Policy Statement

I. 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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. 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.

Related Policies

- Cytochrome P450 Genotype-Guided Treatment Strategy

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 FDA-approved technologies on the basis of medical necessity alone.

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

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 cytochrome P450 2D6 (CYP2D6) enzyme. Plasma concentrations of endoxifen exhibit high inter-individual 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 responses 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 2.

Table 2. Relation Among the *CYP2D6* Genotype, Phenotype, and Clinical Implications

Genotype	Phenotype	Potential Clinical Implications With Use of Tamoxifen
≥3 copies of functional alleles	Ultra-rapid metabolizer	None
Any 1 of the following scenarios: • 1 active allele and 1 inactive allele	Intermediate metabolizer	• Increased risk for relapse of breast cancer • Avoid concomitant use of CYP2D6 inhibitors

Genotype	Phenotype	Potential Clinical Implications With Use of Tamoxifen
• **2 decreased activity alleles** • **1 decreased activity allele and 1 inactive allele**		• 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 White individuals of Northern European descent, 1.9% to 7.3% in Black individuals , and 1% or less in most Asian populations studied. The poor metabolizer phenotype in White individuals 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 Black, Asian, and White individuals, respectively. Few studies have investigated the frequency of *CYP2D6*-variant alleles or poor metabolizers in the Hispanic population.[4,]

Endocrine Therapy Regimens

Tamoxifen has several labeled 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 a 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 the reduction in "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 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.[7,8,9,] Some individuals treated with fluoxetine or paroxetine have changed from an extensive metabolizer phenotype to a poor metabolizer.[7,] The degree of inhibition may depend on the 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.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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 (RCT) 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.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Genotype-Guided Tamoxifen Treatment

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals 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 therapy being considered is cytochrome P450 2D6 (*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 guided tamoxifen treatment.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, medication use, and treatment-related morbidity. The potential beneficial outcomes of primary interest would be a reduction in the rate of recurrence and improvement in disease-free survival or OS. Specific outcomes are listed in Table 3. The follow-up to determine whether genotype-guided tamoxifen treatment reduces adverse events or avoids treatment failure is during the first 10 years after treatment initiation.

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Meta-Analyses and Systematic Reviews

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,] Many of these studies have been summarized in multiple systematic reviews and meta-analyses with inconsistent results.[10,11,] 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 co-administration with CYP2D6 inhibitors. A comparison of the studies included in 2 recent reviews is in Table 4. These reviews analyzed a total of 45 studies published between 2005 and 2017. Characteristics and results of these reviews are summarized in Tables 5 and 6.

Table 4. Comparison of Studies Included in Genotype-Guided Tamoxifen Treatment Systematic Reviews and Meta- Analyses

Study	Ahern et al (2016)[10,]	Drögemöller et al (2019)[11,]
Abraham et al (2010)[12,]	●	●
Abreu et al (2015)[13,]		●
Bijl et al (2009)[14,]	●	●
Brooks et al (2013)[15,]		●
Chamnanphon et al (2013)[16,]	●	●
Damodaran et al (2012)[17,]	●	●
De Ameida Melo et al (2016)[18,]		●
Dezentje et al (2013)[19,]	●	
Goetz et al (2005)[20,*]	●	
Goetz et al (2013)[21,]	●	●
Gor et al (2010)[22,]	●	
Gunaldi et al (2014)[23,]		●
Hertz et al (2017)[24,]		●

