The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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 five- 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 Protocol) 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 (9):

• 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) (10) 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. (11)

For postmenopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction; efficacy equals that of tamoxifen and risk of endometrial hyperplasia is markedly reduced. Currently, raloxifene is not indicated for the treatment of invasive breast cancer, reduction of breast cancer recurrence risk, or noninvasive breast cancer risk reduction. (12)

Pharmacogenomics of tamoxifen have been most often studied in post-menopausal women with endocrine-receptor-positive tumors and require endocrine therapy to prevent recurrence. For this population, the National Comprehensive Cancer Network (NCCN) make no preferential treatment recommendations among the following choices (11):

- aromatase inhibitors (AI) for five years
- tamoxifen for two to three years, followed by AI to complete five years or longer
- tamoxifen to 4.5 to six years, followed by AI for five years
- tamoxifen for five 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, there is no evidence as yet to support AI use in premenopausal women. Tamoxifen also is important for 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 (Model 04381866190) 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 (Formerly Corporate Medical Guideline)

Genotyping to determine cytochrome p450 2D6 (CYP2D6) genetic polymorphisms is considered investigational for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.
Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


17. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). CYP2D6 Pharmacogenomics of Tamoxifen Treatment. TEC Assessments 2011.
18. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). CYP2D6 Pharmacogenomics of Tamoxifen Treatment. TEC Assessments 2013; Volume 28, Tab 8.


