2.04.51	Genetic Testing for Tamoxifen Treatment		
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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

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). Human Genome Variation Society nomenclature is recommended by Human Genome Variation Society, the Human Variome Project, and the HUman Genome Organization.

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 the American College of Medical Genetics and Genomics, the Association for Molecular Pathology, and 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.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding
There is a specific CPT code for this testing:

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

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. The cytochrome P450 (CYP450) metabolic enzyme, CYP2D6, has a major role in tamoxifen metabolism. Some organizations have recommended that patients who are prescribed tamoxifen be genotyped for *CYP2D6*, and that patients who are poor metabolizers be treated with alternative therapy if possible.

Related Policies

- Cytochrome p450 Genotyping

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of the FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

The AmpliChip *CYP450* Test (Model 04381866190; Roche) was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process (K042259) and can be used to identify *CYP2D6* genotype.

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.

Rationale

Background
Tamoxifen Metabolism
Tamoxifen undergoes extensive primary and secondary metabolism, and plasma concentrations of tamoxifen and its metabolites vary widely. The metabolite 4-hydroxytamoxifen (4-OH tamoxifen) has demonstrated a 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation in vitro compared

with the parent drug (summarized in Goetz et al [2080][1]). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has properties and potency identical to 4-OH tamoxifen.[2-5] Because 4-OH tamoxifen represents less than 20% of the product of tamoxifen primary metabolism and because steady-state plasma endoxifen concentrations are on average 5- to 10-fold higher than 4-OH tamoxifen plasma levels, it has been assumed that endoxifen is the major active metabolite of tamoxifen.

The metabolism of tamoxifen into 4-OH tamoxifen is catalyzed by multiple enzymes. However, endoxifen is formed predominantly by CYP2D6. Plasma concentrations of endoxifen exhibit high inter-individual variability, as described in breast cancer patients.[5] 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.

Alternatively and more recently, it has been estimated that, at doses used for adjuvant treatment, which are intended to saturate the estrogen receptor, more than 99% of estrogen receptors are bound by low-affinity tamoxifen and both low- and high-affinity metabolites.[6] Lash et al (2009) modeled the effect of *CYP2D6*-variant alleles on estrogen receptor binding by tamoxifen and metabolites, and found a negligible effect.[7] As they noted, however, modeling cannot account for many metabolic complexities, and mechanistic data would be needed to show how a decrease in high-affinity metabolites associated with *CYP2D6* variants reduces the protection against recurrence conferred by tamoxifen therapy.

Metabolic Enzyme Genotypes

The *CYP2D6* gene exhibits a high degree of polymorphism, with more than 75 allelic variants identified. Although the most prevalent *CYP2D6*1* and **2* alleles (both termed "wild-type" for this evidence review) produce an enzyme with normal activity, there are several variant alleles that result in enzymes with no activity or reduced activity. Because individuals have two *CYP2D6* alleles, various combinations of the possible alleles result in a spectrum of *CYP2D6* function; they have been categorized as extensive metabolizers ("normal"), intermediate metabolizers, and poor metabolizers (PMs). An additional, rare category of ultrarapid metabolizers is defined by possession of 3 or more functional alleles due to gene duplication.

The prevalence of *CYP2D6* PMs 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 PM 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 PMs 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 PMs in the Hispanic population.[8]

Other enzymes metabolize tamoxifen into the active metabolite, 4-OH tamoxifen. Polymorphisms in the genes for these enzymes could have an effect on overall tamoxifen efficacy. Research on the effect of variant alleles for these enzymes is in earlier stages.

Endocrine Therapy Regimens

Tamoxifen has several labelled indications[9]:

- chemoprevention of invasive breast cancer in high-risk women without current disease or with ductal carcinoma in situ
- adjuvant treatment of primary breast cancer 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. The pharmacogenomic evaluation could direct consideration of ovarian ablation or suppression in those found to be *CYP2D6* PMs. In pre- or perimenopausal women with hormone receptor–positive tumors, ovarian ablation is more effective treatment than no adjuvant therapy, but may be accompanied by acute and chronic adverse effects (e.g., hot flushes, sweats, sleep disturbance). Similarly, functional ovarian suppression with gonadotropin-releasing factor analogues in pre- or perimenopausal women with hormone receptor–positive tumors confers benefits comparable with chemotherapy. National Comprehensive Cancer Network (NCCN) guidelines indicate that ovarian ablation or suppression are options in combination with endocrine therapy for premenopausal women who have invasive or recurrent disease and are recommended for premenopausal women with systemic disease.[10]

For postmenopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction. Efficacy equals that of tamoxifen, and risk of endometrial hyperplasia is markedly reduced. Currently, raloxifene is not indicated for treatment of invasive breast cancer; reduction of breast cancer recurrence risk; or noninvasive breast cancer risk reduction.[11]

The pharmacogenomics of tamoxifen have been most often studied in postmenopausal women who have endocrine receptor–positive tumors and require endocrine therapy to prevent recurrence. For this population, the National Comprehensive Cancer Network's 2017 guidelines for the management of breast cancer includes a number of statements related to the use of adjuvant tamoxifen (among other endocrine therapies), which are summarized in Table 1.[10]

Table 1. 2017 NCCN Guidelines for Adjuvant Endocrine Therapy for Postmenopausal Women with Breast Cancer

Recommendation	COR
Premenopausal at Diagnosis	
Tamoxifen for 5 years (with or without ovarian suppression), followed by AI for 5 years if postmenopausal	1
Tamoxifen for 5 years[a*] (with or without ovarian suppression)[a] followed by consideration for tamoxifen for 5 years[b] if postmenopausal	2A
Tamoxifen for 5 years[a] (with or without ovarian suppression)[a] followed by consideration for tamoxifen for 5 y OR no further therapy if still premenopausal	2A
Postmenopausal at diagnosis	
AI for 2-3 years followed by tamoxifen for a total of 5 years of endocrine therapy	1
Tamoxifen for 2-3 years followed by AI for a total of 5 years of endocrine therapy	1
Tamoxifen for 2-3 years followed by up to 5 years of an AI[c]	2A overall
Tamoxifen for 2-3 years followed by 1 of 3 AIs to complete 5 years of endocrine therapy	2B
Tamoxifen for 4.5-6 years followed by AI for 5 years	1
Tamoxifen for 4.5-6 years followed by consideration for tamoxifen for 5 more years	2A
In women with a contraindication to AIs, or who decline or are intolerant of AIs, consideration for tamoxifen for 5 years of tamoxifen for up to 10 years	1

AI: Aromatase Inhibitor; COR: Category of Recommendation.
[a] COR 1.
[b] COR 2A.
[c] COR 2B.

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.[12-14] Some individuals treated with fluoxetine or paroxetine changed from extensive metabolizer phenotype to PM.[12] 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.

Literature Review
Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of a test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

CYP2D6 Genotyping for Tamoxifen Treatment

Clinical Context and Test Purpose

The purpose of testing for *CYP2D6* genotype is to tailor drug selection based on a patient's gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs (e.g., aromatase inhibitor) or strategy (e.g., ovarian ablation in premenopausal women), while minimizing treatment failures or toxicities.

The questions addressed in this evidence review are: (1) is there evidence that testing for *CYP2D6* genotype has clinical validity?; and (2) Does *CYP2D6* genotyping change patient management in a way that potentially improves outcomes as a result of testing?

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
Commercial testing is available from companies listed in Table 2.

Table 2. Commercially Available Genetic Tests for *CYP2D6*

Manufacturer	Test Name	Total No. of Genes Tested
OneOme	OneOme RightMed	22 (including *CYP2D6*)
Roche	AmpliChip	2 (including *CYP2D6*)

Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are overall survival, disease-specific survival, test accuracy, test validity, 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 ovarian ablation in premenopausal women)
Treatment-related morbidity	Reduction in adverse events

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

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse effects from that treatment or under treatment.

Timing
Genetic testing may be used for treatment selection before initiating or during therapy.

Setting
Patients requiring treatment for prevention or treatment for breast cancer are managed by an oncologist and are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
The Roche AmpliChip CYP450 Test for detecting variants in *CYP2D6* has been fully validated for analytic validity; a summary of results submitted for clearance to the U.S. Food and Drug Administration is provided in the agency's decision summary.[15]

Although comparable information on the analytic validity of laboratory-developed tests usually is not available, in an experienced laboratory and with validation of in-house results compared with either sequencing or AmpliChip, accurate and reliable performance should be achievable, as demonstrated by Heller et al (2006).[16]

Section Summary: Analytic Validity
Evidence for the analytic validity of AmpliChip CYP450 Test is provided in the Food and Drug Administration's decision summary. Comparable information on the analytic validity of laboratory-developed tests usually is not available.

