Tamoxifen Therapy and *CYP2D6* Genotype

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Introduction

Tamoxifen is a selective estrogen receptor modulator (SERM) which is used in the treatment and prevention of breast cancer (1).

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, and is one of the main enzymes responsible for converting tamoxifen into its major active metabolite, endofixen. Variants in the *CYP2D6* allele may lead to reduced ("intermediate metabolizer") or absent ("poor metabolizer") enzyme activity. Individuals who carry these variant alleles may have reduced plasma concentrations of endoxifen and benefit less from tamoxifen therapy.

At this time, the FDA-approved drug label for tamoxifen does not discuss genetic testing for *CYP2D6*. The National Comprehensive Cancer Network (NCCN) does not recommend *CYP2D6* testing as a tool to determine the optimal adjuvant endocrine strategy (2), and this recommendation is consistent with the 2010 guidelines from the American Society of Clinical Oncology (ASCO) (2, 3).

In contrast, the Dutch Pharmacogenetics Working Group has made recommendations for tamoxifen therapy based on *CYP2D6* genotypes. For both poor and intermediate metabolizers, their recommendation is to consider using aromatase inhibitors for postmenopausal women due to an increased risk for relapse of breast cancer with tamoxifen. They also recommend that intermediate metabolizers avoid the concomitant use of CYP2D6 inhibitors (Table 1) (4).

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Table 1. *CYP2D6* phenotypes and the therapeutic recommendations for tamoxifen therapy, adapted from the Dutch Pharmacogenetics Working Group

Phenotype	Genotype	Therapeutic recommendation for tamoxifen
Ultrarapid metabolizer	More than two copies of functional alleles	None
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	Increased risk for relapse of breast cancer. Avoid concomitant use of CYP2D6 inhibitors. Consider aromatase inhibitor for postmenopausal women
Poor metabolizer	Two inactive alleles	Increased risk for relapse of breast cancer. Consider aromatase inhibitor for postmenopausal women

The strength of the tamoxifen therapeutic recommendations scored a maximum of 4/4 (the highest quality of evidence). Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (4).

Table 2. Activity status of *CYP2D6* alleles

Allele type	Alleles
Active	*1, *2, *33, *35*
Decreased activity	***9, *10, *17**, *29, *36, ***41**
Inactive	***3, *4, *5, *6, *7**, *8, *11-*16, *19-*21, *38, *40, *42*

Note: The most clinically significant variants are highlighted in bold.

Drug: Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM) that is used in the treatment and prevention of breast cancer. In both men and women, tamoxifen is used to treat metastatic breast cancer—patients with tumors that are estrogen receptor positive (ER+) are more likely to benefit. In post-menopausal women with breast cancer, tamoxifen is used as an adjuvant treatment following surgery and radiation—patients with four or more positive axillary nodes may benefit the most. And tamoxifen is also used to prevent breast cancer in women who have an increased risk, and to reduce the risk of invasive breast cancer in women with ductal carcinoma in situ (DCIS) (1).

Tamoxifen acts on the estrogen receptor (ER) and has both estrogenic and anti-estrogenic actions, depending on the target tissue. In the breast tissue, it acts as an anti-estrogen (inhibitory effect) and competitively inhibits cancerous ER+ cells from receiving the estrogen they need to grow (5, 6).

In other tissues, such as the endometrium, tamoxifen acts as an estrogen agonist (stimulatory effect) leading to some of the adverse effects associated with tamoxifen therapy. These include endometrial hyperplasia, endometrial polyps, and about a 2.5 times

higher risk of developing endometrial cancer. Hot flashes are the most common side effect associated with tamoxifen use, which affect up to 80% of women, and there is also an increased risk of depression (5, 7).

Tamoxifen increases the risk of thromboembolic events, such as deep vein thrombosis (DVT) and pulmonary embolism. The risk of tamoxifen-associated thromboembolic events (TTE) is further increased when tamoxifen is coadministered with chemotherapy. The drug label for tamoxifen states that the risks and benefits of tamoxifen therapy should be carefully considered in women with a history of thromboembolic events.

Some studies suggest that clinicians should consider screening breast cancer patients before prescribing adjuvant tamoxifen to identify women who are at risk of thrombotic embolic disease because of Factor V Leiden (R506Q in the *F5* gene); or have an increased risk of TTE because of a variant in the estrogen receptor gene (*ESR1*) (8-11). However, a small substudy (N=81) of the NSABP P-1 trial found no benefit in screening women for Factor V Leiden or prothombin thrombophilia (G20210A in the *F2* gene) as a means to identify women who may not be appropriate candidates for tamoxifen therapy due to the propensity of thromboembolitic side effects (1, 12).

Tamoxifen is a pro-drug that is metabolized to active metabolites in the liver. The metabolites 4-hydroxytamoxifen and 4-hydroxy-N-desmethyltamoxifen (endoxifen) are thought to be mainly responsible for the clinical effects of tamoxifen. Both of these metabolites have about a 100-fold higher affinity for the ER compared to tamoxifen, but endoxifen is thought to be the major metabolite because plasma levels of endoxifen tend to be several-fold higher than that of 4-hydroxytamoxifen (5, 13). Endoxifen formation mainly occurs via the conversion of the inactive primary metabolite N-desmethyltamoxifen, mediated by CYP2D6.

