Medical Policy

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Title: Genotype-Guided Tamoxifen Treatment

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are treated with tamoxifen for breast cancer or are at high-risk of breast cancer	Interventions of interest are: • *CYP2D6* genotype-guided tamoxifen treatment	Comparators of interest are: • Clinically guided tamoxifen treatment	Relevant outcomes include: • Overall survival • Disease-specific survival • Medication use • Treatment-related morbidity

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-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.

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.

Background

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).1 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.2 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 ~~75~~ 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

Genotype	Phenotype	Potential Clinical Implications With Use of Tamoxifen
≥3 copies of functional alleles	Ultrarapid metabolizer	None
Any one of the following scenarios: • 1 active allele and 1 inactive allele • 2 decreased activity alleles • 1 decreased activity allele and 1 inactive allele	Intermediate metabolizer	• Increased risk for relapse of breast cancer • Avoid concomitant use of CYP2D6 inhibitors • Consider aromatase inhibitor for postmenopausal women
2 inactive alleles	Poor metabolizer	• Increased risk for relapse of breast cancer • 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 metabolizers 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 of poor metabolizers in the Hispanic population.[8]

Endocrine Therapy Regimens

Tamoxifen has several labelled indications[5]:

- 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 likely benefit from tamoxifen treatment. Tamoxifen is currently the most commonly prescribed adjuvant treatment to prevent recurrence of 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 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 changed from extensive metabolizer phenotype to poor metabolizers.[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.

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 also 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 has chosen not to require any regulatory review of this test

Several testing kits for *CYP450* genotyping cleared for marketing by 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 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: 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.

POLICY

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

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Policy Guidelines

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics and 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through April 9, 2018.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and

whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Genotype-GUIDED Tamoxifen Treatment

Clinical Context and Therapy Purpose

The purpose of genotype-guided tamoxifen treatment is to tailor drug selection (eg, tamoxifen or an aromatase inhibitor) or dose selection (eg, tamoxifen 40 mg/d instead of the standard 20 mg/d dose) or strategy (eg, ovarian ablation in premenopausal women) while minimizing treatment failures or toxicities based on a patient's genotype.

The question addressed in this evidence review is: Does a genotyping-guided treatment strategy change patient management in a way that it improves net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients receiving or being considered for tamoxifen therapy:

- Treatment of breast cancer in the adjuvant setting to prevent recurrence (alone or preceding aromatase inhibitor therapy) or for metastatic disease.
- Prevention of breast cancer in high-risk women or women with ductal carcinoma in situ; and absence of contraindications to aromatase inhibitors (for treatment) or raloxifene (for disease prevention).

Interventions

The test being considered is *CYP2D6* genotype-guided tamoxifen treatment. Commercial tests for individual genes or gene panels are available and listed in the Regulatory Status section.

Comparators

The following practice is currently being used: clinically managed tamoxifen treatment.

Outcomes

The general outcomes of interest are overall survival, disease-specific survival, medication use, and treatment-related morbidity. Specific outcomes are listed in Table 3.

Table 3. Outcomes of Interest for Individuals With or at High Risk for Breast Cancer

Outcomes	Details
Medication use	Change to alternative treatment (aromatase inhibitor) or strategy (ovarian ablation in premenopausal women)
Treatment-related morbidity	Reduction in adverse events

The potential beneficial outcomes of primary interest would be a reduction in the rate of recurrence and improvement in disease-free survival or overall survival.

Timing

Follow-up to determine whether genotype-guided tamoxifen treatment reduces adverse events or avoids treatment failure isduring the first 10 years after treatment initiation.

Setting

Patients requiring treatment for prevention or treatment for breast cancer are managed by an oncologist.