Clinical Validity
Four studies have evaluated the *CYP2D6* genotype as a prognostic marker in patients not treated with tamoxifen to ensure that a prognostic association would not confound the effect of genotype on tamoxifen outcomes.[17-20] Although there were limitations in study quality or reporting, none of the studies found that outcomes varied by *CYP2D6* genotype in untreated patients.

Indirect Association between Genotype and Clinical Outcomes
Sixteen prospective cohort studies of adjuvant tamoxifen treatment have provided consistent evidence that *CYP2D6* nonfunctional variant alleles are associated with significantly reduced plasma endoxifen levels.[5,20-34] However, endoxifen levels overlap across all genotypes, suggesting that *CYP2D6* genetic variability does not explain all variation in endoxifen levels; in a 2013 study of 224 Asian women, 10% of the variance in endoxifen levels was explained by *CYP2D6* genotype.[33] Seven of 8 studies reported significant associations between low *CYP2D6* function and reduced plasma 4-hydroxytamoxifen (4-OH tamoxifen) levels.[20,21,23,24,27-29,31] Co-administration of potent *CYP2D6* inhibitors to *CYP2D6* homozygous wild-type patients (extensive metabolizers [EMs]) was associated with endoxifen levels near those of patients who are poor metabolizers (PMs), suggesting that use of *CYP2D6* inhibitors should be taken into account when assigning metabolizer status in clinical studies.

Three studies have reported on the relation between *CYP2D6* genotype and active tamoxifen metabolites and between genotype and clinical outcomes in the same patient population.[20,24,34] Two studies enrolled breast cancer patients from Asian populations, focusing almost exclusively on the reduced (but not absent) function *CYP2D6*10* variants.[20,24] Both studies reported reduced endoxifen and/or 4-OH tamoxifen concentrations in conjunction with 1 or 2

variant alleles and also reported decreasing disease-free survival (DFS) or recurrence-free survival. Both studies were small and had design flaws likely resulting in selection bias. A third study assessing 306 premenopausal white patients reported that the association between serum endoxifen levels and distant relapse-free survival was inconclusive.[34] In 2011, Madlensky et al reported on the association between tamoxifen metabolite levels and breast cancer outcomes in 1370 samples from the Women's Healthy Eating and Living study.[28] The Women's Healthy Eating and Living enrolled 3088 women with early-stage breast cancer who were diagnosed from 1991 to early 2000 and had received tamoxifen.[35] Endoxifen and 4-OH tamoxifen levels were strongly associated with *CYP2D6* phenotype but did not have a linear association with breast cancer outcomes. A threshold effect was identified with endoxifen, such that patients with endoxifen levels greater than 6 ng/mL had a 30% lower risk of additional breast cancer events (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.52 to 0.94). Notably, 24% of PM patients had endoxifen levels above this threshold.

Four prospective studies published in 2011, 2012, and 2014 assessed the impact of an increased tamoxifen dose for patients who were already taking tamoxifen.[25-27,36] These patients were genotyped as intermediate metabolizers (IMs) or PMs (and not administered *CYP2D6* inhibitors). Tamoxifen metabolite levels were measured at baseline and after 2 to 4 months and compared with levels from those EM patients who had no tamoxifen dose change. In general, tamoxifen metabolite concentrations increased with increasing dose; IM patient levels reached those of EM patients, and PM patient levels remained somewhat lower. However, these results were not related to breast cancer outcomes. Moreover, metabolite levels were highly variable across individuals, and, in 1 study, low plasma endoxifen concentrations were found in all *CYP2D6* genotypes.[26] Thus, *CYP2D6* may only account for part of the variability in endoxifen levels,[37] suggesting that The influence of other gene variants on tamoxifen treatment outcomes has been reported.[38-41]

Direct Association between Genotype and Clinical Outcomes

An ideal study assessing a direct association between genotype and outcomes would compare tamoxifen-treated women with those not receiving tamoxifen, stratified by *CYP2D6* genotype to assess whether PMs derive less benefit from tamoxifen than EMs. One group conducted such a study retrospectively, on archived samples from a randomized controlled trial of tamoxifen treatment.[19] Paradoxically, in this trial, Wegman et al (2005) found that EMs treated with tamoxifen received no statistically significant clinical benefit compared with EMs not treated with tamoxifen and that carriers of a *CYP2D6*4* nonfunctional variant allele obtained significant benefit from tamoxifen treatment. There were several limitations to this study.

