2D6 inhibitory medication, have reduced tamoxifen metabolism and lower endoxifen levels compared to better metabolizers, and as a direct result have poorer clinical outcomes. This hypothesis is based on the assumption, not yet supported by evidence, that some level of endoxifen is sufficient and necessary for tamoxifen efficacy, and that this level is not achieved in genotypic and functional CYP2D6 PMs, and possibly not in some IMs. It seems feasible to propose such a study in tamoxifen-treated populations of completed clinical trials, where appropriate specimens are available. The advantage of such a study is that the metabolite itself, rather than the activity of the enzyme producing it, would be directly measured in relation to clinical outcomes. Because tamoxifen metabolism is complex and CYP2D6 does not appear to account for all variability in endoxifen levels, it is conceivable that polymorphisms in other tamoxifen metabolic pathway enzymes may affect active metabolite levels, and direct measurement of the metabolite(s) itself may be the better predictor of benefit from tamoxifen treatment. However, since it takes 8 weeks for tamoxifen metabolites to reach steady-state concentrations, measuring metabolite levels is not practical for clinical applications outside of a retrospective study.

Additionally or alternatively, larger studies of the CYP2D6 genotype-clinical outcomes association are needed to expand and verify initial results, and to accurately identify the exact genotypes that have poorer outcomes and would best benefit from AI treatment alone, versus those that would best benefit from regimens including tamoxifen.

Multiple enzyme genotypes may be needed to confidently predict tamoxifen versus AI treatment benefit; however, there is little data at

⁵ Note that both homozygous nonfunctional variant patients (n=14), and heterozygous nonfunctional variant/reduced function variant (n=16) were both included in the authors' definition of poor metabolizers.

present to recommend combinations. Wegman et al. (2005) studied the risk of recurrence in patients carrying at least one CYP2D6*4 allele and/or two SUL1A1*1 alleles, and found significantly improved survival with tamoxifen treatment vs. no tamoxifen treatment ($p=0.018$). As noted previously, the CYP2D6*4 results in this study are inconsistent with other data. Nowell et al. (2005) reported that tamoxifen-treated women with UGT2B15 and SUL1A1 enzyme allele variants had significantly greater risk of recurrence and poorer survival than those with common alleles ($p=0.05$). Schroth et al. (2007) also found better RFS in tamoxifen-treated women carrying at least one increased activity CYP2C19*17 allele, compared to women carrying *1, *2, or *3 alleles ($p=0.05$). In this study, women with wild-type CYP2D6 status and at least one CYP2C19*17 allele had more favorable outcomes than other combinations ($p=0.02$). Additional studies would be needed to extend and verify these results.

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for primary breast cancer or breast cancer recurrence meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria:

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The Roche AmpliChip CYP450 Test is cleared by the FDA to determine patients' CYP2D6 and CYP2C19 genotypes.

CYP2D6 genotyping assays are also available as laboratory-developed services. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA) and must be licensed by CLIA for high-complexity testing. While the FDA has technical authority to regulate home-brew tests, to date there has been no active oversight with the possible exception of "in vitro diagnostic

multivariate index assay" (IVDMIA) devices, for which a guidance document is currently in the draft stage.

The FDA has been considering updating the product labeling for tamoxifen with information or recommendations regarding CYP2D6 genotyping and impact on tamoxifen efficacy. On October 18, 2006, the FDA held an Advisory Committee meeting to answer specific questions regarding the evidence and recommendations for the label update; the members of the Advisory Committee recommended including information on CYP2D6 genotypes and potential effect on patient outcomes, and information on CYP2D6 genotyping tests. The members did not reach a consensus as to whether testing should be recommended or considered as an option. Since the Advisory Committee meeting, AstraZeneca, the brand name (Nolvadex[®]) manufacturer, has ceased producing tamoxifen and is no longer maintaining the prescribing information. As of the date of this Assessment, no direction has come from the FDA regarding revised labeling of generic versions of tamoxifen to include CYP2D6 genotyping information.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There is no direct evidence of clinical utility. Two indirect evidence chains can be constructed. One depends on demonstrating a significant association between endoxifen and clinical outcomes; this evidence does not exist. The other depends on the association of genotype with clinical outcomes; there are several limitations to this evidence, and as a result it is judged insufficient to support clinical utility.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

There is insufficient evidence to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer.

5. The improvement must be attainable outside the investigational settings.

Whether or not the use of CYP2D6 genotyping for directing endocrine therapy regimen

selection for women at high risk for or with breast cancer improves health outcomes has not been demonstrated in the investigational setting.

Based on the above, CYP2D6 genotyping does not meet the TEC criteria for directing endocrine therapy regimen selection for women at high risk for primary breast cancer or breast cancer recurrence.

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