Prospective Cohort Studies

Multiple retrospective and prospective cohort studies have investigated the association between *CYP2D6* genotype and tamoxifen effectiveness and reported contradictory results with relative risks ranging from 0.08 to 13.1 for the association between variant *CYP2D6* genotypes and breast cancer recurrence or mortality.[10] The contradictory results may be due to differences 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. Many of these studies have also been summarized in multiple systematic reviews and meta-analyses with inconsistent results. Data in most of these studies derived from a convenient sample, which was further limited by relatively small numbers of patients, lack of comprehensive genotype data and patient data (eg, concomitant medications), and detailed clinical outcomes data. Among the most influential studies of the association between *CYP2D6* genotype and tamoxifen effectiveness are 3 nonconcurrent prospective studies nested within large prospective, randomized double-blind trials that compared tamoxifen with anastrozole, letrozole, or combination tamoxifen and anastrozole in postmenopausal women with hormone receptor–positive early-stage breast cancer.[11-13] In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[11] and Breast International Group 1-98 (BIG 1-98) trial,[12] a subset of patients who received tamoxifen and were genotyped for *CYP2D6* variants (n=588 and n=1243, respectively) did not show any statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizer) and breast cancer recurrence. In the Austrian Breast and Colorectal Cancer Study Group trial, a case-control study was done using a subset of patients where cases were defined as those with disease recurrence, contralateral breast cancer, second non-breast cancer, or died and controls were identified from the same treatment arm of similar age, surgery/radiation, and stage.[13] Results showed that patients with 2 poor metabolizer alleles had higher likelihood of recurrence than women with 2 extensive metabolizer alleles. Concerns about the substantial departure from Hardy-Weinberg equilibrium for the *CYP2D6* allele, *4 and analyses not meeting the Simon-Paik-Hayes criteria for nonconcurrent prospective studies have been raised to explain the lack of effect in the ATAC and BIG 1-98 trials.[14]

Trials are important to validate such hypotheses. However, no trials of genotype-directed dosing or drug choice that assessed outcomes of breast cancer recurrence were identified. Ruddy et al

(2013) implemented a tamoxifen adjustment algorithm for 99 patients treated at a cancer treatment institute.[15] Recommendations to modify tamoxifen therapy were made for 18 (18%) patients, all of whom had low endoxifen levels (<6 ng/mL), and 2 of whom also were identified as *CYP2D6* poor metabolizers. Breast cancer recurrence or survival outcomes were not reported.

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. 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 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.

Practice Guidelines and Position Statements

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."[16]

American Society of Clinical Oncology

The 2016 guidelines 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."[17]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01357772	Randomized Placebo-controlled Phase III Trial of Low-dose Tamoxifen in Women With Breast Intraepithelial Neoplasia	1400	Dec 2023

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) 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 of these services as it applies to an individual member.

CPT/HCPCS

81226 CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6 (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)

0028U CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis [Test name-CYP2D6 Genotype Cascade; Manufacturer-Mayo Clinic] (Eff 01-01-2018)

- There is a specific CPT code for this testing: 81226

DIAGNOSIS

Experimental / Investigational for all diagnosis codes related to this medical policy.

REVISIONS	
10-26-2010	Policy added to the bcbsks.com web site.
08-12-2011	Description section updated.
	Rationale section updated.
	In Coding section: Updated nomenclature for CPT codes: 88385, 88386
	Reference section updated.
02-14-2012	In Coding section: ▪ Added CPT code: 81226 (effective 01-01-2012) ▪ Added the following notations: ▪ "81226 should be used for genetic testing for tamoxifen treatment effective 01-01-2012. ▪ 88384, 88385, 88386 should not be used for genetic testing for tamoxifen treatment after 01-01-2012"

REVISIONS	
06-29-2012	Description section updated.
	Rationale section added.
	References section updated.
01-15-2013	In Coding section: ▪ Removed CPT codes: 88384, 88385, 88386 (effective 12-31-2012).
09-25-2013	Description section reviewed
	Rationale section updated
	References updated
10-06-2015	Description section updated
	In Policy section: ▪ Added "2D6" to read "Genotyping to determine cytochrome p450 2D6 (CYP2D6) genetic polymorphisms…" This update did not change the policy intent, rather added clarification to the policy statement.
	Rational section updated
	References updated
11-09-2016	Description section updated
	In Policy section: ▪ In policy statement changed "women" to "individual". ▪ Added Policy Guidelines regarding genetic counseling.
	Rationale section updated
	In Coding section: ▪ Revised coding notations.
	References updated
09-01-2017	Description section updated
	In Policy section: ▪ Replaced "genetic polymorphisms" with "variants" to read "Genotyping to determine cytochrome p450 2D6 (CYP2D6) variants is considered experimental / investigational…" ▪ Policy Guidelines updated with addition of Human Genome Variation Society nomenclature and American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines.
	Rationale section updated
	References updated
09-12-2018	Titled revised to "Genotype-Guided Tamoxifen Treatment" from "Genetic Testing for Tamoxifen"
	Description section updated
	Rationale section updated
	In Coding section: ▪ Added PLA Code: 0028U
	References updated

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