

Corporate Medical Policy

Genetic Testing for Tamoxifen Treatment

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Description of Procedure or Service

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.

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.

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. Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has identical properties and potency compared with 4-OH tamoxifen. 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 interindividual variability, as described in breast cancer patients. The CYP2D6 enzyme has known interindividual variability in activity and therefore has been of great interest in investigating tamoxifen metabolism and variation in circulating active metabolite levels.

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. Lash et al. modeled the effect of CYP2D6 variant alleles on estrogen receptor binding by tamoxifen and metabolites and found negligible effect. 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.

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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 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 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 currently in the discovery stage and will not be further discussed in this policy.

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 (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.

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 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>).

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 NCCN breast cancer guidelines make no preferential treatment recommendations among the following choices:

- aromatase inhibitors (AI) for 5 years

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- 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. Nor is there evidence as yet to support AI use in pre-menopausal 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. 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 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.

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

Policy

Genotyping to determine cytochrome p450 (CYP2D6) genetic polymorphisms is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Genetic Testing for Tamoxifen Treatment

When Genetic Testing for Tamoxifen Treatment is covered

Not applicable.

When Genetic Testing for Tamoxifen Treatment is not covered

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

Policy Guidelines

The available evidence does not clearly support a significant association between CYP2D6 genotype and tamoxifen treatment outcome; an indirect evidence chain supporting the clinical utility of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer cannot be constructed. The impact of testing on net health outcome is not known.

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: 81226

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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

Senior Medical Director Review, 9/2009

Specialty Matched Consultant Advisory Panel – 5/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.51, 4/14/2011

Medical Director – 11/2011

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Specialty Matched Consultant Advisory Panel – 4/2012

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)
- 7/6/10 Specialty Matched Consultant Advisory Panel review 5/24/2010. No change to policy statement. Policy Guideline number removed. References added. (btw)
- 5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. Revised wording in the “Evidence Based Guideline” section, no change to intent. Added “to determine cytochrome p450 (CYP2D6) genetic polymorphisms” and removed “for tamoxifen treatment” from the first statement in the “When Not Recommended” section. Revised “Benefit Applications” statement for consistency.(btw)
- 6/21/11 Reference added. (btw)
- 1/1/12 Evidence based guideline converted to corporate medical policy. “Genotyping to determine cytochrome p450 (CYP2D6) genetic polymorphisms is considered investigational for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.” Added new 2012 CPT code, 81226 to “Billing/Coding” section. Notification given 1/1/2012. Policy effective 4/1/2012. (btw)
- 5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. Description revised. No change to policy intent. (btw)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.