2.04.51	Genotype-Guided 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.

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

Policy Guidelines

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

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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.

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,

Description

Tamoxifen is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor-positive breast cancer recurrence, to treat metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ. Tamoxifen is a pro-drug that undergoes extensive metabolism to yield its active form: 4-hydroxytamoxifen and

endoxifen (primary active form) via the CYP2D6 enzyme. Variants in the *CYP2D6* gene are associated with significant alterations in endoxifen concentrations leading to the hypothesis that *CYP2D6* variation may affect the clinical outcomes of women treated with tamoxifen but not with drugs not metabolized by CYP2D6 such as anastrozole.

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) and PersonaGene Genetic Panels (AIBioTech). 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 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 response to tamoxifen treatment.

Metabolic Enzyme Genotypes

The *CYP2D6* gene exhibits a high degree of polymorphism, with more than 100 allelic variants identified. The relations among genotype, phenotype, and clinical implications are summarized in Table 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	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 metabolizer phenotype in whites is largely accounted for by CYP2D6*3 and *4 nonfunctional variants, and in black and Asian populations, by the **5* nonfunctional variant. Some poor metabolizers may have 1 nonfunctional allele and 1 reduced-function allele. Among reduced-function variants, *CYP2D6*17*, **10*, and **8* are the most important in blacks, Asians, and whites, respectively. Few studies have investigated the frequency of *CYP2D6*-variant alleles or poor metabolizers in the Hispanic population.[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 the endocrine receptor-positive breast cancer in pre- or perimenopausal women.

For postmenopausal women with osteoporosis or at high-risk for invasive breast cancer, raloxifene is an alternative treatment for invasive cancer risk reduction. Currently, raloxifene is indicated for the reduction in "risk of invasive breast cancer in postmenopausal women with osteoporosis" or those at "high risk for invasive breast cancer."[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 extensive metabolizer phenotype to poor metabolizer.[7.] The degree of inhibition may depend on selective serotonin reuptake inhibitor dose.

Thus, *CYP2D6* inhibitor use must be considered in assigning *CYP2D6* functional status, and potent *CYP2D6* inhibitors may need to be avoided when tamoxifen is administered.

Literature Review
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.

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.

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 a patient's genotype.

The question addressed in this evidence review is: Does a genotype-guided tamoxifen treatment strategy change patient management in a way that leads to an improvement in the net health outcome?

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

Populations
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 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 a. (2005)[20]*	●	
Goetz et al. (2013)[21]	●	●
Gor et al. (2010)[22]	●	
Gunaldi et al. (2014)[23]		●
Hertz et al. (2017)[24]		●
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 had 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 had underwent *CYP2D6* genotyping	20,054 (39-4973)	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				
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). 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 first-line tamoxifen therapy	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 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

¥ Median follow-up = 22.9 months.
* Comparison between tamoxifen 40 mg and 20 mg groups with wt/V or V/V genotypes.
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.

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. Clinical context for treatment is unclear; 3. Study population unclear; 4. Study population not representative of intended use; 5. Study population is subpopulation of intended use
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Not CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not presented; 6. Clinically significant difference not supported
[e] Follow-up key: 1. Not sufficient duration for benefits; 2. Not sufficient duration for harms

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 blinded review used to randomly validate outcomes in approximately 28% of patients		6 - 1 patient with progressive disease and 2 patients with inadequate images were excluded from the final analysis		3 - CI/p-value not reported for PFS at 6 months

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. Allocations concealment unclear; 4. Inadequate control for selection bias
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reported; 3. Evidence of selective publication
[d] Follow-up 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)
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference
[f] Statistical key: 1. Test is not appropriate for outcome type: a) continuous; b) binary; c) time to event; 2. Test is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4. Comparative treatment effects not calculated

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.

Observational 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,]

Table 11. Summary of Key Observational Comparative Genotype-Guided Tamoxifen Treatment Study Characteristics

Author (Year)	Study Type	Country/Institution	Dates	Participants	Treatment 1	Treatment 2	Follow-up
Rae et al. 2012; ATAC[43,]	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
Regan et al. 2012; BIG 1-98[44,]	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; ABCSG[21,]	Matched case-control	• Multicenter • Genetic substudy	1996-2009	• Postmenopausal women with ER-positive breast cancer, previously enrolled in RCT	• Arm A: Treated with tam	NA	5 years

	occurred in Austria and United States	• 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	• oxifen for 5 years • Arm B: Treated with tamoxifen for 2 years followed by anastrozole for 3 years	

ABCSG=Austrian Breast and Colorectal Cancer Study Group; ATAC=Arimidex, Tamoxifen, Alone or in Combination trial; BIG=Breast International Group; ER=estrogen receptor; HR=hormone receptor; NA=not applicable; RCT=randomized controlled trial.

Table 12. Summary of Key Observational Comparative 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)*		
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)				

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

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.[59]

Summary of Evidence

For individuals who are treated with tamoxifen for breast cancer or are at high-risk for breast cancer who receive *CYP2D6* genotype-guided tamoxifen treatment, the evidence includes 1 randomized controlled trial (RCT), several meta-analyses and systematic reviews, multiple retrospective and prospective cohort studies, and nonconcurrent prospective studies. Relevant outcomes include OS, disease-specific survival, medication use, and treatment-related morbidity. Published data on the association between *CYP2D6* genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies were derived from a convenience sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data (e.g., concomitant medications), and detailed clinical outcomes data. Three influential nonconcurrent prospective studies nested within large prospective, randomized double-blind, clinical trials in postmenopausal women with hormone receptor-positive early-stage breast cancer also reported contradictory results, with 2 larger studies failing to show statistically significant associations between phenotype (patients classified as poor, intermediate, or extensive metabolizers) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression-free survival between standard dose and increased dose;

however, this trial was limited by its proof of concept design. No trials of genotype-directed drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether *CYP2D6* genotype-guided tamoxifen treatment results in the selection of a treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or OS, or reduce adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information
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.

Clinical Pharmacogenetics Implementation Consortium
In 2018, the Clinical Pharmacogenetics Implementation Consortium issued therapeutic recommendations for tamoxifen prescribing based on CYP2D6 genotype/metabolic phenotype.[60.] 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. 2021) state: "The panel recommends against *CYP2D6* genotype testing for women being considered for tamoxifen treatment."[61.]

American Society of Clinical Oncology
In 2016, the guidelines published by 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."[62.]

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			
NCT03931928	Genotype and Phenotype Guided Supplementation of TAMoxifen Standard Therapy With ENDOXifen in Breast Cancer Patients	750	Dec 202 1
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.

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.
09/01/2021	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 (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.

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:** 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.	**Genotype-Guided Tamoxifen Treatment 2.04.51** **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.