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Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and Tamoxifen Therapy

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Abstract

Tamoxifen is biotransformed by CYP2D6 to 4-hydroxytamoxifen and 4-hydroxy N-desmethyl tamoxifen (endoxifen), both with greater anti-estrogenic potency than the parent drug. Patients with certain *CYP2D6* genetic polymorphisms and patients who receive strong CYP2D6 inhibitors exhibit lower endoxifen concentrations and a higher risk of disease recurrence in some studies of tamoxifen adjuvant therapy of early breast cancer. We summarize evidence from the literature and provide therapeutic recommendations for tamoxifen based on *CYP2D6* genotype.

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CONFLICT OF INTEREST

A.G. is a paid consultant of Millennium Health.

INTRODUCTION

The purpose of this guideline is to provide clinicians information that will allow the interpretation of clinical *CYP2D6* genotype tests so that the results can be used to guide prescribing of tamoxifen. Detailed guidelines for use of tamoxifen as well as analyses of cost effectiveness are beyond the scope of this document. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at www.cpicpgx.org/guidelines/.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6* genotype and tamoxifen use (details in Supplement) was conducted.

GENE: *CYP2D6*

CYP2D6 is highly polymorphic with over 100 known allelic variants and subvariants identified (https://www.pharmvar.org/gene/CYP2D6); ***CYP2D6* Allele Definition Table** (1)). *CYP2D6* alleles have been extensively studied in multiple geographically, racially, and ethnically diverse groups and significant differences in allele frequencies have been observed (***CYP2D6* Frequency Table** (1)). The most commonly reported alleles are categorized into functional groups as follows: Normal function (e.g., *CYP2D6*1* and **2*), decreased function (e.g., *CYP2D6*9*, **10*, *17, and **41*), and no function (e.g., *CYP2D6*3, *4, *5, *6*) (2, 3). Because *CYP2D6* is subject to gene deletions, duplications or multiplications, many clinical laboratories also report copy number variations. *CYP2D6*5* represents a gene deletion (no function allele) whereas gene duplications and multiplications are denoted by "xN" (e.g. *CYP2D6*1xN* with xN representing the number of *CYP2D6* gene copies). Alleles carrying two or more normal function gene copies are categorized as alleles with increased function.

The combination of alleles is used to determine a patient's diplotype (Table 1). Each functional status is assigned an activity value ranging from 0 to 1 (e.g. 0 for no function, 0.5 for decreased and 1.0 for normal function) (3). Table S1 describes the activity score values assigned to selected alleles. If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the *CYP2D6* activity score that is used to define CYP2D6 phenotype is the sum of the values assigned to each allele, which typically ranges from 0 to 3.0 but may exceed 3.0 in rare cases (3). See the ***CYP2D6* Diplotype-Phenotype Table** (1) for a complete list of possible diplotypes and phenotype assignment.

The CYP2D6 activity score has been translated into the phenotype classification system for other CPIC guidelines (4, 5) as follows (***CYP2D6* Allele Definition Table** (1)): patients with an activity score (AS) of 0 are poor metabolizers (PMs), those with a score of 0.5 are considered intermediate metabolizers (IMs), and those with a score of 1.5 or 2.0 represent normal metabolizers (NMs). Patients with a score >2.0 are classified as ultrarapid metabolizers (UMs). However, the activity score of 1.0 has less activity towards tamoxifen compared to those with an AS of 1. 5 or 2.0 and patients with an activity score of 1.0 may be

classified as IMs by some reference laboratories. Thus, for this guideline, an activity score of 1.0 is classified as a CYP2D6 normal metabolizer or intermediate metabolizer, (Table 1). This is in contrast to the classification used in previous guidelines (4, 5). A group of *CYP2D6* experts are currently working to standardize the *CYP2D6* genotype to phenotype translation system. Note that genotypes with an activity score of 1 are classified as NMs in the ***CYP2D6* Genotype to Phenotype Table** (1) and CPIC will update the CPIC website and this table accordingly when the CYP2D6 genotype to phenotype standardization is complete (6). Because reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes, it is advisable to note a patient's *CYP2D6* diplotype and to calculate an activity score before making therapeutic decisions about tamoxifen therapy.