The mechanism of action of tamoxifen is complex and involves tamoxifen metabolites binding to the ER and inducing a conformational change that blocks or changes the expression of estrogen-dependent genes. It is also likely that tamoxifen interacts with other protein cofactors (both activators and repressors), and binds with different estrogen receptors (ER-alpha or ER-beta), to produce estrogenic and anti-estrogenic effects in different tissues. Certain tamoxifen metabolites such as norendoxifen have also been found to act as aromatase inhibitors in vitro (albeit at high concentrations)—decreasing the amount of estrogen available by inhibiting the conversion of steroids to estradiol (14).

The response to tamoxifen (i.e., clinical efficacy and side effects) varies widely between individuals; this may be partly caused by differences in metabolism because of variations in genes such as *CYP2D6* (15).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP*

genes are often polymorphic and can result in reduced, absent, or increased enzyme activity.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. CYP2D6 is the main enzyme that catalyzes the rate-limited step in the metabolism of tamoxifen to its potent metabolite, endoxifen. Other CYP enzymes involved in tamoxifen metabolism include CYP2C19, CYP2B6, CYP3A4, and CYP3A5.

CYP2D6 is a particularly complex gene that is difficult to genotype because of the large number of variants (more than 100 alleles have been described (16)), and the presence of gene deletions, duplications, multiplications and pseudogenes. The complexity of genetic variation complicates making a correct determination of CYP2D6 genotype.

There is substantial variation in CYP2D6 genotypes among different populations. CYP2D6*1 is the wild-type allele and is associated with normal enzyme activity and the normal "extensive metabolizer" phenotype. The CYP2D6 alleles *2, *33, and *35 are also considered to have near-normal activity. Other alleles include variants that produce a non-functioning enzyme (e.g., *3, *4, *5, and *6) (17-20) or an enzyme with reduced activity (e.g., *10, *17, and *41) (21-23) (see Table 2). There are large inter-ethnic differences in the frequency of these alleles, with *3, *4, *5, *6, and *41 being more common in the Caucasian population, *17 more common in Africans, and *10 more common in Asians (24).

Individuals who are intermediate or poor metabolizers carry copies of reduced-activity or non-functioning CYP2D6 alleles (Table 1). Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. In these populations, only half of CYPD6 alleles are fully functional, with the reduced function *10 variant being very common (~40%, compared to ~2% in Caucasians) (25). As a result, Asians are more likely to be intermediate metabolizers than Caucasians (24). Similarly, in Africans and African Americans, only half of CYPD6 alleles are functional. However, a wider range of variants account for the remaining alleles (24, 26, 27).

Approximately 6-10% of European Caucasians and their descendants are poor metabolizers, mainly due to the more prevalent nonfunctional *4 and *5 alleles (24). Notably, less than 40% are homozygous extensive metabolizers (carrying two copies of *1 allele), and more than 50% belong to a mixed group of intermediate metabolizers and heterozygote carriers of one functional allele in combination with either a deficient or non-functional allele (20, 28-30).

Because CYP2D6 is the main enzyme involved in converting tamoxifen into its most potent anti-estrogenic metabolites, endoxifen and 4-hydroxytamoxifen, genetic polymorphisms of CYP2D6 may influence tamoxifen metabolism (31). High plasma levels of endoxifen require the presence of fully functional CYP2D6 alleles, in poor metabolizers, endoxifen levels are decreased (13, 32).

The role of CYP2D6 in tamoxifen response has yet to be fully determined (33). Some studies suggest that genetic polymorphisms of *CYP2D6* may be important predictors of the clinical outcomes of tamoxifen treatment for patients with metastatic breast cancer (34) and for patients with early breast cancer who receive tamoxifen as an adjuvant treatment following surgery (32, 35-37).

However, the high degree of inter-individual variability of tamoxifen metabolism and treatment outcomes is not fully accounted for by *CYP2D6* variation (38). Additional contributors may include genetic variation in other metabolic pathways and the sequestration of lipophilic tamoxifen metabolites into fat tissues (13, 32).

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient's result is reported as a diplotype, such as *CYP2D6 *1/*1*. A result for copy number is also important when interpreting results for this gene.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores, e.g., poor metabolizers have an activity score of 0; intermediate metabolizers have an activity score between 0.5 and 1.5 and metabolizers have an activity score of 2 and up (39).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2013 Statement from the US Food and Drug Administration (FDA): "Tamoxifen is extensively metabolized after oral administration. N-desmethyl tamoxifen is the major metabolite found in patients' plasma. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. 4-Hydroxytamoxifen and a side chain primary alcohol derivative of tamoxifen have been identified as minor metabolites in plasma. Tamoxifen is a substrate of cytochrome P-450 3A, 2C9 and 2D6, and an inhibitor of P-glycoprotein."

Please review the complete therapeutic recommendations that are located here: (1).