A 2013 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment identified 24 other studies evaluating the association between *CYP2D6* genotype and clinical outcomes in women treated with tamoxifen.[42]

- Nine small studies (N range, 21-282 patients) in Asian populations focused on the *CYP2D6*10* reduced function allele,[20,23,24,39,43-47] and 5 reported significant results for the association between *CYP2D6* genotype and outcomes of tamoxifen treatment.[20,23,24,46,47] However, some of these studies may have been influenced in unpredictable ways by different biases (e.g., by selecting among survivors at a time distant from diagnosis and surgery to draw whole blood for *CYP2D6* genotyping [survivor selection bias]). Two studies that reported no association might have had less potential for bias.[43,44] One larger study (N=716) of Korean patients with breast cancer who received adjuvant tamoxifen therapy (most with adjuvant chemotherapy) found no significant *CYP2D6* genotype–associated difference in recurrence-free survival, regardless of treatment or prognostic subgroup.[29]
- Thirteen studies evaluated samples from primarily white patients administered tamoxifen for adjuvant treatment of invasive breast cancer and 1 study for metastatic breast cancer.[17,18,48-59] Of the 5 largest studies, 4 reported no significant association for time to recurrence.[48,50-52] Two of the negative studies were retrospective analyses of clinical trial samples,[50,51] and a third was a case-control study nested in a population-based cancer

registry.[48] All 3 were designed to minimize the potential for bias; their size (N range, 588-991 patients) permitted comparison of homozygous nonfunctional *CYP2D6* genotypes with fully functional wild-type genotypes (i.e. the most extreme comparison and most likely to reveal a true association). The largest of the 5 studies (N=1345 patients) reported significant results; however, this study combined samples from different sources, some of which had already been analyzed for this hypothesis.[49] Additionally, it is unclear from the report whether nearly half of the samples were obtained from patients who had survived and were available at a time distant from their diagnosis and surgery, a type of selection bias that can unpredictably affect results. The remaining 8 small studies reported a variety of significant and non-significant results; no pattern of bias, genotyping or group scheme, or accounting for *CYP2D6* inhibitor use (among possibilities) explained the differences in results. The heterogeneity of results across all studies and clear results of no genotype–tamoxifen treatment outcome in 3 large studies with the least apparent potential for bias strongly would suggest a lack of support for clinical validity in postmenopausal patients treated with adjuvant tamoxifen for breast cancer.

- Two nested, matched, case-control studies examined patients originally enrolled in chemoprevention trials using tamoxifen.[60,61] In neither the larger (591 cases, 1126 controls) nor the smaller study (47 cases, 135 controls) was *CYP2D6* genotype associated with the risk of developing breast cancer. A 2013 matched case-control study from the Women's Environment Cancer and Radiation Epidemiology study sample reported no association between *CYP2D6* variants and risk for contralateral breast cancer in tamoxifen-treated women (139 cases, 338 controls).[62] The Women's Environment Cancer and Radiation Epidemiology participants (998 cases [women with contralateral breast cancer], 2112 controls [women without contralateral breast cancer]) were women from 4 U.S. cancer registries and 1 Danish registry who were diagnosed with localized invasive breast cancer before age 55.

Published literature on the association between *CYP2D6* genotype and tamoxifen therapy effectiveness for treatment of non-metastatic breast cancer has yielded inconsistent results. A 2012 review tried to identify factors that may have led to discrepant findings.[63] The authors selected 6 factors to compare across 11 negative and 6 positive studies; they identified 3 factors that could account for contradictory results: tamoxifen combination therapy (defined as any additional therapy, including radiotherapy); genotyping comprehensiveness (how many and which alleles were tested); and *CYP2D6* inhibitor co-administration. Studies that enrolled patients on tamoxifen monotherapy, genotyped *CYP2D6* more comprehensively, and accounted for *CYP2D6* inhibitor co-administration were more likely to have positive findings. To elucidate the impact of germline genotype misclassification in studies where DNA was genotyped from tumor-infiltrated tissues, Ahern et al (2017) systematically reviewed 6 studies on the concordance between genotypes obtained from paired nonneoplastic and breast tumor-infiltrated tissues, all of which showed excellent *CYP2D6* genotype agreement but found no clinically important association between *CYP2D6* genotype and breast cancer survival in tamoxifen-treated women.[64]

