



Louisiana

Genotype-Guided Tamoxifen Treatment

Policy # 00269

Original Effective Date: 09/15/2010

Current Effective Date: 11/09/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Cytochrome P450 Genotype-Guided Treatment Strategy is addressed separately in medical policy 00169.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genotyping to determine cytochrome p450 2D6 (CYP2D6) variants for the purpose of managing treatment with tamoxifen for women at high risk for or with breast cancer to be **investigational**.*

Background/Overview

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 inter-individual 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.

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

Genotype	Phenotype	Potential Clinical Implications With Use of Tamoxifen
≥3 copies of functional alleles	Ultrarapid metabolizer	None
Any one of the following scenarios: <ul style="list-style-type: none"> • 1 active allele and 1 inactive allele • 2 decreased activity alleles • 1 decreased activity allele and 1 inactive allele 	Intermediate metabolizer	<ul style="list-style-type: none"> • Increased risk for relapse of breast cancer • Avoid concomitant use of CYP2D6 inhibitors • Consider aromatase inhibitor for postmenopausal women
2 inactive alleles	Poor metabolizer	<ul style="list-style-type: none"> • Increased risk for relapse of breast cancer • Consider aromatase inhibitor for postmenopausal women

Adapted from Swen et al (2011).

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.

Endocrine Therapy Regimens

Tamoxifen has several labeled 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

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- 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 reduction in "risk of invasive breast cancer in postmenopausal women with osteoporosis" or those at "high risk for invasive breast cancer."

Pharmacologic Inhibitors of Metabolic Enzymes

CYP2D6 activity may be affected not only by genotype but also by co-administered 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. Some individuals treated with fluoxetine or paroxetine have changed from extensive metabolizer phenotype to poor metabolizer. The degree of inhibition may depend on selective serotonin reuptake inhibitor 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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.

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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 2.

Table 2. 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) and PersonaGene Genetic Panels (AIBioTech). These panel tests are beyond the scope of this evidence review.

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Rationale/Source

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.

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 1 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, 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 metabolizer) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression free survival between 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 overall survival, 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

In 2018, the Clinical Pharmacogenetics Implementation Consortium 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.4.2020) state: "The panel recommends against *CYP2D6* genotype testing for women being considered for tamoxifen treatment."

American Society of Clinical Oncology

In 2016, the guidelines published from the American Society of Clinical Oncology 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.

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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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03931928	Genotype and Phenotype Guided Supplementation of TAMoxifen Standard Therapy With ENDOXifen in Breast Cancer Patients	750	Dec 2020
NCT01357772	Randomized Placebo-controlled Phase III Trial of Low-dose Tamoxifen in Women With Breast Intraepithelial Neoplasia	1400	Dec 2023

NCT: national clinical trial.

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Louisiana

Genotype-Guided Tamoxifen Treatment

Policy # 00269

Original Effective Date: 09/15/2010

Current Effective Date: 11/09/2020

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Policy History

Original Effective Date: 09/15/2010

Current Effective Date: 11/09/2020

- 09/09/2010 Medical Policy Committee review
- 09/15/2010 Medical Policy Implementation Committee approval. New policy.
- 09/01/2011 Medical Policy Committee review
- 09/14/2011 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/06/2012 Medical Policy Committee review
- 09/19/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/23/2013 Coding updated
- 09/05/2013 Medical Policy Committee review
- 09/18/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/04/2014 Medical Policy Committee review
- 09/17/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/03/2015 Medical Policy Committee review
- 09/23/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 09/08/2016 Medical Policy Committee review
- 09/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
- 09/07/2017 Medical Policy Committee review

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- 09/20/2017 Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature; coverage eligibility otherwise unchanged.
- 02/06/2018 Coding update
- 10/04/2018 Medical Policy Committee review
- 10/17/2018 Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for Tamoxifen Treatment” to “Genotype Guided Tamoxifen Treatment”. Coverage eligibility unchanged.
- 10/03/2019 Medical Policy Committee review
- 10/09/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 10/01/2020 Medical Policy Committee review
- 10/07/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U, 81226
HCPCS	No codes
ICD-10 Diagnosis	C50.011-C50.019, C50.111-C50.119, C50.211-C50.219, C50.311-C50.319, C50.411-C50.419, C50.511-C50.519, C50.611-C50.619 C50.811-C50.819, C50.911-C50.919

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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