MEDICAL POLICY

POLICY TITLE	GENOTYPE-GUIDED TAMOXIFEN TREATMENT
POLICY NUMBER	MP 2.307

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

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 general 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.

Cross-reference:

MP-2.234 Cytochrome p450 Genotype Guided Treatment Strategy

II. PRODUCT VARIATIONS

TOP

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

FEP PPO - Refer to FEP Medical Policy Manual. 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

TOP

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.

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). 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 inter-individual variability, as described in breast cancer patients. 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 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	Ultra-rapid 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 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.

Endocrine Therapy Regimens

Tamoxifen has several labeled 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 indicated for the reduction in “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 (CLIA). *CYP2D6* genotyping assays are also 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 FDA through the 510(k) process (FDA product code: NTI) are summarized in Table 2.

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

Device Name	Manufacturer	Approval Date
xTAG CYP2D6 Kit V3	Luminex Molecular Diagnostics	2017
xTAG CYP2C19 Kit V3	Luminex Molecular Diagnostics	2013
Spartan RX CYP2C19 Test System	Spartan Bioscience	2013
xTAG CYP2D6 Kit V3 (including TDAS CYP2D6)	Luminex Molecular Diagnostics	2013
Verigene CYP2C19 Nucleic Acid Test (CYP2C19)	Nanosphere	2012
Infiniti CYP2C19 Assay	AutoGenomics	2010
xTAG CYP2D6 Kit V3, Model I030C0300	Luminex Molecular Diagnostics	2010
Invader UGT1A1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip CYP450 Test	Roche Molecular Systems	2005

FDA: Food and Drug Administration

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

IV. RATIONALE

TOP

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 a single randomized controlled trial (RCT), several meta-analyses and systematic reviews, multiple retrospective and prospective cohort studies, and nonconcurrent prospective studies. Relevant outcomes include overall survival, disease-specific survival, medication use, and treatment-related morbidity. Published data on the association between CYP2D6 genotype and tamoxifen treatment outcomes have yielded inconsistent results. Data in most of these studies were 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 metabolizers) and recurrence of breast cancer. The RCT examining genotype-directed dosing found no difference in progression-free survival between a 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 overall survival, or reduce adverse events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

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

TOP

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

TOP

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

TOP

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:

Procedure Codes								
81226	0070U	0071U	0072U	0073U	0074U	0075U	0076U	

IX. REFERENCES

TOP

1. *Goetz MP, Kamal A, Ames MM. Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. Clin Pharmacol Ther. Jan 2008; 83(1): 160-6. PMID 17882159*
2. *Stearns V, Johnson MD, Rae JM, et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst. Dec 03, 2003; 95(23): 1758-64. PMID 14652237*
3. *Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther. May 2011; 89(5): 662-73. PMID 21412232*
4. *Bernard S, Neville KA, Nguyen AT, et al. Interethnic differences in genetic polymorphisms of CYP2D6 in the U.S. population: clinical implications. Oncologist. Feb 2006; 11(2): 126-35. PMID 16476833*
5. *Drugs.com. Tamoxifen. 2017*
6. *Eli Lilly. Highlights from Prescribing Information: Evista (raloxifene hydrochloride) tablet for oral use. 2018*
7. *Alfaro CL, Lam YW, Simpson J, et al. CYP2D6 status of extensive metabolizers after multiple-dose fluoxetine, fluvoxamine, paroxetine, or sertraline. J Clin Psychopharmacol. Apr 1999; 19(2): 155-63. PMID 10211917*
8. *Alfaro CL, Lam YW, Simpson J, et al. CYP2D6 inhibition by fluoxetine, paroxetine, sertraline, and venlafaxine in a crossover study: intraindividual variability and plasma concentration correlations. J Clin Pharmacol. Jan 2000; 40(1): 58-66. PMID 10631623*
9. *Lam YW, Gaedigk A, Ereshefsky L, et al. CYP2D6 inhibition by selective serotonin reuptake inhibitors: analysis of achievable steady-state plasma concentrations and the effect of ultrarapid metabolism at CYP2D6. Pharmacotherapy. Aug 2002; 22(8): 1001-6. PMID 12173784*
10. *Ahern TP, Hertz DL, Damkier P, et al. Cytochrome P-450 2D6 (CYP2D6) Genotype and Breast Cancer Recurrence in Tamoxifen-Treated Patients: Evaluating the Importance of Loss of Heterozygosity. Am J Epidemiol. Jan 15, 2017; 185(2): 75-85. PMID 27988492*
11. *Drogemoller BI, Wright GEB, Shih J, et al. CYP2D6 as a treatment decision aid for ER-positive non-metastatic breast cancer patients: a systematic review with accompanying clinical practice guidelines. Breast Cancer Res Treat. Feb 2019; 173(3): 521-532. PMID 30411242*
12. *Abraham JE, Maranian MJ, Driver KE, et al. CYP2D6 gene variants: association with breast cancer specific survival in a cohort of breast cancer patients from the United Kingdom treated with adjuvant tamoxifen. Breast Cancer Res. 2010; 12(4): R64. PMID 20731819*
13. *Abreu MH, Gomes M, Menezes F, et al. CYP2D6*4 polymorphism: A new marker of response to hormonotherapy in male breast cancer? Breast. Aug 2015; 24(4): 481-6. PMID 25963137*
14. *Bijl MJ, van Schaik RH, Lammers LA, et al. The CYP2D6*4 polymorphism affects breast cancer survival in tamoxifen users. Breast Cancer Res Treat. Nov 2009; 118(1): 125-30. PMID 19189212*
15. *Brooks JD, Teraoka SN, Malone KE, et al. Variants in tamoxifen metabolizing genes: a case-control study of contralateral breast cancer risk in the WECARE study. Int J Mol Epidemiol Genet. 2013; 4(1): 35-48. PMID 23565321*

