Medical Policy
Genetic Testing for Tamoxifen Treatment

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Policy Number: 067
BCBSA Reference Number: 2.04.51
NCD/LCD: Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

Related Policies
Cytochrome p450 Genotyping, #256

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genotyping to determine cytochrome p450 (CYP2D6) variants is INVESTIGATIONAL for the purpose of managing treatment with Tamoxifen for women at high risk for or with breast cancer.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below

Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.
CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

According to the policy statement above, the following CPT code is considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81226</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants</td>
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**Description**

**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 a 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 al [2080]). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has properties and potency identical to 4-OH tamoxifen. 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 5- 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 into 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. Because CYP2D6 enzyme activity is known to vary across individuals, variants in the CYP2D6 gene are 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. Lash et al (2009) modeled the effect of CYP2D6-variant alleles on estrogen receptor binding by tamoxifen and metabolites, and found a negligible effect. As they 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 evidence review)
produce an enzyme with normal activity, there are several variant 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; they have been categorized as extensive metabolizers ("normal"), intermediate metabolizers, and poor metabolizers (PMs). An additional, rare category of ultrarapid metabolizers is defined by possession of 3 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 nonfunctional variant. Some PMs may have 1 nonfunctional allele and 1 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 PMs in the Hispanic population.

Other enzymes metabolize tamoxifen into 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.

**Endocrine Therapy Regimens**

Tamoxifen has several labelled 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 a likely benefit from tamoxifen treatment.

Tamoxifen is currently the most commonly prescribed adjuvant treatment to prevent recurrence of the endocrine receptor-positive breast cancer in pre- or perimenopausal women. The pharmacogenomics 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 (eg, hot flushes, 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 that 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.

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.

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
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<tbody>
<tr>
<td><strong>Premenopausal at Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Tamoxifen for 5 years (with or without ovarian suppression), followed by AI for 5 years if postmenopausal</td>
<td>1</td>
</tr>
<tr>
<td>Tamoxifen for 5 years(^a) (with or without ovarian suppression) followed by consideration for tamoxifen for 5 years(^b) if postmenopausal</td>
<td>2A</td>
</tr>
<tr>
<td>Tamoxifen for 5 years(^a) (with or without ovarian suppression)(^c) followed by consideration for tamoxifen for 5 y OR no further therapy if still premenopausal</td>
<td>2A</td>
</tr>
<tr>
<td><strong>Postmenopausal at diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>AI for 2-3 years followed by tamoxifen for a total of 5 years of endocrine therapy</td>
<td>1</td>
</tr>
<tr>
<td>Tamoxifen for 2-3 years followed by AI for a total of 5 years of endocrine therapy</td>
<td>1</td>
</tr>
<tr>
<td>Tamoxifen for 2-3 years followed by up to 5 years of an AI(^c)</td>
<td>2A</td>
</tr>
<tr>
<td>overall</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen for 2-3 years followed by 1 of 3 AIs to complete 5 years of endocrine therapy</td>
<td>2B</td>
</tr>
<tr>
<td>Tamoxifen for 4.5-6 years followed by AI for 5 years</td>
<td>1</td>
</tr>
<tr>
<td>Tamoxifen for 4.5-6 years followed by consideration for tamoxifen for 5 more years</td>
<td>2A</td>
</tr>
<tr>
<td>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</td>
<td>1</td>
</tr>
</tbody>
</table>

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 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 extensive metabolizer phenotype to PM.\(^{12}\) The degree of inhibition may depend on selective serotonin reuptake inhibitors 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.

**Summary**

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptorpositive breast cancer recurrence, to treat metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ. 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 that patients who are poor metabolizers be treated with alternative therapy if possible.

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 \textit{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.

\textbf{Policy History}

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>8/2017</td>
<td>BCBSA National medical policy review. Background and summary updated. 8/1/2017</td>
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<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>8/2015</td>
<td>Added coding language.</td>
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<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L34499) added.</td>
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<td>7/2015</td>
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</tr>
<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<tr>
<td>8/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>1/2009</td>
<td>Format updated. No changes to policy statements.</td>
</tr>
<tr>
<td>9/2008</td>
<td>Medical policy 067 created.</td>
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\textbf{Information Pertaining to All Blue Cross Blue Shield Medical Policies}

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

\textbf{References}


15. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). CYP2D6 Pharmacogenomics of Tamoxifen Treatment TEC Assessments. 2011.

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


