Title: Genetic Testing for Tamoxifen Treatment

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DESCRIPTION
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 have been hypothesized to have a negative impact on tamoxifen treatment efficacy.

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 patients who are poor metabolizers (PMs) be treated with alternative therapy, if possible.

**Background**

**Tamoxifen Metabolism**
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 (1). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has identical properties and potency compared with 4-OH tamoxifen. (2-5) Because 4-OH tamoxifen represents less than 20% of the product of tamoxifen primary metabolism and steady-state plasma endoxifen concentrations are on average 5- to 10-fold higher than 4-OH tamoxifen, 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 CYP2D6. The plasma concentration of endoxifen exhibits high inter-individual variability, as described in breast cancer patients. (5) 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. Moreover, the known variability in endoxifen levels has been hypothesized to result in variable response to tamoxifen treatment.

Alternatively and more recently, it has been estimated that at doses used for adjuvant treatment, which is intended to saturate the estrogen receptor, more than 99% of estrogen receptors are bound by low-affinity tamoxifen and both low- and high-affinity metabolites. (6) Lash et al. modeled the effect of CYP2D6 variant alleles on estrogen receptor binding by tamoxifen and metabolites and found negligible effect. (7) As the authors note, however, modeling cannot account for many metabolic complexities, and mechanistic data would be needed to show how the decrease in high-affinity metabolites associated with CYP2D6 variants reduces the protection against recurrence conferred by tamoxifen therapy.

**Metabolic Enzyme Genotypes**
The CYP2D6 gene exhibits a high degree of polymorphism, with more than 75 allelic variants identified. While the most prevalent CYP2D6 *1 and *2 alleles (both termed “wild-type” for this Policy) produce an enzyme with normal activity, there are several variant (V) alleles that result in enzymes with no activity or reduced activity. 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). An additional, rare category of ultra-rapid metabolizers (UM) is defined by possession of three or more functional alleles due to gene duplication.

The prevalence of CYP2D6 PMs 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 and by the *5 non-functional variant in African-American and Asian populations. 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. (8)

Several other enzymes are involved in the metabolism of tamoxifen to the active metabolite 4-OH tamoxifen. Polymorphisms in the genes for these enzymes could have an effect on overall tamoxifen efficacy. Research regarding the effect of variant alleles for these enzymes is in earlier stages of discovery.

**Endocrine Therapy Regimens**

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 (approximately 20% of all new breast cancer, (9) 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 but may be accompanied by acute and chronic side effects, e.g., hot flushes, sweats, and sleep disturbance. Ovarian ablation does not appear to add benefit to adjuvant chemotherapy. 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) guidelines 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. (10)

For prevention of cancer in postmenopausal women, raloxifene is an alternative treatment option, with efficacy equal to that of tamoxifen 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 online at: http://pi.lilly.com/us/evista-pi.pdf).

The pharmacogenomics of tamoxifen have been most often studied in post-menopausal women with endocrine-receptor-positive tumors who require endocrine therapy to prevent recurrence. For this population, the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (10) 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 to AI treatment.
In clinical practice, AIs may eventually replace tamoxifen because of fewer adverse effects and equal or better efficacy. However, it is not yet clear that AI treatment alone maintains or improves long-term outcomes compared to sequential use of tamoxifen and AI. (11) There is also no 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.

**Pharmacologic Inhibitors of Metabolic Enzymes**

CYP2D6 activity may be affected not only by genotype but also by co-administration of drugs that block the metabolic activity of CYP2D6. 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. (12-14) Some individuals treated with fluoxetine or paroxetine changed from EM phenotype to PM. (12) The degree of inhibition may depend upon the SSRI dose.

Thus, CYP2D6 inhibitor use must be considered in assigning CYP2D6 functional status, and potent CYP2D6 inhibitors may need to be avoided when tamoxifen is administered.