16. *Chamnanphon M, Pechatanan K, Sirachainan E, et al. Association of CYP2D6 and CYP2C19 polymorphisms and disease-free survival of Thai post-menopausal breast cancer patients who received adjuvant tamoxifen. Pharmgenomics Pers Med. 2013; 6: 37-48. PMID 23776391*
17. *Damodaran SE, Pradhan SC, Umamaheswaran G, et al. Genetic polymorphisms of CYP2D6 increase the risk for recurrence of breast cancer in patients receiving tamoxifen as an adjuvant therapy. Cancer Chemother Pharmacol. Jul 2012; 70(1): 75-81. PMID 22623212*
18. *De Ameida Melo M, De Vasconcelos-Valenca RJ, Neto FM, et al. CYP2D6 gene polymorphisms in Brazilian patients with breast cancer treated with adjuvant tamoxifen and its association with disease recurrence. Biomed Rep. Nov 2016; 5(5): 574-578. PMID 27882219*
19. *Dezentje VO, van Schaik RH, Vletter-Bogaartz JM, et al. CYP2D6 genotype in relation to tamoxifen efficacy in a Dutch cohort of the tamoxifen exemestane adjuvant multinational (TEAM) trial. Breast Cancer Res Treat. Jul 2013; 140(2): 363-73. PMID 23842856*
20. *Goetz MP, Rae JM, Suman VJ, et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol. Dec 20, 2005; 23(36): 9312-8. PMID 16361630*
21. *Goetz MP, Suman VJ, Hoskin TL, et al. CYP2D6 metabolism and patient outcome in the Austrian Breast and Colorectal Cancer Study Group trial (ABCSG) 8. Clin Cancer Res. Jan 15, 2013; 19(2): 500-7. PMID 23213055*
22. *Gor PP, Su HI, Gray RJ, et al. Cyclophosphamide-metabolizing enzyme polymorphisms and survival outcomes after adjuvant chemotherapy for node-positive breast cancer: a retrospective cohort study. Breast Cancer Res. 2010; 12(3): R26. PMID 20459744*
23. *Gunaldi M, Eriksi M, Afsar C, et al. Evaluation of CYP2D6 Polymorphic Types and Their Effect on Tamoxifen Efficacy Among Turkish Tamoxifen Users with Breast Cancer. International Journal of Hematology and Oncology. 2014;3(24):157-62.*
24. *Hertz DL, Kidwell KM, Hilsenbeck SG, et al. CYP2D6 genotype is not associated with survival in breast cancer patients treated with tamoxifen: results from a population-based study. Breast Cancer Res Treat. Nov 2017; 166(1): 277-287. PMID 28730340*
25. *Johansson H, Gandini S, Serrano D, et al. A pooled analysis of CYP2D6 genotype in breast cancer prevention trials of low-dose tamoxifen. Breast Cancer Res Treat. Aug 2016; 159(1): 97-108. PMID 27484880*
26. *Karle J, Bolbrinker J, Vogl S, et al. Influence of CYP2D6-genotype on tamoxifen efficacy in advanced breast cancer. Breast Cancer Res Treat. Jun 2013; 139(2): 553-60. PMID 23686417*
27. *Kiyotani K, Mushiroda T, Imamura CK, et al. Significant effect of polymorphisms in CYP2D6 and ABCC2 on clinical outcomes of adjuvant tamoxifen therapy for breast cancer patients. J Clin Oncol. Mar 10, 2010; 28(8): 1287-93. PMID 20124171*
28. *Kiyotani K, Mushiroda T, Hosono N, et al. Lessons for pharmacogenomics studies: association study between CYP2D6 genotype and tamoxifen response. Pharmacogenet Genomics. Sep 2010; 20(9): 565-8. PMID 20574415*
29. *Lammers LA, Mathijssen RH, van Gelder T, et al. The impact of CYP2D6-predicted phenotype on tamoxifen treatment outcome in patients with metastatic breast cancer. Br J Cancer. Sep 07, 2010; 103(6): 765-71. PMID 20700120*

