FEP Medical Policy Manual

FEP 2.04.51 Genotype-Guided Tamoxifen Treatment

Effective Policy Date: October 1, 2023

Original Policy Date: June 2012

Related Policies:

2.04.38 - Cytochrome P450 Genotype-Guided Treatment Strategy

Genotype-Guided Tamoxifen Treatment

Description

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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 cytochrome P450 2D6 (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 individuals with breast cancer or those who are at high-risk of developing breast cancer.

POLICY STATEMENT

Genotyping to determine cytochrome P450 2D6 (*CYP2D6*) variants is considered **investigational** for the purpose of managing treatment with tamoxifen for individuals at high risk for or with breast cancer.

POLICY GUIDELINES

None

BENEFIT APPLICATION

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

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.

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 (CLIA). *CYP2D6* genotyping assays are available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA 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

Device Name	Manufacturer	Approval Date
xTAG CYP2D6 Kit V3	Luminex Molecular Diagnostics	2017
xTAG CYP2C19 Kit V3	Luminex Molecular Diagnostics	2013
Spartan RX CYP2C19 Test System	Spartan Bioscience	2013
xTAG CYP2D6 Kit V3 (including TDAS CYP2D6)	Luminex Molecular Diagnostics	2013
Verigene CYP2C19 Nucleic Acid Test (CYP2C19)	Nanosphere	2012
Infiniti CYP2C19 Assay	AutoGenomics	2010
xTAG CYP2D6 Kit V3, Model I030C0300	Luminex Molecular Diagnostics	2010
Invader UGT1A1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip CYP450 Test	Roche Molecular Systems	2005

FDA: U.S. 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). 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 at high-risk for breast cancer who receive *CYP2D6* genotype-guided tamoxifen treatment, the evidence includes a single randomized controlled trial (RCT), several meta-analyses and systematic reviews, multiple retrospective and prospective cohort studies, and nonconcurrent prospective studies. Relevant outcomes include overall survival (OS), 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 were derived from a convenience 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 2 larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizers) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression-free survival between a standard dose and increased dose; however, this trial was limited by its proof of concept design. No trials of genotype-directed 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology

In 2016, the guidelines published by the American Society of Clinical Oncology (ASCO) 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."[61,]

A 2022 update to the ASCO guideline stated that the recommendation against use of CYP2D6 polymorphisms to guide adjuvant endocrine therapy had been archived.[62,]

Clinical Pharmacogenetics Implementation Consortium

In 2018, the Clinical Pharmacogenetics Implementation Consortium issued therapeutic recommendations for tamoxifen prescribing based on *CYP2D6* genotype/metabolic phenotype.[63,] 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 outcomes.

National Comprehensive Cancer Network

Regarding the use of *CYP2D6* genotyping before prescribing tamoxifen, the National Comprehensive Cancer Network breast cancer guidelines (v.4.2023) state: "CYP2D6 genotype testing is not recommended for patients considering tamoxifen."[64,]

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

Date	Action	Description
June 2012	New 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
September 2013	Replace policy	Policy updated with literature search. References added, updated renumbered and removed. Extensive revisions to rationale. No change to policy statement.
September 2014	Replace policy	Policy updated with literature search. References added, updated renumbered and removed. Extensive revisions to rationale. No change to policy statement.
September 2015	Replace policy	Policy updated with literature review; references 37, 39, 43-44, 69 and 74 added. Policy statements unchanged
September 2016	Replace policy	Policy updated with literature review through June 13, 2016; reference 78 added; policy statement unchanged
September 2018	Replace policy	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
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review through May 20, 2020; references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through May 19, 2021; no references added, reference 61 updated. Policy statement unchanged.
September 2022	Replace policy	Policy updated with literature review through May 18, 2022; no references added. Minor editorial refinement to policy statement; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through May 18, 2023; references added. Policy statement unchanged.