MEDICAL POLICY

POLICY TITLE	GENOTYPE-GUIDED TAMOXIFEN TREATMENT
POLICY NUMBER	MP-2.307

Original Issue Date (Created):	**4/1/2012**
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I. POLICY

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. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital BlueCross when determining medical necessity according to this policy.

POLICY GUIDELINES

Genetics Nomenclature Update

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

The American College of Medical Genetics and Genomics and Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from 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

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Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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

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

Cross-reference:

MP-2.234 Cytochrome p450 Genotype Guided Treatment Strategy

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO-Refer to FEP Medical Policy Manual MP-2.04.51, Genetic Testing for Tamoxifen Treatment. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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 CYP2D6 enzyme. Plasma concentrations of endoxifen exhibit high interindividual variability, as described in breast cancer patients.2 Because CYP2D6 enzyme activity is known to vary across individuals, variants in the CYP2D6 gene are of great interest for understanding tamoxifen metabolism variability and variation in levels of circulating active metabolites. Moreover, known variability in endoxifen levels has been hypothesized to result in variable response to tamoxifen treatment.

Metabolic Enzyme Genotypes

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The CYP2D6 gene exhibits a high degree of polymorphism, with more than 75 100 allelic variants identified. The relations among genotype, phenotype, and clinical implications are summarized in Table 1.

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

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

Adapted from Swen et al (2011).

The prevalence of CYP2D6 poor metabolizers is approximately 7% to 10% in whites of Northern European descent, 1.9% to 7.3% in blacks, and 1% or less in most Asian populations studied. The poor metabolizer phenotype in whites is largely accounted for by CYP2D6*3 and *4 nonfunctional variants, and in black and Asian populations, by the *5 nonfunctional variant. Some poor metabolizers may have 1 nonfunctional allele and 1 reduced-function allele. Among reduced function variants, CYP2D6*17, *10, and *8 are the most important in blacks, Asians, and whites, respectively. Few studies have investigated the frequency of CYP2D6-variant alleles or poor metabolizers in the Hispanic population.

Endocrine Therapy Regimens

Tamoxifen has several labelled indications:

- Chemoprevention of invasive breast cancer in high-risk women without current disease or with ductal carcinoma in situ; **and**
- 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 not indicated for treatment of reduction in the "risk of invasive breast cancer in postmenopausal women with osteoporosis" or those at "high risk for invasive breast cancer"

Pharmacologic Inhibitors of Metabolic Enzymes

CYP2D6 activity may be affected not only by genotype but also by co-administered drugs that block or induce CYP2D6 function. Studies of selective serotonin reuptake inhibitors, in particular, have shown that fluoxetine and paroxetine, but not sertraline, fluvoxamine, or venlafaxine, are potent CYP2D6 inhibitors. Some individuals treated with fluoxetine or paroxetine have changed from extensive metabolizer phenotype to poor metabolizer. The degree of inhibition may depend on selective serotonin reuptake inhibitors dose.

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *CYP2D6* genotyping assays are also available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Several testing kits for CYP450 genotyping cleared for marketing by FDA through the 510(k) process (FDA product code: NTI) are summarized in Table 2.

Table 2. Testing Kits for CYP450 Genotyping Cleared for Marketing by FDA

Device Name	Manufacturer	Approval Date
xTAG CYP2D6 Kit V3	Luminex Molecular Diagnostics	2017
xTAG CYP2C19 Kit V3	Luminex Molecular Diagnostics	2013

Spartan RX CYP2C19 Test System	Spartan Bioscience	2013
xTAG CYP2D6 Kit V3 (including TDAS CYP2D6)	Luminex Molecular Diagnostics	2013
xTAG CYP2D6 Kit V3 (including TDAS CYP2D6)	Luminex Molecular Diagnostics	2013
Verigene CYP2C19 Nucleic Acid Test (CYP2C19)	Nanosphere	2012
Infiniti CYP2C19 Assay	AutoGenomics	2010
xTAG CYP2D6 Kit V3, Model I030C0300	Luminex Molecular Diagnostics	2010
Invader UGT1A1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip CYP450 Test	Roche Molecular Systems	2005

FDA: Food and Drug Administration.

Several manufacturers market diagnostic genotyping panel tests for CYP450 genes, such as the YouScript Panel (Genelex Corp.), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4, and CYP3A5. Other panel tests include both CYP450 and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health) and PersonaGene Genetic Panels (AIBioTech). These panel tests are beyond the scope of this evidence review.

IV. RATIONALE

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Summary of Evidence

For individuals who are treated with tamoxifen for breast cancer or are high risk for breast cancer who receive CYP2D6 genotype-guided tamoxifen treatment, the evidence includes multiple retrospective and prospective cohort studies and nonconcurrent prospective studies. Relevant outcomes include overall survival, disease-specific survival, 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. Data in most of these studies derived from a convenient sample, which was further limited by relatively small numbers of patients and lack of comprehensive genotype data, patient data (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 metabolizer) and recurrence of breast cancer. No trials of genotype-directed dosing or drug choice that compared health outcomes for patients managed with and without the test were identified. It is not known whether CYP2D6 genotype guided tamoxifen treatment results in the selection of a

treatment strategy that would reduce the rate of breast cancer recurrence, improve disease-free survival or overall survival, or reduce adverse events. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS

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GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational, therefore not covered in genetic testing for tamoxifen treatment:

CPT Codes®								
81226	0070U	0071U	0072U	0073U	0074U	0075U	0076U	

IX. REFERENCES

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20. Blue Cross Blue Shield Association Medical Policy Reference Manual.2.04.51, Genotype-Guided Tamoxifen Treatment. August 2020.

X. POLICY HISTORY

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MP-2.307	**CAC 11/22/11** New policy adopting BCBSA. The information related to Tamoxifen treatment was extracted from Cytochrome p450 Genotyping (formerly Drug Metabolism Genetic and Pharmacogenomic Testing) and a separate policy was created. Policy statement unchanged remains investigational.
	07/18/13 Admin update. Coding review completed
	CAC 9/24/13 Consensus review. References update but no changes to the policy statements. Rationale added. FEP variation revised to refer to the FEP policy manual.
	CAC 7/22/14 Consensus review. References and rationale updated. No changes to the policy statements.
	CAC 7/21/15 Consensus review. References and rationale updated. No change to policy statements. Added Medicare variation to reference L33640 Biomarkers Overview. No coding changes.
	11/2/15 Administrative update. LCD number changed from L33640 to L35062 due to Novitas update to ICD-10
	CAC 7/26/16 Consensus review. No change to the policy statement. No new references added. Appendix added. Coding reviewed.
	Admin update 1/1/17. Product variation section reformatted.

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	CAC 9/26/17 Consensus review. Clarification added to the policy statement: cytochrome abbreviation revised and 'women' changed to 'individuals' for a gender neutral policy statement. Policy Guidelines section added. Description/Background, Rationale and Reference sections updated. Coding reviewed.
	1/1/18 Admin Update: Medicare variations removed from Commercial Policies.
	7/12/18 Consensus review. Policy title revised to "Genotype-Guided Tamoxifen Treatment". No change to the policy statement. Background and rationale revised. References updated. Appendix removed.
	5/20/2019 Consensus review. Policy statement unchanged. Tables reformatted. References updated.
	4/30/2020 Consensus review. Policy statement unchanged. Policy Guideline, Background, References, Product Variation, Benefit Variation, and Disclaimer updated. Coding reviewed.
	4/19/2021 Consensus review. Policy statement unchanged. NCCN statement added. References updated. Coding updated, added codes 0070U-0076U.

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