Medical Policy

Genotype-Guided 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 Genotype-Guided Treatment Strategy, #256

Policy

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

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.

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

Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.
Outpatient

| Commercial Managed Care (HMO and POS) | This is not a covered service. |
| Commercial PPO and Indemnity | This is not a covered service. |
| Medicare HMO BlueSM | Prior authorization is not required. |
| Medicare PPO BlueSM | Prior authorization is not required. |

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.

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:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
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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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</tbody>
</table>

Description

TAMOXIFEN METABOLISM

Tamoxifen is a pro-drug that undergoes extensive metabolism to yield its active form: 4-hydroxytamoxifen (4-OH tamoxifen) and 4-hydroxy-N-desmethyltamoxifen (endoxifen). Among these 2 metabolites, endoxifen is thought to be the major metabolite that exerts the pharmacodynamic effect of tamoxifen. The metabolism of tamoxifen into 4-OH tamoxifen is catalyzed by multiple enzymes while endoxifen is formed predominantly by the CYP2D6 enzyme. 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.

Metabolic Enzyme Genotypes

The CYP2D6 gene exhibits a high degree of polymorphism, with more than 100 allelic variants identified. The relations among genotype, phenotype, and clinical implications are summarized in Table 1.

Table 1. Relation among the CYP2D6 Genotype, Phenotype, and Clinical Implications

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
<th>Potential Clinical Implications With Use of Tamoxifen</th>
</tr>
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<tbody>
<tr>
<td>≥3 copies of functional alleles</td>
<td>Ultrarapid metabolizer</td>
<td>None</td>
</tr>
<tr>
<td>Any one of the following scenarios:</td>
<td>Intermediate metabolizer</td>
<td>• Increased risk for relapse of breast cancer</td>
</tr>
<tr>
<td>• 1 active allele and 1 inactive allele</td>
<td></td>
<td>• Avoid concomitant use of CYP2D6 inhibitors</td>
</tr>
<tr>
<td>• 2 decreased activity alleles</td>
<td></td>
<td>• Consider aromatase inhibitor for postmenopausal women</td>
</tr>
<tr>
<td>• 1 decreased activity allele and 1 inactive allele</td>
<td>Poor metabolizer</td>
<td>• Increased risk for relapse of breast cancer</td>
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</tbody>
</table>
Consider aromatase inhibitor for postmenopausal women

Adapted from Swen et al (2011).³

The prevalence of CYP2D6 poor metabolizers 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 poor metabolizer 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 poor metabolizers 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 poor metabolizers in the Hispanic population.⁴

Endocrine Therapy Regimens
Tamoxifen has several labeled indications⁵:
- 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.

For postmenopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction. Currently, raloxifene is indicated for the treatment of reduction in the "risk of invasive breast cancer in postmenopausal women with osteoporosis" or those at "high risk for invasive breast cancer."⁶

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.⁷ ⁹ Some individuals treated with fluoxetine or paroxetine have changed from extensive metabolizer phenotype to poor metabolizer.⁷ 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 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. Tamoxifen is a pro-drug that undergoes extensive metabolism to yield its active form: 4-hydroxy tamoxifen and endoxifen (primary active form) via the CYP2D6 enzyme. Variants in the CYP2D6 gene are associated with significant alterations in endoxifen concentrations leading to the hypothesis that CYP2D6 variation may affect the clinical outcomes of women treated with tamoxifen but not with drugs not metabolized by CYP2D6 such as anastrozole.

For individuals who are treated with tamoxifen for breast cancer or are high risk for breast cancer who receive CYP2D6 genotype-guided tamoxifen treatment, the evidence includes multiple retrospective and prospective cohort studies and nonconcurrent prospective studies. Relevant outcomes include overall survival, disease-specific survival, medication use, and treatment-related morbidity. Published data on the association between CYP2D6 genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies derived from a convenient sample, which was further limited by
relatively small numbers of patients and lack of comprehensive genotype data, patient data (e.g., concomitant medications), and detailed clinical outcomes data. Three influential nonconcurrent prospective studies nested within large prospective, randomized double-blind clinical trials in postmenopausal women with hormone receptor–positive early-stage breast cancer also reported contradictory results, with 2 larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and recurrence of breast cancer. No trials of genotype-directed dosing or drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether CYP2D6 genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer 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 History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>9/2018</td>
<td>BCBSA National medical policy review. Policy title changed to “Genotype-Guided Tamoxifen Treatment.” Policy statement otherwise unchanged. 9/1/2018</td>
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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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<tr>
<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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<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<td>8/2013</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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**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

**References**


