

Evidence Based Guideline

Genetic Testing for Tamoxifen Treatment

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Description of Procedure or Service

Tamoxifen (TAM) 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 TAM 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 TAM may have poorer outcomes than patients with relatively normal CYP2D6 activity. Some have recommended that patients who are to be prescribed TAM be genotyped for CYP2D6, and patients who are poor metabolizers (PMs) be treated with alternative therapy, if possible.

Tamoxifen Metabolism

Tamoxifen metabolites, rather than TAM itself, are likely the primary effectors of TAM benefit. Tamoxifen undergoes extensive primary and secondary metabolism, and the plasma concentrations of TAM and its metabolites vary widely. 4-Hydroxytamoxifen (4-OH TAM) 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. Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has identical properties and potency compared with 4-OH TAM. Because 4-OH TAM represents less than 20% of the product of TAM primary metabolism and steady-state plasma endoxifen concentrations are on average 5- to 10-fold higher than 4-OH TAM, it has been assumed that endoxifen is the major active metabolite of TAM.

The metabolism of TAM to 4-OH TAM is catalyzed by multiple enzymes. However, endoxifen is formed predominantly by CYP2D6. The plasma concentration of endoxifen exhibits high interindividual variability, as described in breast cancer patients. The CYP2D6 enzyme has known inter-individual variability in activity and therefore has been of great interest in investigating TAM 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. 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

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ultra-rapid metabolizers (UM) is defined by possession of three or more functional alleles due to gene duplication. The UMs have greater functional activity than EM genotypes because of additional expression of enzyme from the extra gene(s).

Griese et al studied the correlation of CYP2D6 functional categories with genotypes in 195 Caucasian individuals in Germany. While all poor metabolizers were “unambiguously identified as carriers of two non-functional alleles...the most frequent functional genotypes extensively overlapped.” 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, assignment of other genotypes with function in between these two is inconsistent among authors making it difficult to compare results across studies.

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 non-functional variants, and by the *5 non-functional variant in African-American and Asian populations. Some PMs may reflect the combination of a non-functional 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.

Several other enzymes are involved in the metabolism of TAM to the active metabolite 4-OH TAM. Polymorphisms in the genes for these enzymes could have an effect on overall TAM efficacy. Research regarding the effect of variant alleles for these enzymes is currently in the discovery stage and will not be further discussed in this policy.

Endocrine Therapy Regimens

TAM 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 TAM treatment.

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

TAM 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 flashes, sweats, and sleep disturbance. Ovarian ablation does not appear to add benefit to adjuvant chemotherapy. Similarly, functional ovarian suppression with gonadotropin releasing factor analogues 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.

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>).

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The pharmacogenomics of TAM 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 NCCN breast cancer guidelines make no preferential treatment recommendations among the following choices:

- aromatase inhibitors (AI) for 5 years
- TAM for 2–3 years, followed by AI to complete 5 years or longer
- TAM to 4.5–6 years, followed by AI for 5 years
- TAM 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 TAM 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 TAM and AI. Nor is there evidence as yet to support AI use in pre-menopausal women. Finally, TAM is important in the treatment of metastatic cancer, where either TAM 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. Some individuals treated with fluoxetine or paroxetine changed from EM phenotype to PM. 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 TAM 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.

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Evidence Based Guideline for Genetic Testing for Tamoxifen Treatment

Genetic Testing for tamoxifen treatment is not appropriate for the purpose of managing treatment with tamoxifen for women.

Medical Evidence regarding Genetic Testing for Tamoxifen Treatment indicates it is not recommended in the following situations:

Genetic testing for tamoxifen treatment is not recommended for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

Evidence is insufficient 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.

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Benefits Application

Please refer to certificate for availability of benefit. This guideline relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore certificate language should be reviewed before applying the terms of the policy.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: There are no specific CPT or HCPCS codes for this service

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.51, 7/9/09

Senior Medical Director Review, 9/2009

Policy Implementation/Update Information

10/26/09 New Evidence Based Guideline written. Reviewed with the Senior Medical Director 9/30/2009. Genetic testing for tamoxifen treatment is not recommended for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer. (btw)

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