Study	Ahern et al (2016)[10]	Drögemöller et al (2019)[11]
Johansson et al (2016)[25]		●
Karle et al (2013)[26]		●
Kiyotani et al (2010)[27]	●	●
Kiyotani et al (2010)[28]		●
Lammers et al (2010)[29]		●
Lash et al (2011)[30]	●	●
Lei et al (2016)[31]		●
Margolin et al (2013)[32]		●
Markkula et al (2014)[33]	●	
Martins et al (2014)[34]		●
Morrow et al (2012)[35]		●
Mwinyi et al (2014)[36]	●	
Newman et al (2008)[37]		●
Nowell et al (2005)[38]		●
Okishiro et al (2009)[39]	●	●
Park et al (2011)[40]	●	●
Park et al (2012)[41]		●
Province et al (2014)[42]		●
Rae et al (2012)[43]	●	●
Regan et al (2012)[44]	●	●
Schroth et al (2007)[45,*]	●	
Schroth et al (2009)[46,*]		●
Sirachainan et al (2012)[47]	●	●
Stingl et al (2010)[48]		●
Sukasem et al (2012)[49]	●	●
Teh et al (2012)[50]	●	●
Thompson et al (2011)[51]		●
Toyama et al (2009)[52]		●
Wegman et al (2005)[53]		●
Wegman et al (2007)[54]		●
Xu et al (2008)[55]	●	●
Yazdi et al (2015)[56]		●

*Schroth et al 2007 and Goetz et al 2005 include the same sample as Schroth et al 2009.

Table 5. Systematic Reviews & Meta-Analyses of Genotype-Guided Tamoxifen Treatment: Characteristics

Study (Year)	Dates	Trials	Participants	N (Range)	Design	Duration
Ahern et al (2016)[10]	2005-2014	31 total (21 included in the analysis)	Women treated with tamoxifen for breast cancer who underwent *CYP2D6* genotyping	NR (NR)	Observational	NR
Drögemöller et al (2019)[11]	2005-2016	48 total (representing 38 unique study populations)	Women treated with tamoxifen for breast cancer who underwent *CYP2D6* genotyping	20,054 (39 to 4973)	Observational	NR

NR: not reported.

Table 6. Systematic Reviews & Meta-Analyses of Genotype-Guided Tamoxifen Treatment: Results

Study (Year)	Overall survival	Rate of Recurrence	Disease-free survival	Adverse events	Change to alternative treatment or strategy
Ahern et al (2016)[10]	*Composite of mortality or recurrence*		NA	NA	NA
RR (95% CI)	1.71 (1.24 to 2.36)				
P for homogeneity	<.001				

Study (Year)	Overall survival	Rate of Recurrence	Disease-free survival	Adverse events	Change to alternative treatment or strategy
Adjusted RR (95% CI)[1]	1.80 (1.28 to 2.54)				
Drögemöller et al (2019)[11,]	*Association between CYP2D6* and *tamoxifen survival outcomes*	NA	NA	NA	NA
Studies reporting at least 1 statistically significant association, n/N (%)	20/38 (52.6%)				
Studies reporting no statistically significant association, n/N (%)	18/38 (47.4%)				

[1] Adjusted for bias due to tissue sampling.
CI=confidence interval; NA=not applicable; RR=relative risk.

Drögemöller et al (2019) conducted a systematic review of the association between CYP2D6 genetic variation and survival outcomes after tamoxifen treatment.[11,] Included studies showed conflicting conclusions. In multivariate analyses, there was no significant relationship between survival outcomes and the confounders of sample size (p=.83), ethnicity (p=.33), or source of DNA (p=.14).

Comprehensive genotyping panels were more likely to report a significant association with CYP2D6-survival outcome: 11 of 13 studies that used comprehensive genotyping found a significant association between CYP2D6 and survival outcomes. Limitations of the studies identified by the review authors included differences in survival outcome definitions, differences in metabolizer group classifications, low consent rates, and not controlling for CYP2D6 inhibitor use. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients, lack of comprehensive genotype data and patient data (e.g., concomitant medications), and detailed clinical outcomes data.