Other studies also have reported discrepant results. Two large studies (2013, 2014) from Scandinavia (total N=1365 patients) reported no association between *CYP2D6* genotype and disease recurrence in tamoxifen-treated women with early breast cancer.[65,66] In contrast, a 2013 German study of 94 women with advanced breast cancer reported significantly shorter progression-free survival and OS in patients without any fully functional *CYP2D6* allele (IM/IM, IM/PM, PM/PM) compared with those who had at least 1 functional allele (EM/EM, EM/IM, EM/PM) (HR for disease progression or death, 2.19; 95% CI, 1.15 to 4.18; p=0.017; HR for death from any cause, 2.79; 95% CI, 1.12 to 6.99; p=0.028).[67] Martins et al (2014) found no association between *CYP2D6* genotype and DFS in 58 Brazilian women with locally invasive breast cancer, although the study was likely underpowered to detect a difference (only 1 patient was classified PM).[68] Some authors have suggested that *CYP2D6* genotyping may be clinically relevant in premenopausal women,[34] but not for postmenopausal women,[69] and others support its clinical relevance for postmenopausal women.[70]

Several 2013 and 2014 meta-analyses have published inconsistent results. None included studies on the concomitant use of *CYP2D6*-inhibiting drugs in their analyses. These analyses may be considered exploratory because of varying inclusion criteria, outcome definitions, and comparisons of interest across reviews. Relevant meta-analyses are discussed next.

In 2014 the International Tamoxifen Pharmacogenomics Consortium pooled retrospective data from 12 participating sites.[71] Results from 1996 postmenopausal women with estrogen receptor–positive breast cancer who were prescribed tamoxifen 20 mg daily for 5 years (40% of the total sample) reported a significant association between *CYP2D6* PM status and both reduced invasive DFS (HR for invasive disease or death, 1.25; 95% CI, 1.06 to 1.47; p=0.009) and reduced breast cancer–free interval (HR for recurrence, 1.27; 95% CI, 1.01 to 1.61; p=0.041), presumably compared with EMs (the comparison group was not explicitly defined). Statistical heterogeneity was non-significant (Cochran Q, p>0.05) for both outcomes. For analyses using less stringent inclusion criteria (e.g., pre- and postmenopausal women combined), associations between *CYP2D6* metabolizer status and survival outcomes were not statistically significant. A critique of this meta-analysis is that adjustments for multiple comparisons were not performed; the reported associations may not have been statistically significant adjustments for multiple comparisons had been reported.[72] Additionally, the pre-specified end point of OS was not reported in the published article.[73]

Lum et al (2013) conducted a systematic review and meta-analysis to January 2012 and pooled results from 22 retrospective studies (total N=4936 patients).[74] For the outcome of all-cause mortality, the relative risk (RR) for *CYP2D6* PMs or IMs compared with EMs or ultrarapid metabolizers was not statistically significant (RR=1.11; 95% CI, 0.94 to 1.31; p=0.237). Statistical heterogeneity was low (I^2=20%). When outcomes were expanded to include progression-free survival (RR=1.27; 95% CI, 1.11 to 1.45; p<0.001) and recurrence (RR=1.19; 95% CI, 1.07 to 1.33; p=0.002), relative risks were statistically significant, but statistical heterogeneity was moderate to substantial (I^2=56% and 53%, respectively).

Zeng et al (2013) conducted a meta-analysis to February 2013 and pooled 20 retrospective studies (total N=11,701 patients).[75] Among several comparisons (PM vs EM, IM vs EM, PM/IM vs EM, PM vs IM/EM), the association between *CYP2D6* metabolizer status and both DFS and OS was statistically significant only for the comparison of any variant allele versus wild-type EM (HR for DFS=1.37; 95% CI, 1.12 to 1.69; p=0.002; HR for OS=1.24; 95% CI, 1.03 to 1.50; p=0.021). Statistical heterogeneity was substantial for the analysis of DFS (I^2=67%) but minimal for OS (I^2=0%). There was evidence of publication bias for the DFS outcome.

Jung and Lim (2014) pooled results from 10 retrospective studies (total N=5183 patients) and found an increased risk of recurrence among carriers of *CYP2D6* variant alleles compared with wild-type EMs (pooled HR=1.64; 95% CI, 1.07 to 2.79).[76] However, this result is questionable because of the inclusion of 4 small studies (N range, 18-282 patients) with unstable risk estimates (HRs >3 with large CIs).

Section Summary: Clinical Validity

Multiple studies have evaluated the association between *CYP2D6* genotype and the consequences of altered metabolism of tamoxifen on clinical outcomes. Results have been conflicting. However, most of the earlier studies were retrospective and evaluated small numbers of patients. In an attempt to settle this issue, investigators assessed archived samples from a large randomized controlled trial but results did not demonstrate the expected associations. Subsequent meta-analyses have also shown inconsistent results. The inconsistencies may be due to differences across studies in the types of additional therapies patients received, how many and which *CYP2D6* alleles were tested, tissue type examined (tumor or germline DNA), and co-administration of *CYP2D6* inhibitors.

