

(20451)

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| Medical Benefit | | Effective Date: 10/01/12 | Next Review Date: 07/18 |
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This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. 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.

| Populations | Interventions | Comparators | Outcomes |
|---|---|--|---|
| Individuals: <ul style="list-style-type: none"> Who are treated with tamoxifen for breast cancer or high risk of breast cancer | Interventions of interest are: <ul style="list-style-type: none"> Testing for CYP2D6 metabolizer status by CYP2D6 genotyping | Comparators of interest are: <ul style="list-style-type: none"> Clinical management without CYP2D6 genotyping | Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Test validity Treatment-related morbidity Medication use Treatment-related morbidity |

Description

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor-positive breast cancer recurrence, to treat 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. Some organizations have recommended that patients who are prescribed tamoxifen be genotyped for *CYP2D6*, and patients who are poor metabolizers be treated with alternative therapy if possible.

Summary of Evidence

For individuals who are treated with tamoxifen for breast cancer or high risk of breast cancer who receive testing for CYP2D6 metabolizer status by CYP2D6 genotyping, the evidence includes multiple retrospective studies, post hoc analysis of randomized controlled trials, and meta-analysis. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, medication use, and treatment-related morbidity. Published data on the association between CYP2D6 genotype and tamoxifen treatment outcomes have yielded inconsistent results. Some inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients received, how many and which CYP2D6 alleles were tested, tissue type examined (tumor or germline DNA), and coadministration with CYP2D6 inhibitors. The largest, most well-designed studies do not support a significant association. At present, the clinical utility of CYP2D6 testing is also poorly defined. An interventional study of CYP2D6-specific tamoxifen dosing found that personalized dosing was associated with changes in endoxifen level, but it has not been demonstrated that endoxifen level is associated with improved

outcomes. It is not known whether clinical management guided by CYP2D6 genotyping improves patient outcomes such as appropriate selection of a treatment strategy that would reduce the rate of recurrence, improve disease-free survival or overall survival, or reduce adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genotyping to determine cytochrome p450 2D6 (CYP2D6) variants is considered **investigational** for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer.

Policy Guidelines

Genetics Nomenclature Update

Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (Table PG1). Human Genome Variation Society nomenclature is recommended by Human Genome Variation Society, the Human Variome Project, and the HUman Genome Organization.

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from the American College of Medical Genetics and Genomics, the Association for Molecular Pathology, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

| Previous | Updated | Definition |
|----------|----------------------------|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence |
| | Variant | Change in the DNA sequence |
| | Familial variant | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

| Variant Classification | Definition |
|-----------------------------------|--|
| Pathogenic | Disease-causing change in the DNA sequence |
| Likely pathogenic | Likely disease-causing change in the DNA sequence |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign | Likely benign change in the DNA sequence |
| Benign | Benign change in the DNA sequence |

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter

the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background

Tamoxifen Metabolism

Tamoxifen undergoes extensive primary and secondary metabolism, and plasma concentrations of tamoxifen and its metabolites vary widely. The metabolite 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 cell proliferation in vitro compared with the parent drug (summarized in Goetz et al¹). 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 because steady-state plasma endoxifen concentrations are on average five- to 10-fold higher than 4-OH tamoxifen plasma levels, 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. Plasma concentrations of endoxifen exhibit high interindividual variability, as described in breast cancer patients.⁵ Because CYP2D6 enzyme activity is known to vary across individuals, CYP2D6 is of great interest for understanding tamoxifen metabolism variability and variation in levels of circulating active metabolites. Moreover, 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 are 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 (2009) modeled the effect of *CYP2D6*-variant alleles on estrogen receptor binding by tamoxifen and metabolites and found negligible effect.⁷ As the authors noted, however, modeling cannot account for many metabolic complexities, and mechanistic data would be needed to show how a 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. Although 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 alleles that result in enzymes with no activity or reduced activity. Because individuals have 2 *CYP2D6* alleles, various combinations of the possible alleles result in a spectrum of *CYP2D6* function; they have been categorized as extensive metabolizers (EMs or “normal”), intermediate metabolizers (IMs), and poor metabolizers (PMs). An additional, rare category of ultrarapid metabolizers (UMs) is defined by possession of three or more functional alleles due to gene duplication.