Genetic Test Interpretation

Clinical laboratories rarely sequence the entire *CYP2D6* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine high frequency allele haplotypes using the star-allele (*) nomenclature system, found at the Pharmacogene Variation Consortium website (http://www.PharmVar.org). Table S1 and tables found on the CPIC and PharmGKB website contain a list of *CYP2D6* alleles, the specific combination of variants that can be used to determine the allele, functional status, and frequency across major ethnic populations as reported in the literature (1, 6).

The limitations of genetic testing as described here include: (1) rare variants may not be detected; (2) known star (*) alleles not tested for will not be reported, and instead, the allele will be reported as a **1* and **3* tests are not designed to detect unknown or *de novo* variants. The Supplemental Material (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

Available Genetic Test Options

See Supplemental Material and www.ncbi.nlm.nih.gov/gtr/ for more information on commercially available clinical testing options.

Incidental findings

Currently, there are no diseases or conditions that have been consistently linked to variation in the *CYP2D6* gene independently of drug metabolism and response.

Other considerations

Chromosomal instability, i.e. loss of heterozygosity, is frequently observed in breast tumor tissue (7, 8). Genotype information derived from such tissue may therefore not accurately reflect the germline genotype that determines CYP2D6 activity in the liver where tamoxifen is metabolized. We therefore strongly recommend genotype testing be performed on non-tumor DNA isolated from a peripheral blood, or a saliva/buccal swab sample.

DRUG: TAMOXIFEN

Background

About 65–75% of breast cancer expresses estrogen receptors (ER) or progesterone receptors (PR) (9). In this group of patients, endocrine therapy represents the most important treatment modality. Tamoxifen, a selective estrogen receptor modulator (SERM), has been studied and utilized in breast cancer for more than 40 years. When administered to women with ER-positive breast cancer for five years after surgery, tamoxifen almost halves the annual recurrence rate and reduces the breast cancer mortality rate by one-third in both pre- and post-menopausal women (10). While tamoxifen has multiple Food and Drug Administration (FDA) approvals for both the prevention and treatment of premenopausal and postmenopausal breast cancer, tamoxifen's continued importance is reflected by its status as the only hormonal agent approved by the FDA for the prevention of premenopausal breast cancer, the treatment of ductal carcinoma *in situ*, and the adjuvant and metastatic treatment of premenopausal invasive breast cancer.

The pharmacology of tamoxifen is complex. Tamoxifen is a weak anti-estrogen that is extensively metabolized, and its metabolites exhibit similar, less, or more potent anti-estrogenic activity (11, 12). Furthermore, tamoxifen can exhibit either antiestrogenic or pro-estrogenic properties, depending on the target tissue and the presence or absence of co-activators or co-repressors (13, 14).

Tamoxifen undergoes extensive primary and secondary liver metabolism by cytochrome P450 enzymes via two major pathways: N-demethylation and 4-hydroxylation (Figure 1). The predominant metabolic pathway (considered to contribute to over 90% of tamoxifen metabolism) is the demethylation of tamoxifen to N-desmethyltamoxifen primarily mediated by CYP3A4 (15), followed by CYP2D6-mediated oxidation to 4-hydroxy-N-desmethyltamoxifen (endoxifen) (16). A minor metabolic pathway is hydroxylation of tamoxifen (mediated mainly by CYP2D6 but also catalyzed by CYP3A4 and CYP2C19) to 4-hydroxytamoxifen (4HT), which can then be further metabolized to endoxifen (17, 18). While tamoxifen and its metabolites undergo glucuronidation and sulfation, no consistent effect of pharmacogenetic variation in any of the UGT or SULT isoforms on either tamoxifen pharmacokinetics or clinical outcomes has been observed to date.

The hydroxylation of either tamoxifen or N-desmtheyltamoxifen is considered to bioactivate tamoxifen. Both 4HT and endoxifen exhibit nearly 100-fold greater anti-estrogenic potency than the parent drug (11, 19–24). Maximum inhibition of estrogen-induced stimulation and ER transcription is achieved with endoxifen concentrations of ranging between 100–1000 nM (11). However, even low Z-endoxifen levels were necessary to block estrogen-mediated cell growth in models mimicking estrogen concentrations of pre- or postmenopausal women that were treated with tamoxifen and its metabolites (25, 26).