2014 Statement from the National Comprehensive Cancer Network (NCCN): "The cytochrome P-450 (CYP450) enzyme, CYP2D6, is involved in the conversion of

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[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

tamoxifen to endoxifen. Over 100 allelic variants of *CYP2D6* have been reported in the literature. Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen. However, the BIG 1-98 trial reported on the outcome based on *CYP2D6* genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive breast cancer. The study found no correlation between *CYP2D6* allelic status and disease outcome or between *CYP2D6* allelic status and tamoxifen-related adverse effects. A genetic analysis of the ATAC trial found no association between *CYP2D6* genotype and clinical outcomes. Given the limited and conflicting evidence at this time, the NCCN Breast Cancer Panel does not recommend *CYP2D6* testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines."

Please review the complete therapeutic recommendations that are located here: (2)

2010 Excerpt from the American Society of Clinical Oncology (ASCO) guideline[2]:

"Are There Specific Patient Populations That Derive Differing Degrees of Benefit From an AI Compared With Tamoxifen?

Recommendation: Direct evidence from randomized trials does not identify a specific marker or clinical subset that predicted which adjuvant treatment strategy—tamoxifen, AI monotherapy, or sequential therapy—would maximally improve outcomes for a given patient. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The Update Committee recommends against using *CYP2D6* genotype to select adjuvant endocrine therapy. The Committee encouraged caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, fluoxetine; see Table 11 in the full guideline for a complete list of inhibitors) and tamoxifen because of the known drug-drug interactions.

Comment: The adjuvant endocrine therapy recommendations in this update are for all women, irrespective of any specific clinical subset or prognostic marker. AI therapy has not been evaluated in men, thus the continued recommendation that men with breast cancer receive adjuvant tamoxifen.

Data suggest that variability in tamoxifen metabolism affects the likelihood of cancer recurrence in patients treated with tamoxifen. Factors that contribute to this variability include concurrent use of other drugs that inhibit the CYP2D6 isoenzyme and pharmacogenetic variation (polymorphisms) in *CYP2D6* alleles. It is not yet known

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[2] The 2014 ASCO practice guideline focused update does not address pharmacogenetic testing (JCO July 20, 2014 vol. 32 no. 212255-2269).

whether these variations account for differences in outcomes among patients treated with tamoxifen.

Available data on CYP2D6 pharmacogenetics are insufficient to recommend testing as a tool to determine an adjuvant endocrine strategy. Patients who clearly benefit from known CYP2D6 inhibitors might consider avoiding tamoxifen because of potential pharmacologic interactions. Conversely, patients who receive tamoxifen may prefer to avoid concurrent use of known CYP2D6 inhibitors if suitable alternatives are available."

Please review the complete therapeutic recommendations that are located here: (3)

2011 Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): "For CYP2D6 poor metabolizers (PMs), defined as patients carrying two defective alleles […] With respect to tamoxifen, an increased risk for breast cancer relapse is present, and it is advised that an aromatase inhibitor be considered for treating postmenopausal women with breast cancer. Other recommendations included the selection of an alternative drug, therapeutic drug monitoring, increased alertness to adverse drug events and to reduced efficacy, and the recording of an electrocardiogram.

For CYP2D6 intermediate metabolizers (IMs), defined as patients carrying two decreased-activity alleles or one active/decreased-activity allele and one inactive allele […] For tamoxifen, the use of an aromatase inhibitor for treating postmenopausal women with breast cancer and the avoidance of concomitant use of a CYP2D6 inhibitor are advised. Other recommendations are comparable to the recommendations for PMs."

Please review the complete therapeutic recommendations that are located here: (4).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Not applicable—variant occurs in a non-coding region	rs3892097
*CYP2D6*5*		Not applicable—variant results in a whole gene deletion		
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

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Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.5:c. 320C>T NM_000106.5:c. 886T>C	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.5:c. 985+39G>	Not applicable—variant occurs in a non-coding region	rs28371725

*In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

Acknowledgments

Version History

To view an earlier version of this summary (Created: October 7, 2014), please click here.

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Related Summaries by Gene

Amitriptyline Therapy and *CYP2D6* and *CYP2C19* Genotype

Aripiprazole Therapy and *CYP2D6* Genotype

Atomoxetine Therapy and *CYP2D6* Genotype

Carvedilol Therapy and *CYP2D6* Genotype

Clozapine Therapy and *CYP2D6, CYP1A2,* and *CYP3A4* Genotypes

Codeine Therapy and *CYP2D6* Genotype

Imipramine Therapy and *CYP2D6* and *CYP2C19* Genotype

Metoprolol Therapy and *CYP2D6* Genotype

Propafenone Therapy and *CYP2D6* Genotype

Risperidone Therapy and *CYP2D6* Genotype

Thioridazine Therapy and *CYP2D6* Genotypes

Tramadol Therapy and *CYP2D6* Genotype

Venlafaxine Therapy and *CYP2D6* Genotype

Tests in GTR by Condition

Tamoxifen response

Tests in GTR by Gene

CYP2D6 gene