**Regulatory Status**

The Roche AmpliChip CYP450 Test is cleared by the U.S. Food and Drug Administration (FDA) and can be used to identify a patient's CYP2D6 genotype.

CYP2D6 genotyping assays are also available as non-FDA-cleared laboratory-developed services; 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.

Although the FDA has considered updating the label for tamoxifen (brand and generics) with information or recommendations regarding CYP2D6 genotyping and impact on tamoxifen efficacy, and has held an Advisory Committee meeting to answer specific questions regarding the evidence and recommendations, no label update has yet been issued.

**POLICY**

Genotyping to determine cytochrome p450 (CYP2D6) genetic polymorphisms is considered experimental / investigational for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

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RATIONALE
This policy is based on a 2011 TEC Assessment. (15) Additional details concerning the studies described in this section are available in the Assessment.

Potential indications for CYP2D6 pharmacogenomic testing include patients who are to be treated with tamoxifen (alone or prior to treatment with an aromatase inhibitor [AI]), for prevention of breast cancer in high-risk women or women with ductal carcinoma in situ (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). If there is evidence supporting poorer outcomes of tamoxifen treatment in CYP2D6-poor metabolizers (PMs), postmenopausal patients determined to be CYP2D6 PMs could avoid tamoxifen therapy and be treated with aromatase inhibitors alone. Premenopausal patients might consider ovarian ablation. For any indication, co-administration of drugs that inhibit CYP2D6 activity would be taken into account.

Analytic Validity (technical performance of the assay)
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 clearance by the U.S. Food and Drug Administration (FDA) is provided in the product insert (available online at: http://www.amplichip.us/documents/CYP450_P.I._US-IVD_Sept_15_2006.pdf).

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 as demonstrated by Heller et al. (16)

Clinical Validity (association of genetic marker with intermediate or clinical outcomes)
Four studies evaluated CYP2D6 genotype as a prognostic marker in patients not treated with tamoxifen to ensure that a prognostic association would not confound the effect of genotype on tamoxifen outcomes. (17-20) While there were limitations in study quality or reporting, none of the studies found that outcome varied by CYP2D6 genotype in untreated patients.

Indirect Association of Genotype with Clinical Outcomes. Eleven prospective cohort studies of adjuvant tamoxifen treatment provide consistent evidence that CYP2D6 nonfunctional variant alleles are associated with significantly reduced plasma endoxifen levels. (5, 20-29) However, endoxifen levels overlap across all genotypes, suggesting that CYP2D6 genetic variability does not explain all variability in endoxifen levels. Six of seven studies report a significant association of low CYP2D6 function with reduced plasma 4-hydroxytamoxifen (4-OH tamoxifen) levels. (20, 21, 23, 24, 27-29) 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 PMs; thus use of CYP2D6 inhibitors should be taken into account in assigning metabolizer status in clinical studies.

Two studies report on the relationship between CYP2D6 genotype and active tamoxifen metabolites and between genotype and clinical outcomes in the same patient population. (20, 24) All studies enrolled breast cancer patients from Asian populations, focusing almost exclusively on the reduced (but not absent) function CYP2D6*10 variant. Two studies reported reduced endoxifen and/or 4-OH tamoxifen concentrations in conjunction with 1 or 2 variant alleles and in
conjunction reported decreasing disease- or recurrence-free survival; the largest study (29) reported no association of genotype with recurrence-free survival. Both studies are small and have study design flaws likely resulting in selection bias. More recently, the association of tamoxifen metabolite levels with breast cancer outcomes was studied in 1,370 samples from the Women's Healthy Eating and Living (WHEL) Study, which enrolled a large sample of women with early-stage breast cancer diagnosed from 1991 to early 2000 and treated with tamoxifen. (28) Tamoxifen metabolites endoxifen and 4-OH tamoxifen levels were strongly associated with CYP2D6 phenotype but were not linearly associated with breast cancer outcome. A threshold effect was identified with endoxifen, such that those patients with endoxifen levels >6 ng/mL had a 30% lower risk of additional breast cancer events (hazard ratio [HR]: 0.70, 95% confidence interval [CI]: 0.52-0.94). Notably, 24% of PM patients had endoxifen levels above this threshold.

