Commentary
The ethics of CYP2D6 testing for patients considering tamoxifen

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Abstract

The *CYP2D6* gene is responsible for the majority of tamoxifen metabolism. Recent compelling, yet limited data have determined that postmenopausal women who carry a functional polymorphism in the *CYP2D6* gene have a worse clinical outcome than women who have a wild-type genotype. In this commentary we discuss the level of evidence needed to change clinical practice and whether *CYP2D6* genotyping is appropriate for all women considering tamoxifen as part of their adjuvant therapy.

The emerging field of pharmacogenetics holds the promise for determining effective treatment options and improving outcomes. It also raises the issues of when and how practicing physicians decide to incorporate emerging science into their practice. The case of tamoxifen and cytochrome P450 *CYP2D6* genotyping illustrates how this problem can be approached by evaluating the risks and benefits of testing in specific subsets of patients.

Recent research, including prospective studies, evaluating *CYP2D6* genetics and tamoxifen metabolism and a retrospective analysis of *CYP2D6* genetics and outcomes from a prospective trial strongly suggest that the *CYP2D6* genotype, as well as the use of CYP2D6 inhibitors, is predictive of tamoxifen efficacy [1-4]. At the American Society of Clinical Oncology (ASCO) Clinical Science Symposium in June 2006, Knox and colleagues [4] presented compelling data from a retrospective cohort of 256 postmenopausal, hormone-positive patients treated with tamoxifen alone in the adjuvant setting. They found that certain functional polymorphisms of *CYP2D6*, as determined for a subset of 171 patients, correlated with worse relapse-free survival and disease-free survival. At this same symposium, Grabinski and colleagues [5] demonstrated that patients with specific functional *CYP2D6* polymorphisms produce extremely low levels of active tamoxifen metabolites. On 18 October 2006 the FDA Clinical Pharmacology Subcommittee unanimously agreed that this new clinical

evidence demonstrates that the *CYP2D6* gene is an important predictor of tamoxifen efficacy.

The CYP2D6 enzyme is part of the P450 enzyme system and is responsible for metabolizing tamoxifen to its most active form, endoxifen. Humans all inherit two alleles for the *CYP2D6* gene, one from each parent. Each allele may be normal (designated '*wt*') or variant type (designated '*vt*'). Thus, genotypically, an individual may be homozygous wild type (*wt/wt*), heterozygous (*wt/vt*), or homozygous variant (*vt/vt*). Each of these genotypes may lead to variable metabolism of drugs like tamoxifen. Individuals with *CYP2D6* polymorphisms that render the gene product inactive, termed 'poor metabolizers', produce endoxifen at very low levels [2,5]. Approximately 7% to 10% of the Caucasian population are poor metabolizers. The evidence presented at ASCO suggests these poor metabolizer patients are at increased risk of breast cancer recurrence because of lack of tamoxifen efficacy resulting from their *CYP2D6* genotype. In addition, certain inhibitors of the CYP2D6 enzyme, such as the selective serotonin reuptake inhibitors, which are frequently given to breast cancer patients to combat hot flashes and treat depression, may result in altered tamoxifen activity, and lead to poorer clinical outcomes [2,4].

These extraordinarily important findings have resulted from analyses of only a few hundred patients and are retrospectively derived; however, they may potentially affect many thousands of women worldwide who take adjuvant tamoxifen as part of therapy for breast cancer.

Under what circumstances should patients considering tamoxifen as an adjuvant therapy be tested for *CYP2D6* and under what circumstances should patients taking tamoxifen avoid potent inhibitors of CYP2D6? There is concern over the widespread clinical use of *CYP2D6* genotyping to guide decision-making about adjuvant therapies without prospectively validated data and because of the relatively small

AI = aromatase inhibitor.

number of patients from which the outcomes in tamoxifen-treated patients have been derived. The problem with such retrospective data is that it is impossible to exclude the possibility that some factor other than the factor analyzed (in this case, *CYP2D6* genotype) may account for or contribute to the imbalance found in the outcomes. Prospective trials can attempt to control for such confounding imbalances through randomization and other techniques. When the potential benefits of a proposed therapy are large, as they are in the case of adjuvant tamoxifen, the standards of validation for a predictive test used to determine whether or not that therapy should be provided must be high. This is true unless there are other, acceptable alternatives that provide similar potential benefits, as in the case for postmenopausal women contemplating tamoxifen as part of their adjuvant hormonal therapy and for women on tamoxifen who are taking selective serotonin reuptake inhibitors, such as paroxetine and fluoxetine, that are potent inhibitors of CYP2D6.

Postmenopausal, hormone-positive breast cancer patients contemplating tamoxifen as part of their adjuvant hormonal therapy have a clear choice between an aromotase inhibitor (AI) for five years or sequencing tamoxifen and an AI [6,7]. Because both alternatives are acceptable and currently widely used in practice, providing postmenopausal women with information about their *CYP2D6* genotype will allow them to make an informed choice about their adjuvant hormonal treatment and, most importantly, avoid the potential of taking a therapy that may lack efficacy when there are acceptable alternatives. Because AI treatment provides a benefit of equal if not superior magnitude to tamoxifen in postmenopausal women, poor metabolizers will be able to avoid tamoxifen by taking an AI and, consequently, decrease their risk of breast cancer recurrence. The Breast Intergroup has tentatively approved a randomized study to further evaluate the role of *CYP2D6* status and treatment with an AI upfront versus tamoxifen followed by an AI in postmenopausal women.

Pre- and perimenopausal women who are considering taking tamoxifen in an adjuvant setting do not have such alternatives. More prospectively derived outcomes data are needed to confidently extend the recommendation for *CYP2D6* geno-typing to these patients. Although a reasonable alternative to tamoxifen for these women might be an AI in addition to ovarian suppression, no randomized trials have demonstrated equivalence between these two alternatives, although the Suppression of Ovarian Function Trial (SOFT) is currently addressing this question [8]. In addition, ovarian suppression has undesirable side effects, may affect fertility, and is irreversible if surgical oophorectomy is performed. Thus, in contrast to the situation for postmenopausal patients, proven, equivalent alternatives to tamoxifen do not exist. For these reasons we conclude that *CYP2D6* genotyping should not be routinely performed as a predictive test used to make treatment decisions for pre- and perimenopausal women until we have more definitive data.

Conclusions
Our ethical responsibility to our patients is to carefully balance risks and benefits in helping them to make decisions. At times, we are in a position of uncertainty with respect to the magnitude of risks as well as benefits. In such cases, especially when the magnitude of potential benefit is large (as it is in the case of tamoxifen) and the magnitude of risk is uncertain, we should err on the side of caution and continue to recommend therapies for which there is strong or definitive evidence. This responsibility can sometimes require waiting until a therapy or test has prospectively proven efficacy before prescribing it to our patients, or until there are proven alternatives available.

Competing interests
Dr Hartman reports being a medical consultant to DNA Direct, Inc.

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