30. *Lash TL, Cronin-Fenton D, Ahern TP, et al. CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark. J Natl Cancer Inst. Mar 16, 2011; 103(6): 489-500. PMID 21325141*
31. *Lei L, Wang X, Wu XD, et al. Association of CYP2D6*10 (c.100C T) polymorphisms with clinical outcome of breast cancer after tamoxifen adjuvant endocrine therapy in Chinese population. Am J Transl Res. 2016; 8(8): 3585-92. PMID 27648149*
32. *Margolin S, Lindh JD, Thoren L, et al. CYP2D6 and adjuvant tamoxifen: possible differences of outcome in pre- and post-menopausal patients. Pharmacogenomics. Apr 2013; 14(6): 613-22. PMID 23570465*
33. *Markkula A, Hjertberg M, Rose C, et al. No association found between CYP2D6 genotype and early breast cancer events in tamoxifen-treated patients. Acta Oncol. Feb 2014; 53(2): 195-200. PMID 24125101*
34. *Martins DM, Vidal FC, Souza RD, et al. Determination of CYP2D6 *3, *4, and *10 frequency in women with breast cancer in Sao Luis, Brazil, and its association with prognostic factors and disease-free survival. Braz J Med Biol Res. Nov 2014; 47(11): 1008-15. PMID 25296365*
35. *Morrow PK, Serna R, Broglio K, et al. Effect of CYP2D6 polymorphisms on breast cancer recurrence. Cancer. Mar 01, 2012; 118(5): 1221-7. PMID 21823108*
36. *Mwinyi J, Vokinger K, Jetter A, et al. Impact of variable CYP genotypes on breast cancer relapse in patients undergoing adjuvant tamoxifen therapy. Cancer Chemother Pharmacol. Jun 2014; 73(6): 1181-8. PMID 24682508*
37. *Newman WG, Hadfield KD, Latif A, et al. Impaired tamoxifen metabolism reduces survival in familial breast cancer patients. Clin Cancer Res. Sep 15, 2008; 14(18): 5913-8. PMID 18794105*
38. *Nowell SA, Ahn J, Rae JM, et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat. Jun 2005; 91(3): 249-58. PMID 15952058*
39. *Okishiro M, Taguchi T, Jin Kim S, et al. Genetic polymorphisms of CYP2D6 10 and CYP2C19 2, 3 are not associated with prognosis, endometrial thickness, or bone mineral density in Japanese breast cancer patients treated with adjuvant tamoxifen. Cancer. Mar 01, 2009; 115(5): 952-61. PMID 19156902*
40. *Park HS, Choi JY, Lee MJ, et al. Association between genetic polymorphisms of CYP2D6 and outcomes in breast cancer patients with tamoxifen treatment. J Korean Med Sci. Aug 2011; 26(8): 1007-13. PMID 21860550*
41. *Park IH, Ro J, Park S, et al. Lack of any association between functionally significant CYP2D6 polymorphisms and clinical outcomes in early breast cancer patients receiving adjuvant tamoxifen treatment. Breast Cancer Res Treat. Jan 2012; 131(2): 455-61. PMID 21437611*
42. *Province MA, Goetz MP, Brauch H, et al. CYP2D6 genotype and adjuvant tamoxifen: meta-analysis of heterogeneous study populations. Clin Pharmacol Ther. Feb 2014; 95(2): 216-27. PMID 24060820*
43. *Rae JM, Drury S, Hayes DF, et al. CYP2D6 and UGT2B7 genotype and risk of recurrence in tamoxifen-treated breast cancer patients. J Natl Cancer Inst. Mar 21, 2012; 104(6): 452-60. PMID 22395643*