Three prospective studies increased tamoxifen dose for patients already taking tamoxifen and genotyped as intermediate metabolizers (IMs) or PMs (and not administered CYP2D6 inhibitors), and measured tamoxifen metabolite levels at baseline and after 2 to 4 months compared to EM patients with no dose change. (25-27) In general, tamoxifen metabolite concentrations rose with increased dose, with IM patient levels reaching those of EM patients while PM patient levels remained somewhat lower. However, these results were not related to breast cancer outcomes. Moreover, metabolite levels were highly variable among individuals, and in one study it was noted that low plasma endoxifen concentrations were found in all CYP2D6 genotypes. (26) Thus it is likely that CYP2D6 accounts for only part of the variability in endoxifen levels. (30) The influence of other gene variants on tamoxifen treatment outcomes has been reported. (31, 32)

**Direct 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 poor metabolizers (PMs) derive less benefit from tamoxifen than EMs. One group conducted such a study retrospectively, on archived samples from a randomized controlled trial (RCT) of tamoxifen treatment. (19) 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.

The remaining 21 studies evaluated the association between CYP2D6 genotype and clinical outcomes in women treated with tamoxifen.

Eight small studies (range of N, 21-282) in Asian populations focused on the CYP2D6*10 reduced function allele (20, 23, 24, 32-36) and 5 reported significant results for the association of CYP2D6 genotype with outcomes of tamoxifen treatment. (20, 23, 24, 36) However, some of these studies may be affected in unpredictable ways by different types of bias, for example, by selecting among survivors at a time distant from diagnosis and surgery to draw whole blood for CYP2D6 genotyping (survivor selection bias). Two studies that reported no association may have less potential for bias. (33, 34) One larger study (n=716) of Korean patients with breast cancer receiving tamoxifen adjuvant therapy (and most also having had chemotherapy) found no CYP2D6 genotype-associated significant difference in recurrence-free survival (RFS) regardless of treatment or prognostic subgroup. (29)

Thirteen studies evaluated samples from primarily Caucasian patients administered tamoxifen for adjuvant treatment of invasive breast cancer or, in one study, for metastatic breast cancer. (17,
18, 37-48) Of the 5 largest studies, 4 reported no significant association for time to recurrence. (37, 39-41) Two of the negative studies were retrospective analyses of clinical trial samples, (39, 40) and a third was a case-control study nested in a population-based cancer registry. (37) All 3 were designed to minimize the potential for bias; their size (range of N, 588-991) allowed comparison of homozygous nonfunctional CYP2D6 genotypes with fully functional wild-type genotypes, i.e., the most extreme comparison and most likely to reveal a true association. The largest of the 5 studies (N=1,345) reported significant results; this study combined samples from different sources, some of which had already been analyzed for this hypothesis. (38) In addition, it is not clear from the report whether nearly half of the samples were obtained from patients who had survived and were available at a time distant from their diagnosis and surgery, a type of selection bias that can unpredictably affect results. The remaining 8 small studies reported a variety of significant and non-significant results; no pattern of bias, genotyping or group scheme, or accounting for CYP2D6 inhibitor use (among possibilities) explains the differences in results. The heterogeneity of results across all studies and clear results of no genotype-tamoxifen treatment outcome in 3 large trials with the least apparent potential for bias strongly suggests lack of support for clinical validity in post-menopausal patients treated with adjuvant tamoxifen for breast cancer.

Two nested matched case-control trials studied patients who were originally enrolled in chemoprevention trials using tamoxifen. (49, 50) In neither the larger (591 cases, 1,126 controls) nor the smaller study (47 cases, 135 controls) was CYP2D6 genotype associated with the risk of developing breast cancer.