Both inter- and intra-individual variation in the concentration of tamoxifen and its metabolites have been described (16, 22, 27–29). As it relates to the active metabolites, 4HT concentrations are low, typically <5 nM (17, 22) and the role of interpatient variability in 4HT as it relates to breast cancer outcomes is not well understood. In contrast, endoxifen

plasma concentrations are up to 10 fold higher than 4HT, exhibiting substantial variability (17, 22, 30). Patients with low CYP2D6 enzyme activity, as a result of *CYP2D6* genetic polymorphisms or the co-administration of strong CYP2D6 inhibitors, exhibit significantly lower endoxifen concentrations when treated with tamoxifen (22, 31).

Clinical studies to evaluate the association between endoxifen concentrations and *CYP2D6* polymorphisms with tamoxifen outcome have yielded conflicting results. Initial (32) and follow-up data (33, 34) demonstrated that CYP2D6 PMs had an approximately two- to three-fold higher risk of breast cancer recurrence (compared to CYP2D6 NMs) and led an FDA special emphasis panel to recommend a tamoxifen label change to incorporate data that *CYP2D6* genotype was an important biomarker associated with tamoxifen efficacy (35). However, this label change was not implemented because of conflicting data from secondary analyses of 5 year tamoxifen prospective trials including ATAC (36), BIG1-98 (37), and ABCSG 8 (38). Multiple other studies were summarized in a meta-analysis that demonstrated an association between *CYP2D6* genotype and disease-free survival but only in patients that received tamoxifen as adjuvant therapy at a dose of 20 mg/day for five years (39).

Regarding the role of measurement of endoxifen concentrations, Madlensky *et al* identified an association between low endoxifen (lowest quintile) and recurrence (40). In a separate study of premenopausal patients, Saldores *et al* demonstrated similar findings that patients with low endoxifen concentrations (<14 nM) exhibited a higher risk for distant relapse or death compared with those with high concentrations (>35 nM) (41).

Given these conflicting data, a working group within CPIC was convened to review and summarize the strength of the data and to provide therapeutic recommendations for those patients in which *CYP2D6* genotype is known and for whom adjuvant tamoxifen is recommended.

Linking genetic variability to variability in drug-related phenotypes

Endoxifen concentrations—There is substantial evidence linking *CYP2D6* genotype with phenotypic variability in endoxifen concentrations. As outlined in Table S2, the evidence was considered uniformly strong that CYP2D6 PMs (AS=0) have lower plasma endoxifen concentrations among patients taking adjuvant tamoxifen compared to CYP2D6 NMs, and that reduced CYP2D6 activity (AS=0 to 1) is associated with lower plasma endoxifen concentrations among patients taking adjuvant tamoxifen compared to normal CYP2D6 activity. *CYP2D6* genotype explains 34–52% of the variability in absolute endoxifen concentrations (31). Of particular note, for populations with a high frequency of the decreased function *CYP2D6*10* allele, there was strong evidence that patients with CYP2D6 activity scores of 0 to 1 had significantly lower plasma endoxifen concentrations compared to those with normal CYP2D6 activity (AS=1.5 and 2).

Pharmacodynamic markers (Ki–67)—One prospective clinical study examined the association between *CYP2D6* genotype and change in tumor Ki-67, a phenotype linked to drug efficacy, in patients with early stage breast cancer receiving neoadjuvant tamoxifen. In

this study, patients with *CYP2D6*10/*10* and *CYP2D6*5/*10* genotypes had significantly lower Ki-67 response compared to patients genotyped as *CYP2D6*1/*1* (42).

Breast cancer recurrence and survival—Because of the extensive biological variability across the various clinical settings where tamoxifen is administered (prevention, ductal carcinoma in situ, premenopausal and postmenopausal adjuvant setting, and metastatic), the current CPIC guidelines focuses only on the role of *CYP2D6* genotype in the adjuvant treatment of ER+ breast cancer, using the endpoints of recurrence, recurrence-free survival, disease-free survival, distant relapse-free survival, breast cancer specific survival, and overall survival. The body of evidence for each of these clinical endpoints is summarized in Table S2. For the clinical endpoints of recurrence and event free-survival, the evidence was graded as moderate for the statements that CYP2D6 PMs (AS=0) have a higher risk of recurrence or worse event free survival. However, for the comparison of other metabolizer groups (IM, NM, and UM) and other clinical endpoints, the evidence was considered weak regarding an association between CYP2D6 metabolizer groups and clinical outcome (Table S2).