Clinical Utility

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. The strongest direct evidence comes from randomized controlled trials.

No direct evidence of clinical utility was identified. Ruddy et al (2013) implemented a tamoxifen adjustment algorithm for 99 patients treated at a cancer treatment institute.[77] 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* PMs. Survival outcomes were not reported.

In a 2016 study, Hertz et al increased tamoxifen doses from 20 to 40 mg per day based on genotype.[78] Endoxifen concentrations in IM patients were similar to those of EM patients, but endoxifen levels in PM patients were not. The dose escalation did not increase toxicity or reduce the quality of life, raising the possibility that more effective doses of tamoxifen might be given. A beneficial effect on survival with this increase in tamoxifen dose would be needed to demonstrate clinical utility.

Chain of Evidence

It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

Section Summary: Clinical Utility

Multiple studies have evaluated the association between *CYP2D6* genotype and resulting altered tamoxifen metabolism on clinical outcomes, and have reported conflicting results. However, most of the earlier studies were retrospective and evaluated small numbers of patients. In an attempt to settle this issue, investigators conducted multiple reanalyses of large, prospective randomized controlled trials and meta-analyses. They too reported conflicting results. It is thought the inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients received, how many and which *CYP2D6* alleles were tested, tissue type examined (tumor or germline DNA), and co-administration of *CYP2D6* inhibitors.

No direct evidence of clinical utility was identified. One prospective cohort study implemented a tamoxifen adjustment algorithm but did not report outcomes. In another prospective cohort study of *CYP2D6* genotype-guided tamoxifen dose escalation, dose escalation in PM or IM patients increased the endoxifen concentrations but not toxicity. However, the study did not attempt to delineate whether increased endoxifen levels were associated with greater efficacy. A beneficial effect on survival with the increase in tamoxifen dose would be needed to demonstrate clinical utility. It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

Summary of Evidence

For individuals who are treated with tamoxifen for breast cancer or high risk of breast cancer who receive testing for *CYP2D6* metabolizer status by *CYP2D6* genotyping, the evidence includes multiple retrospective studies, post hoc analysis of randomized controlled trials, and meta-analysis. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, medication use, and treatment-related morbidity. Published data on the association between *CYP2D6* genotype and tamoxifen treatment outcomes have yielded inconsistent results. Some inconsistencies in the literature may be due to differences across studies in the types of additional therapies patients received, how many and which *CYP2D6* alleles were tested, tissue type examined (tumor or germline DNA), and co-administration with *CYP2D6* inhibitors. The largest, most well-designed studies do not support a significant association. At present, the clinical utility of *CYP2D6* testing is also poorly defined. An interventional study of *CYP2D6*-specific tamoxifen dosing found that personalized dosing was

associated with changes in endoxifen level, but it has not been demonstrated that endoxifen level is associated with improved outcomes. It is not known whether clinical management guided by *CYP2D6* genotyping improves patient outcomes such as appropriate selection of a treatment strategy that would reduce the rate of 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.

Supplemental Information

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.2.2017) state: "*CYP2D6* genotype testing is not recommended in women who are considering tamoxifen."[10]

American Society of Clinical Oncology

A 2010 guideline update from the American Society of Clinical Oncology "recommend[ed] against using *CYP2D6* genotype to select adjuvant endocrine therapy.... [and] encouraged caution with concurrent use of *CYP2D6* inhibitors...."[79] A 2013 guideline update from the American Society of Clinical Oncology affirmed that position: "Data from the NSABP-P1 and STAR trials do not support the use of *CYP2D6* testing to identify women not likely to benefit from tamoxifen therapy for breast cancer prevention."[80]

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.

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			
NCT01220076	Phase II Study Evaluating According to the Polymorphism of CYP2D6, the Rate of Biological Response to Treatment With Tamoxifen (TAM) Administered in Pre-operative Situation in Patients With Breast Cancer Non Metastatic HR+	265	Nov 2016 (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.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	0028U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis ***(Code effective 1/1/2018)***
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
03/02/2016	BCBSA Medical Policy adoption	Medical Policy Committee
09/01/2016	Policy revision without position change	Medical Policy Committee
08/01/2017	Policy revision without position change	Medical Policy Committee
05/01/2018	Coding update	Administrative Review

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.