44. *Regan MM, Leyland-Jones B, Bouzyk M, et al. CYP2D6 genotype and tamoxifen response in postmenopausal women with endocrine-responsive breast cancer: the breast international group 1-98 trial. J Natl Cancer Inst. Mar 21, 2012; 104(6): 441-51. PMID 22395644*
45. *Schroth W, Antoniadou L, Fritz P, et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol. Nov 20, 2007; 25(33): 5187-93. PMID 18024866*
46. *Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early-stage breast cancer treated with tamoxifen. JAMA. Oct 07, 2009; 302(13): 1429-36. PMID 19809024*
47. *Sirachainan E, Jaruhathai S, Trachu N, et al. CYP2D6 polymorphisms influence the efficacy of adjuvant tamoxifen in Thai breast cancer patients. Pharmgenomics Pers Med. 2012; 5: 149-53. PMID 23226070*
48. *Stingl JC, Parmar S, Huber-Wechselberger A, et al. Impact of CYP2D6*4 genotype on progression free survival in tamoxifen breast cancer treatment. Curr Med Res Opin. Nov 2010; 26(11): 2535-42. PMID 20849243*
49. *Sukasem C, Sirachainan E, Chamnanphon M, et al. Impact of CYP2D6 polymorphisms on tamoxifen responses of women with breast cancer: a microarray-based study in Thailand. Asian Pac J Cancer Prev. 2012; 13(9): 4549-53. PMID 23167378*
50. *Teh LK, Mohamed NI, Salleh MZ, et al. The risk of recurrence in breast cancer patients treated with tamoxifen: polymorphisms of CYP2D6 and ABCB1. AAPS J. Mar 2012; 14(1): 52-9. PMID 22183189*
51. *Thompson AM, Johnson A, Quinlan P, et al. Comprehensive CYP2D6 genotype and adherence affect outcome in breast cancer patients treated with tamoxifen monotherapy. Breast Cancer Res Treat. Jan 2011; 125(1): 279-87. PMID 20809362*
52. *Toyama T, Yamashita H, Sugiura H, et al. No association between CYP2D6*10 genotype and survival of node-negative Japanese breast cancer patients receiving adjuvant tamoxifen treatment. Jpn J Clin Oncol. Oct 2009; 39(10): 651-6. PMID 19596663*
53. *Wegman P, Vainikka L, Stal O, et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res. 2005; 7(3): R284-90. PMID 15987423*
54. *Wegman P, Elingarami S, Carstensen J, et al. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res. 2007; 9(1): R7. PMID 17244352*
55. *Xu Y, Sun Y, Yao L, et al. Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol. Aug 2008; 19(8): 1423-1429. PMID 18407954*
56. *Yazdi MF, Rafieian S, Gholi-Nataj M, et al. CYP2D6 Genotype and Risk of Recurrence in Tamoxifen Treated Breast Cancer Patients. Asian Pac J Cancer Prev. 2015; 16(15): 6783-7. PMID 26434912*
57. *Tamura K, Imamura CK, Takano T, et al. CYP2D6 Genotype-Guided Tamoxifen Dosing in Hormone Receptor-Positive Metastatic Breast Cancer (TARGET-1): A Randomized, Open-Label, Phase II Study. J Clin Oncol. Feb 20, 2020; 38(6): 558-566. PMID 31821071*

58. Ruddy KJ, Desantis SD, Gelman RS, et al. Personalized medicine in breast cancer: tamoxifen, endoxifen, and CYP2D6 in clinical practice. Breast Cancer Res Treat. Oct 2013; 141(3): 421-7. PMID 24062210

59. Blancas I, Linares-Rodríguez M, Martínez de Dueñas E, et al. Early increase in tamoxifen dose in CYP2D6 poor metaboliser breast cancer patients and survival: A propensity score matching analysis. Breast. Jun 2023; 69: 342-348. PMID 37011481

60. Goetz MP, Ratain M, Ingle JN. Providing Balance in ASCO Clinical Practice Guidelines: CYP2D6 Genotyping and Tamoxifen Efficacy. J Clin Oncol. Nov 10, 2016; 34(32): 3944-3945. PMID 27551126

61. Harris LN, Ismaila N, McShane LM, et al. Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women With Early-Stage Invasive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. Apr 01, 2016; 34(10): 1134-50. PMID 26858339

62. Andre F, Ismaila N, Allison KH, et al. Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer: ASCO Guideline Update. J Clin Oncol. Jun 01 2022; 40(16): 1816-1837. PMID 35439025

63. Goetz MP, Sangkuhl K, Guchelaar HJ, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and Tamoxifen Therapy. Clin Pharmacol Ther. May 2018; 103(5): 770-777. PMID 29385237

64. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: breast cancer. Version 4.2023

20. Blue Cross Blue Shield Association Medical Policy Reference Manual.2.04.51, Genotype-Guided Tamoxifen Treatment. August 2023

X. POLICY HISTORY

TOP

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.

POLICY TITLE	GENOTYPE-GUIDED TAMOXIFEN TREATMENT
POLICY NUMBER	MP 2.307

	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.
	08/04/2022 Consensus review. No change to policy statement. Policy Variation, Rationale and References updated.
	08/24/2023 Consensus review. No change to policy statement. References updated.
	1/19/2024 Administrative update. Clinical benefit added.

TOP