Therapeutic Recommendations

Table 2 summarizes the therapeutic recommendations for tamoxifen prescribing based on CYP2D6 phenotype. Based on current evidence (Table S2), CYP2D6 UMs and NMs are expected to achieve therapeutic endoxifen concentrations after administration of tamoxifen and should receive the recommended standard of care doses of tamoxifen. CYP2D6 PMs and IMs (including patients with an activity score of 1.0, see Supplement) are expected to have lower endoxifen concentrations compared to NMs and have a higher risk of breast cancer recurrence, and worse event-free survival compared to NMs. For CYP2D6 PMs, a “strong” therapeutic recommendation was provided to recommend alternative hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype (43, 44) and based on knowledge that CYP2D6 PMs patients who switch from tamoxifen to anastrozole do not exhibit an increased risk of recurrence (38). Given that escalation of tamoxifen dose from 20–40 mg/day in CYP2D6 PM significantly increases endoxifen concentrations (but not to concentrations achieved in CYP2D6 NMs (45)), the use of an aromatase inhibitor (+/− ovarian function suppression) is recommended in this setting. Tamoxifen 40 mg/day can be considered for CYP2D6 PM if there are contraindications to AI use. There are no clinical data that toremifene, another selective estrogen receptor modulator that also undergoes bioactivation (46), should be substituted for tamoxifen based on *CYP2D6* genotype.

For CYP2D6 IMs and *CYP2D6*10/*10* or *CYP2D6*10*/decreased function allele, a “moderate” recommendation was made to consider use of an alternative hormonal therapy (i.e. aromatase inhibitor) for postmenopausal women or aromatase inhibitor plus ovarian function suppression in premenopausal women is recommended. In CYP2D6 IMs, if aromatase inhibitors are contraindicated, consideration can be given for the use of a higher FDA-approved dose of tamoxifen (40 mg/day), which is known to result in significantly higher endoxifen concentrations without an increase in toxicity (45). Based on extrapolation

from evidence in *10 individuals, a similar recommendation applies to individuals who carry other decreased function alleles resulting in an activity score of 1.0 but with an “optional” recommendation, given the paucity of data for this group.

In general, prolonged overlap of tamoxifen with strong and moderate CYP2D6 inhibitors should be avoided in tamoxifen-treated patients (47), whereas weak inhibitors are also contraindicated in CYP2D6 IMs.

Recommendations for Incidental Findings

Not applicable

Other considerations

Pharmacogenetic variation in other cytochrome P450 genes such as *CYP2C9* and *CYP3A4* or *CYP3A5* is associated with a small effect on plasma concentrations of both 4HT and endoxifen with unclear effects on clinical efficacy of tamoxifen. *CYP2C19* genotype has also been associated with therapy outcome, where IMs and PMs showed an increased survival (HR 0.70), and direct effects on endoxifen plasma concentrations were described (48–51). Possibly, there is also an increase in tamoxifen drug concentrations, as recently suggested (52). While a meta-analysis demonstrated an association between *CYP2C19* genotype and increased survival in tamoxifen treated breast cancer patients (53), an analysis of the International Tamoxifen Consortium dataset failed to find this correlation (54), leaving the clinical role of *CYP2C19* genotyping for tamoxifen therapy unclear at the moment.

Implementation of this guideline—The guideline supplement contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* sections of Supplement and the CPIC website (6)).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of using *CYP2D6* genotype to guide tamoxifen use is that patients with genotypes that are associated with a higher risk of breast cancer recurrence, event-free survival (e.g., CYP2D6 IMs and PMs) may be identified and alternative doses (e.g. 40 mg) and agents administered. Given that the alternative drug treatments (aromatase inhibitors either with or without ovarian function suppression) have been demonstrated to be superior to tamoxifen (44, 43), and that CYP2D6 PMs switched from tamoxifen to anastrozole do not exhibit an increased risk of recurrence (38), it is expected the risks to use *CYP2D6* genotyping to guide hormonal treatment would be low. Further research is necessary, however, to determine whether *CYP2D6* genotypes associated with therapeutic endoxifen concentrations (e.g., NMs and UMs) should be preferentially maintained on tamoxifen. As with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, along with the presence of a rare genomic variant not tested for, which could have long-term adverse health implications for patients.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2D6* variants may not be included in the genotype test used and patients with rare variants may be assigned a "wild-type" (*CYP2D6*1*) genotype by default. Thus, an assigned “wild-type” allele could potentially harbor a no or decreased function variant. Therefore, it is important that test reports do include information on which variant alleles were tested. Furthermore, it is important that the genetic testing platform includes testing for gene copy number.

Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider when making their therapeutic choice for each patient. For example, for the treatment of ER+ breast cancer, there are well accepted tumor somatic factors that drive endocrine response, including the tumor expression of ER, PR and HER2 expression, and other multigene assays which are associated with endocrine sensitivity (55). Although there are very few data, the implication of reduced CYP2D6 metabolism in patients with low risk breast cancer (e.g., early stage breast cancer where the risk of distant recurrence is low) may be substantially different than in patients with later stage disease with a much higher risk of distant recurrence.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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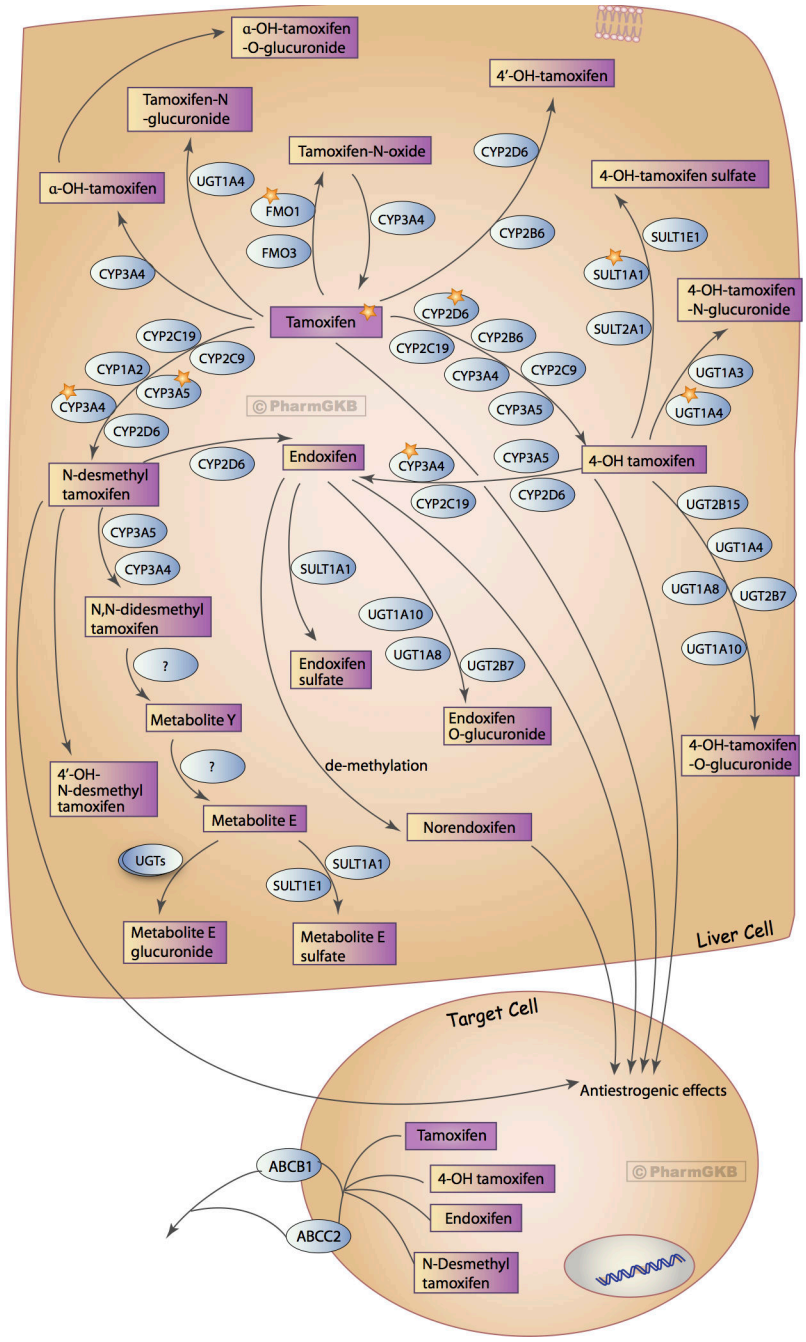

Figure 1.

Tamoxifen Pathway, Pharmacokinetics (57). Permission has been given by PharmGKB and Stanford to use figure.

