Genotype-Guided Tamoxifen Treatment

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. Tamoxifen is a pro-drug that undergoes extensive metabolism to yield its active form: 4-hydroxytamoxifen 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.

OBJECTIVE

The objective of this evidence review is to determine whether genotype-guided tamoxifen treatment improves the net health outcome in patients with breast cancer or those who are at high-risk of developing breast cancer.

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POLICY STATEMENT

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

The 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 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>

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### Variant of uncertain significance

<table>
<thead>
<tr>
<th>Variant of uncertain significance</th>
<th>Change in DNA sequence with uncertain effects on disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

### BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

### FDA REGULATORY STATUS

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 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 (FDA) has chosen not to require any regulatory review of this test.

Several testing kits for *CYP450* genotyping cleared for marketing by the FDA through the 510(k) process (FDA product code: NTI) are summarized in Table 1.

#### Table 1. Testing Kits for *CYP450* Genotyping Cleared for Marketing by the FDA

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>xTAG CYP2D6 Kit V3</td>
<td>Luminex Molecular Diagnostics</td>
<td>2017</td>
</tr>
<tr>
<td>xTAG CYP2C19 Kit V3</td>
<td>Luminex Molecular Diagnostics</td>
<td>2013</td>
</tr>
<tr>
<td>Spartan RX CYP2C19 Test System</td>
<td>Spartan Bioscience</td>
<td>2013</td>
</tr>
</tbody>
</table>

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FDA: Food and Drug Administration.

Several manufacturers market diagnostic genotyping panel tests for CYP450 genes, such as the YouScript Panel (Genelex Corp.), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4, and CYP3A5. Other panel tests include both CYP450 and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health) and PersonaGene Genetic Panels (AllBioTech). These panel tests are beyond the scope of this evidence review.

**Rationale**

**Summary of Evidence**

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. The 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 (eg, 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 two 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 OS, or reduce adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Clinical Pharmacogenetics Implementation Consortium

The Clinical Pharmacogenetics Implementation Consortium (2018) issued therapeutic recommendations for tamoxifen prescribing based on CYP2D6 genotype/metabolic phenotype. For the clinical endpoints of recurrence and event-free survival, the evidence was graded as moderate for the statements that CYP2D6 poor metabolizers have a higher risk of breast cancer recurrence or worse event-free survival. However, for the comparison of other metabolizer groups and other clinical endpoints, the evidence was considered weak regarding an association between CYP2D6 metabolizer groups and clinical outcome.

National Comprehensive Cancer Network

Regarding the use of CYP2D6 genotyping before prescribing tamoxifen, the National Comprehensive Cancer Network breast cancer guidelines (v.1.2018) state: "The panel recommends against CYP2D6 genotype testing for women being considered for tamoxifen treatment."

American Society of Clinical Oncology

The guidelines from the American Society of Clinical Oncology (2016) on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer stated the following for CYP2D6 variants to guide adjuvant endocrine therapy selection:

- "The clinician should not use CYP2D6 polymorphisms to guide adjuvant endocrine therapy selection (Type: Evidence-based; Evidence quality: Intermediate; Strength of recommendation: Moderate).
- The ability of polymorphisms in CYP2D6 to predict tamoxifen benefit has been extensively studied. The results of these pharmacogenomics studies have been controversial, with more recent studies being negative. At this point, data do not support the use of this marker to select patients who may or may not benefit from tamoxifen therapy."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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REFERENCES


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### POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>June 2012</td>
<td>New policy</td>
<td>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</td>
</tr>
<tr>
<td>September 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature search. References added, updated renumbered and removed. Extensive revisions to rationale. No change to policy statement.</td>
</tr>
<tr>
<td>September 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature search. References added, updated renumbered and removed. Extensive revisions to rationale. No change to policy statement.</td>
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<tr>
<td>September 2015</td>
<td>Replace policy</td>
<td>Policy updated with literature review; references 37, 39, 43-44, 69 and 74 added. Policy statements unchanged</td>
</tr>
<tr>
<td>September 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 13, 2016; reference 78 added; policy statement unchanged</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 9, 2018; reference 18, 22, and 26 added; reference 5 updated. Policy title changed to “Genotype-Guided Tamoxifen Treatment”. Policy statement otherwise unchanged</td>
</tr>
<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through May 29, 2019; references added. Policy statement unchanged.</td>
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