Randomized Controlled Trial

One trial of genotype-directed dosing that assessed outcomes of breast cancer recurrence was identified (TARGET-1: *CYP2D6* Genotype-Guided Tamoxifen Dosing in Hormone Receptor-Positive Metastatic Breast Cancer trial; Tables 7 through 10). The RCT is a phase II, proof-of-concept study performed at multiple centers in Japan. A total of 184 patients were included in this study, of which 136 had at least 1 *CYP2D6* variant-type allele. Only 1 patient classified as a poor metabolizer with 2 null alleles was included in this trial. The results of this trial did not find a significant difference in outcomes between increased tamoxifen dosing and standard dosing in patients with CYP2D6 genotypic variants.[57,]

Table 7. Summary of TARGET-1 Characteristics

Author (Year); Study	Countries	Sites	Dates	Participants	Active	Comparator
Tamura et al (2020); TARGET-1[57,]	Japan	54	2012-2016	Patients with HR-positive metastatic breast cancer, without visceral spread, needing	Tamoxifen 40 mg daily (n=70 patients with *CYP2D6* genotype wt/V or V/V)	Tamoxifen 20 mg daily (n=66 patients with *CYP2D6* genotype wt/V or V/V; n=48 patients

Author (Year); Study	Countries	Sites	Dates	Participants	Active	Comparator
				first-line tamoxifen therapy		with *CYP2D6* genotype wt/wt)

HR: hormone receptor; V/V: variant/variant; wt/V: wild type/variant; wt/wt: wild type/wild type.

Table 8. Summary of Key TARGET-1 Results

Study (Year)	Disease-free survival		Adverse events
Tamura et al (2020)[57,]	*PFS rate at 6 months, %*	*Median PFS (months)*[¥]	*Tamoxifen related, any grade, n (%)*
N	180	132	183
Tamoxifen 40 mg daily (wt/V or V/V)	67.6%	14.4	49 (70.0%)
Tamoxifen 20 mg daily (wt/V or V/V)	66.7%	11.8	43 (66.2%)
Tamoxifen 20 mg daily (wt/wt)	63.0%	NR	29 (60.4%)
HR (95% CI)*	NS/NR	0.75 (0.50 to 1.14)	NS/NR

CI: confidence interval; HR: hazard ratio; NR: not reported; NS: not significant; PFS: progression free survival; V/V: variant/variant; wt/V: wild type/variant; wt/wt: wild type/wild type.
¥ Median follow-up = 22.9 months.
* Comparison between tamoxifen 40 mg and 20 mg groups with wt/V or V/V genotypes.

The TARGET-1 trial has limited generalizability to all patients, due to its single-country design and small sample size.[57,] No significant difference was seen in progression-free survival with genotype-guided dosing, even though the trial detected significant differences in tamoxifen metabolite concentrations between tamoxifen doses and allelic variations. Because the trial was a proof-of-concept, phase II design, the median follow-up for clinical outcomes was only 22.9 months. The study did not address outcomes of OS or recurrence. Additionally, the primary analysis comparing progression-free survival only included patients with variant alleles, and patients with 2 wild-type alleles were not included in reported analyses.

Table 9. Study Relevance Limitations of TARGET-1

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-up[e]
Tamura et al (2020)[57,]	5 - Study population from Japan				1,2. Less than 10 years

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 10. Study Design and Conduct Limitations of TARGET-1

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-up[d]	Power[e]	Statistical[f]
Tamura et al (2020)[57,]		1,2 - Open-label study 3 - Outcome assessed locally; central		6 - 1 patient with progressive disease and 2 patients with inadequate		3 - CI/p-value not reported for PFS at 6 months

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Follow-up[d]	Power[e]	Statistical[f]
		blinded review used to randomly validate outcomes in approximately 28% of patients		images were excluded from the final analysis		

CI: confidence interval; PFS: progression free survival.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

No trials examining genotype-directed drug or strategy choice were identified. Ruddy et al (2013) implemented a tamoxifen adjustment algorithm for 99 patients treated at a cancer treatment institute.[58,] 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.