Table 1

Assignment of Likely Phenotypes Based on Diplotypes

Phenotype[a]		**Genotype**	**Examples of *CYP2D6* diplotypes**[b]
Metabolizer	**Activity Score**		
CYP2D6 Ultrarapid metabolizer	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[c]
CYP2D6 Normal metabolizer	1.5 and 2.0	An individual carrying two normal function alleles or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*9, *1/*41, *2/*2,*
CYP2D6 Normal metabolizeror Intermediate metabolizer (controversy remains)[d]	1.0	An individual carrying two decreased function alleles or one normal function and one no function allele. *An activity score (AS) of 1.0 is associated with decreased tamoxifen metabolism to endoxifen compared to those with an AS of 1.5 or 2.*	**1/*4, *1/*5, *41/*41*
CYP2D6 Intermediate metabolizer	0.5	An individual carrying one decreased function and one no function allele	**4/*10,*4/*41, *5/*9*
CYP2D6 Poor metabolizer	0	An individual carrying only no functional alleles	**3/*4,*4/*4, *5/*5, *5/*6*

[a] See the ***CYP2D6* frequency table** (1) for race-specific allele and phenotype frequencies.

[b] For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the ***CYP2D6* genotype to phenotype table** (1, 6). Note that genotypes with an activity score of 1 are classified as NMs in the online *CYP2D6* genotype to phenotype table.

[c] Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes.

[d] Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. A group of CYP2D6 experts are currently working to standardize the *CYP2D6* genotype to phenotype translation system. CPIC will update the CPIC website accordingly (***CYP2D6* genotype to phenotype table** (1, 6)).

Table 2

Dosing Recommendations for tamoxifen based on *CYP2D6* phenotype

Phenotype		**Implications**	**Therapeutic Recommendation**[b]	**Classification of Recommendation**[a]
Metabolizer Status	**Activity Score**			
CYP2D6 Ultrarapid metabolizer	>2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 Normal metabolizer	1.5 to 2.0	Therapeutic endoxifen concentrations	Avoid moderate and strong CYP2D6 inhibitors. Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day).	Strong
CYP2D6 Normal metabolizeror Intermediate metabolizer (controversy remains)[b]	1.0 (no *10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype (43). If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day)(45). Avoid CYP2D6 strong to weak inhibitors.	Optional[b]
CYP2D6 Normal metabolizeror Intermediate metabolizer (controversy remains)[b]	1.0 (*10 allele present)[b]	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype (43). If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day)(45). Avoid CYP2D6 strong to weak inhibitors.	Moderate[b]
CYP2D6 Intermediate metabolizer	0.5	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence-free survival compared to normal metabolizers.	Consider hormonal therapy such as an aromatase inhibitor for postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women, given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype (43). If aromatase inhibitor use is contraindicated, consideration should be given to use a higher but FDA approved tamoxifen dose (40 mg/day)(45). Avoid CYP2D6 strong to weak inhibitors.	Moderate
CYP2D6 Poor metabolizer	0	Lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer	Recommend alternative hormonal therapy such as an aromatase inhibitor for	Strong

Phenotype		Implications	Therapeutic Recommendation[b]	Classification of Recommendation[a]
Metabolizer Status	**Activity Score**			
		recurrence, event-free and recurrence-free survival compared to normal metabolizers.	postmenopausal women or aromatase inhibitor along with ovarian function suppression in premenopausal women given that these approaches are superior to tamoxifen regardless of *CYP2D6* genotype (43) and based on knowledge that *CYP2D6* poor metabolizers switched from tamoxifen to anastrozole do not have an increased risk of recurrence (38). Note, higher dose tamoxifen (40 mg/day) increases but does not normalize endoxifen concentrations and can be considered if there are contraindications to aromatase inhibitor therapy (45, 56).	

[a] Rating scheme described in Supplement.

[b] CPIC has generally classified patients with an activity score of 1 as a "normal metabolizer". However, in the case of tamoxifen, prescribing recommendations for those with an AS of 1.0 are allele dependent, based on the presence of the **10* allele. Those patients with an AS of 1.0 on the basis a **10* allele are provided a "moderate," recommendation. In contrast, prescribing recommendations for those with an activity score of 1 based on the presence of *CYP2D6* alleles other than *10 are graded as "optional" because the recommendations are primarily extrapolated from evidence generated from *10 individuals (i.e. limited data for clinical outcomes and pharmacokinetics for this group).