The prevalence of *CYP2D6* PMs is approximately 7% to 10% in whites of Northern European descent, 1.9% to 7.3% in blacks, and 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 in black and Asian populations, by the *5 non-functional variant. Some PMs may have one nonfunctional allele and one reduced function allele. Among reduced function variants, *CYP2D6**17, *10, and *8 are the most important in blacks, Asians, and whites, respectively. Few studies have investigated the frequency of *CYP2D6*-variant alleles or of PMs in the Hispanic population.⁸

Other enzymes metabolize tamoxifen to the active metabolite, 4-OH tamoxifen. Polymorphisms in the genes for these enzymes could have an effect on overall tamoxifen efficacy. Research on the effect of variant alleles for these enzymes is in earlier stages of discovery.

Endocrine Therapy Regimens

Tamoxifen has several labelled indications⁹:

- 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 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 more effective treatment than no adjuvant therapy but may be accompanied by acute and chronic adverse effects (e.g., hot flashes, sweats, sleep disturbance). Similarly, functional ovarian suppression with gonadotropin-releasing factor analogues in pre- or perimenopausal women with hormone receptor-positive tumors confers benefits comparable with chemotherapy. National Comprehensive Cancer Network (NCCN) guidelines indicate ovarian ablation or suppression are options in combination with endocrine therapy for premenopausal women who have invasive or recurrent disease and are recommended for premenopausal women with systemic disease.¹⁰

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 treatment of invasive breast cancer; reduction of breast cancer recurrence risk; or noninvasive breast cancer risk reduction.¹¹

Pharmacogenomics of tamoxifen have been most often studied in postmenopausal women who have endocrine receptor-positive tumors and require endocrine therapy to prevent recurrence. For this population, the National Comprehensive Cancer Network's 2017 guidelines for the management of breast cancer includes a number of statements related to the use of adjuvant tamoxifen (among other endocrine therapies), which are summarized in Table 1.¹⁰

Table 1. 2017 NCCN Guidelines for Adjuvant Endocrine Therapy for Postmenopausal Women With Breast Cancer

| Recommendation | COR |
|--|------------|
| Premenopausal at Diagnosis | |
| Tamoxifen for 5 years (with or without ovarian suppression), followed by AI for 5 years if postmenopausal | 1 |
| Tamoxifen for 5 years ^a (with or without ovarian suppression) ^a followed by consideration for tamoxifen for 5 years ^b if postmenopausal | 2A |
| Tamoxifen for 5 years ^a (with or without ovarian suppression) ^a followed by consideration for tamoxifen for 5 y OR no further therapy if still premenopausal | 2A |
| Postmenopausal at diagnosis | |
| AI for 2-3 years followed by tamoxifen for a total of 5 years of endocrine therapy | 1 |
| Tamoxifen for 2-3 years followed by AI for a total of 5 years of endocrine therapy | 1 |
| Tamoxifen for 2-3 years followed by up to 5 years of an AI ^c | 2A overall |
| Tamoxifen for 2-3 years followed by 1 of 3 AIs to complete 5 years of endocrine therapy | 2B |
| Tamoxifen for 4.5-6 years followed by AI for 5 years | 1 |
| Tamoxifen for 4.5-6 years followed by consideration for tamoxifen for 5 more years | 2A |
| In women with a contraindication to AIs, or who decline or are intolerant of AIs, consideration for tamoxifen for 5 years of tamoxifen for up to 10 years | 1 |

AI: aromatase inhibitor; COR: category of recommendation.

^a COR 1; ^b COR 2A; ^c COR 2B

Pharmacologic Inhibitors of Metabolic Enzymes

CYP2D6 activity may be affected not only by genotype but also by coadministered drugs that block or induce CYP2D6 function. 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 on 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 AmpliChip CYP450 Test (Model 04381866190; Roche) was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process (K042259) and can be used to identify CYP2D6 genotype.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. CYP2D6 genotyping assays are also available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Related Protocol

Cytochrome P450 Genotyping

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.**

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

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