Other Prospective Studies

Tables 11 and 12 describe relevant observational or non-randomized prospective studies. 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.[43,44,21,] A more recent prospective cohort study assigned treatment doses according to CYP2D6 metabolizer status and compared outcomes using propensity score matching.[59,]

Table 11. Summary of Key Observational and Non-randomized Genotype-Guided Tamoxifen Treatment Study Characteristics

Author (Year)	Study Type	Country/Institution	Dates	Participants	Treatment 1	Treatment 2	Follow-up
Rae et al (2012); [43,] **ATAC**	Observational cohort	• 381 centers in 81 countries • Patients from United Kingdom included in genetic study; all other countries were used as comparators in certain analyses	1996-2000	• Postmenopausal women with non-metastatic, invasive breast cancer • Eligible to receive adjuvant hormonal therapy • Had underwent *CYP2D6* genotyping during prospective RCT period • N=588	• Treated with tamoxifen	NA	10 years

Author (Year)	Study Type	Country/Institution	Dates	Participants	Treatment 1	Treatment 2	Follow-up
Regan et al (2012); [44]BIG 1-98	Observational cohort	International, multicenter	1998-2003	• Postmenopausal women with HR-positive breast cancer, previously enrolled in RCT • Had a tissue sample available for *CYP2D6* analysis from original RCT period • N=4393	• Treated with tamoxifen	NA	Median: 76 months
Goetz et al (2013); [21]ABCSG	Matched case-control	• Multicenter • Genetic substudy occurred in Austria and United States	1996-2009	• Postmenopausal women with ER-positive breast cancer, previously enrolled in RCT • Had a tissue sample available for *CYP2D6* analysis from original RCT period • Cases were identified by disease recurrence, contralateral breast cancer, second non-breast cancer, or death • n=319 cases and 557 controls	• Arm A: Treated with tamoxifen for 5 years • Arm B: Treated with tamoxifen for 2 years followed by anastrozole for 3 years	NA	5 years
Blancas et al (2023)[59]	Prospective cohort with propensity score matching	Single center in Spain	2000-2010	• Women with HR-positive breast cancer planned for adjuvant tamoxifen for ≥5 y • Participants (N=220) underwent *CYP2D6* genotyping and were assigned metabolizer status (PM, n=13; IM, n=84; NM, n=119; UM, n=4) according to CPIC guidelines	• PM: Tamoxifen 20 mg/d for 4 months, then 40 mg/d for 4 months, then 60 mg/d for 4 months, then 20 mg/d for remainder of 5 y • All others: Tamoxifen 20 mg/d for 5 y	NA	Mean: 112 months

ABCSG: Austrian Breast and Colorectal Cancer Study Group; ATAC: Arimidex, Tamoxifen, Alone or in Combination trial; BIG: Breast International Group; CPIC: Clinical Pharmacogenetics Implementation Consortium; ER: estrogen receptor; HR: hormone receptor; IM: intermediate metabolizer; NA: not applicable; NM: normal metabolizer; PM: poor metabolizer; RCT: randomized controlled trial; UM: ultra metabolizer.

Table 12. Summary of Key Observational and Non-randomized Genotype-Guided Tamoxifen Treatment Study Results

Study (Year)	Overall survival	Disease free survival	Recurrence		Adverse events	
Rae et al (2012)[43]	NA	NA	*Distant recurrence in 10 years*	*Any recurrence in 10 years*	NA	NA
N			588	588		
All, n (%)[¥]			89 (15.1%)	115 (19.6%)		
PM vs. IM [score 0.5], HR (95% CI)			2.8 (0.93 to 8.46)	2.15 (0.85 to 5.40)		
PM vs. IM [score 1.0], HR (95% CI)			1.31 (0.49 to 3.48)	0.94 (0.43 to 2.08)		
PM vs. IM [score 1.5], HR (95% CI)			0.76 (0.20 to 2.84)	0.68 (0.23 to 1.96)		