The published literature on the association of CYP2D6 genotype with the effectiveness of tamoxifen therapy in the treatment of non-metastatic breast cancer has produced inconsistent results. A 2012 review tried to identify factors that may have led to the discrepant findings in published studies. (51) The review included a total of 17 independent published studies, and selected 6 factors to compare across 11 negative and 6 positive studies. The comparison of the factors across different studies suggested that tamoxifen combination therapy (defined as any additional therapy, including radiation), genotyping comprehensiveness (how many and which alleles were tested) and CYP2D6 inhibitor coadministration may account for some of the contradictory results. The review found that studies that enrolled patients on tamoxifen monotherapy, genotyped the CYP2D6 gene more comprehensively, and accounted for CYP2D6 inhibitor coadministration were more likely to have positive findings.

Clinical Utility (impact of using the test on medical decision making and 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 in vivo endoxifen levels and clinical outcomes; this evidence is insufficient. The other depends on the association of genotype with clinical outcomes, summarized in the section on clinical validity. There are several limitations to the overall body of evidence, but the largest, most well-designed studies do not support a significant association. As a result, this indirect evidence chain fails, and therefore the evidence does not support clinical utility.

Ongoing clinical trials
A search of online site Clinicaltrials.gov identified 3 Phase 3 trials determining CYP2D6 genotyping in patients receiving tamoxifen for breast cancer. One study is examining clinical outcomes of tamoxifen-treated male breast cancer patients and the influence of CYP2D6 activity
(NCT01638247), one study is in breast intraepithelial neoplasia to determine risk of progression to invasive disease (NCT01357772), and one study is examining different plasma concentrations of tamoxifen and its metabolites with different daily schedules of drug (NCT00963209).

Summary
The published data on the association between CYP2D6 genotype and tamoxifen treatment outcome have yielded inconsistent results. Some of the inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients were receiving, how many and which CYP2D6 alleles were tested, and coadministration of CYP2D6 inhibitors. Thus, because the impact of testing on net health outcome is not known, this is considered investigational.

Practice Guidelines and Position Statements
Regarding the use of CYP2D6 genetic testing prior to prescribing tamoxifen, the National Comprehensive Cancer Network (NCCN) breast cancer guidelines state “At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Co-administration of strong inhibitors of CYP2D6 should be used with caution.” (10)

The American Society of Clinical Oncology’s (ASCO) 2010 guideline update states: “The Update Committee recommends against using CYP2D6 genotype to select adjuvant endocrine therapy. The Update Committee encourages caution with concurrent use of CYP2D6 inhibitors.” (52)

CODING
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- 81226 should be used for genetic testing for tamoxifen treatment effective 01-01-2012.

DIAGNOSIS
Experimental / Investigational for all diagnosis codes related to this medical policy.

REVISIONS
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<td>10-26-2010</td>
<td>Policy added to the bcbsks.com web site.</td>
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<tr>
<td>08-12-2011</td>
<td>Description section updated.</td>
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<td>Rationale section updated.</td>
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<td>In Coding section:</td>
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<td>Updated nomenclature for CPT codes: 88385, 88386</td>
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<td>Reference section updated.</td>
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In Coding section:
- Added CPT code: 81226 (effective 01-01-2012)
- Added the following notations:
  - “81226 should be used for genetic testing for tamoxifen treatment effective 01-01-2012.
  - 88384, 88385, 88386 should not be used for genetic testing for tamoxifen treatment after 01-01-2012”

Description section updated.
Rationale section added.
References section updated.

In Coding section:
- Removed CPT codes: 88384, 88385, 88386 (effective 12-31-2012).

Description section reviewed
Rationale section updated
References updated

REFERENCES
15. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). CYP2D6 Pharmacogenomics of Tamoxifen Treatment. TEC Assessments 2011: Volume 26, Tab TBA.