Study (Year)	Overall survival	Disease free survival	Recurrence		Adverse events	
PM vs. EM, HR (95% CI)			1.25 (0.50 to 3.15)	0.99 (0.48 to 2.08)		
Regan et al (2012)[44,]	NA	NA	*Any Recurrence*		*Treatment induced hot flashes within 2 years*	
			WITHOUT previous chemotherapy	*WITH previous chemotherapy*	WITHOUT previous chemotherapy	WITH previous chemotherapy
N			973	270	487	1706
EM, n (%)			75 (12.3%)	37 (22.2%)	42%	38%
IM, n (%)			40 (14.4%)	12 (15.6%)	49%	39%
IM vs. EM, HR (95% CI)			0.95 (0.50 to 1.40)	0.57 (0.29 to 1.10)	1.23 (1.05 to 1.43)	NR/NS
PM, n (%)			8 (9.3%)	3 (11.5%)	48%	30%
PM vs. EM, HR (95% CI)			0.58 (0.28 to 1.21)	0.76 (0.23 to 2.48)	1.24 (0.96 to 1.59)	NR/NS
Goetz et al (2013)[21,]	*Composite of disease recurrence, contralateral breast cancer, second non-breast cancer, or death at 5 years*[¥]					
	Arm A	Arm B				
EM/IM and IM/IM vs. EM/EM, OR (95% CI)	1.23 (0.58 to 2.61)	1.02 (0.52 to 2.01)				
PM/PM vs. EM/EM, OR (95% CI)	2.45 (1.05 to 5.73)	0.60 (0.15 to 2.37)				
EM/PM and PM/IM vs. EM/EM, OR (95% CI)	1.67 (0.95 to 2.93)	0.76 (0.43 to 1.31)				
Blancas et al (2023)[59,]			NA	NA	NA	NA
IM and PM (rapid) vs NM and UM (slow), HR (95% CI)	• Overall cohort: 0.77 (0.34 to 1.76) • Propensity-matched: 0.85 (0.28 to 2.52)	• Overall cohort: 1.27 (0.67 to 2.42) • Propensity-matched: 1.37 (0.62 to 3.03)				

CI: confidence interval; EM: extensive metabolizer; HR: hazard ratio; IM: intermediate metabolizer; NA: not applicable; NM: normal metabolizer; NR: not reported; NS: not significant; OR: odds ratio; PM: poor metabolizer; UM: ultra metabolizer.
¥ Number and percentage of cases and controls with each phenotype not reported.

In the Arimidex, Tamoxifen, Alone or in Combination trial[43,] and Breast International Group 1-98 trial,[44,] 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.[21,] Results showed that patients with 2 poor metabolizer alleles had a 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 Arimidex, Tamoxifen, Alone or in Combination trial and Breast International Group 1-98 trials.[60,]Poor metabolizers constituted less than 10% of the overall cohort in the study by Blancas et al (2023), suggesting that the study may have been underpowered to detect any differences in survival outcomes driven by genotype-guided tamoxifen regimen differences.[59,]

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 12.

Table 12. 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	500	Dec 2028
NCT05525481	Tamoxifen Prediction Study in Patients With ER+ Breast Cancer (PREDICTAM)	100	Jul 2023
Unpublished			
NCT03931928	Genotype and Phenotype Guided Supplementation of TAMoxifen Standard Therapy With ENDOXifen in Breast Cancer Patients	356	May 2021 (completed)

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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements *are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	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	

Policy History

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

Effective Date	Action
03/01/2016	BCBSA Medical Policy adoption
09/01/2016	Policy revision without position change
08/01/2017	Policy revision without position change
05/01/2018	Coding update
09/01/2018	Policy title change from Genetic Testing for Tamoxifen Treatment Policy revision without position change
10/01/2018	Coding update
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement. Literature review updated.

Effective Date	Action
09/01/2021	Annual review. No change to policy statement. Literature review updated.
10/01/2022	Annual review. Policy statement, guidelines and literature updated.
09/01/2023	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
Genotype-Guided Tamoxifen Treatment 2.04.51 **Policy Statement:** I. 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.	**Genotype-Guided Tamoxifen Treatment 2.04.51** **Policy Statement:** I. 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.