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# Pharmacogenetic testing affects choice of therapy among women considering tamoxifen treatment

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## Abstract

**Background:** Pharmacogenetic testing holds major promise in allowing physicians to tailor therapy to patients based on genotype. However, there is little data on the impact of pharmacogenetic test results on patient and clinician choice of therapy. *CYP2D6* testing among tamoxifen users offers a potential test case of the use of pharmacogenetic testing in the clinic. We evaluated the effect of *CYP2D6* testing in clinical practice to determine whether genotype results affected choice of hormone therapy in a prospective cohort study.

**Methods:** Women planning to take or currently taking tamoxifen were considered eligible. Participants were enrolled in an informational session that reviewed the results of studies of *CYP2D6* genotype on breast cancer recurrence. *CYP2D6* genotyping was offered to participants using the AmpliChip CYP450 Test. Women were classified as either poor, intermediate, extensive or ultra-rapid metabolizers. Results were provided to clinicians without specific treatment recommendations. Follow-up was performed with a structured phone interview 3 to 6 months after testing to evaluate changes in medication.

**Results:** A total of 245 women were tested and 235 completed the follow-up survey. Six of 13 (46%) women classified as poor metabolizers reported changing treatment compared with 11 of 218 (5%) classified as intermediate, extensive or ultra-rapid metabolizers ( $P < 0.001$ ). There was no difference in treatment choices between women classified as intermediate and extensive metabolizers. In multi-variate models that adjusted for age, race/ethnicity, educational status, method of referral into the study, prior knowledge of *CYP2D6* testing, the patients' *CYP2D6* genotype was the only significant factor that predicted a change in therapy (odds ratio 22.8; 95% confidence interval 5.2 to 98.8). Genetic testing did not affect use of co-medications that interact with *CYP2D6*.

**Conclusions:** *CYP2D6* genotype testing led to changes in therapy among poor metabolizers, even in the absence of definitive data that an alternative medicine improved outcomes. Pharmacogenetic testing can affect choice of therapy, even in the absence of definitive data on clinical impact.

## Background

Pharmacogenetics may improve health outcomes by allowing clinicians to tailor medications to patients' individual genetic profiles. Once the genetic determinants of drug response are identified, additional work will be required to translate these findings into practice [1-3]. One major question regarding the implementation of

pharmacogenetic testing is how clinicians will incorporate the results into practice and whether the genotypic results will lead to a change in therapy.

Tamoxifen, a selective estrogen receptor modulator, acts as an estrogen receptor antagonist in breast tissue. In the adjuvant setting, tamoxifen reduces breast cancer recurrence [4] and mortality [5,6] among women with hormone receptor-positive breast cancer. Tamoxifen also reduces the risk of breast cancer in high risk women [7]. It is metabolized to 4-hydroxy-N-desmethyl-tamoxifen, also known as endoxifen [8-10], which is

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considered the primary pharmacologically active metabolite of tamoxifen [9-11]. Cytochrome P450 2D6 enzyme (*CYP2D6*) is the rate-limiting enzyme that converts N-desmethyl-tamoxifen into endoxifen [10,12,13].

The *CYP2D6* gene is highly polymorphic and has several alleles that decrease or completely abolish its enzymatic activity. Several studies suggest that breast cancer patients on tamoxifen with a 'poor metabolizer' phenotype (two inactive alleles) [11,14-18] or with two alleles with reduced enzymatic activity [16,19-24] have a higher rate of breast cancer recurrence compared to patients with other phenotypes. Recent retrospective analyses from two large randomized trials comparing tamoxifen with aromatase inhibition as treatment for early stage breast cancer in post-menopausal women demonstrated no impact of *CYP2D6* genotype on outcome [25,26]. Nonetheless, the impact of genotype on the effectiveness of tamoxifen remains uncertain [11,13-23,27,28].

Although there is considerable controversy regarding the predictiveness of *CYP2D6* genotypes on outcomes, there are alternatives to tamoxifen treatment. Aromatase inhibitors (AIs) are considered more effective at reducing breast cancer recurrence than tamoxifen alone in post-menopausal women with hormone receptor-positive breast cancer [29-33], although no impact has been demonstrated on mortality. In pre-menopausal women with early stage hormone receptor-positive breast cancer, tamoxifen with or without ovarian suppression (OS) remains the preferred treatment for standard adjuvant therapy since no current data demonstrate improved outcomes of pre-menopausal women on AIs plus OS [34,35]. However, OS alone or with AIs in pre-menopausal women may be considered an alternative in pre-menopausal women who do not tolerate tamoxifen [35-37]. Therefore, *CYP2D6* testing may be considered a useful test case of the use of pharmacogenetic testing in the clinic since there are alternative treatments.

We prospectively evaluated the effect of *CYP2D6* testing in clinical practice and the impact of providing genotype to practitioners and patients in a prospective cohort study. Specifically, we recruited women who had recently started or were considered candidates to start tamoxifen. They were offered *CYP2D6* genotype testing and results were sent to the participant's clinician. We then followed women who underwent testing to determine whether the genotypes affected choice of therapy.

## Materials and methods

### Study population

Potential participants included women who were currently on tamoxifen or who were considered candidates for tamoxifen, either for treatment or prevention of breast cancer. Patients were recruited by physician referral or after receiving a contact letter sent to all patients

from the University of California San Francisco (UCSF) Breast Oncology Clinic who met eligibility criteria. Participants were excluded if they could not give informed consent or could not participate in the educational session due to limited English proficiency. Recruitment took place between March 2008 and May 2010. Most of the women, 222, were referred to the study from physicians' offices. Of these, 15 (7%) did not agree to participate, leaving 207 (93%) referred women who consented to the study. Another 194 women were contacted by letter. Of those, 102 (52%) did not respond, 54 (28%) said they were not interested ( $n = 34$ ) or not on tamoxifen ( $n = 20$ ), leaving 38 (20%) women who were recruited by letter. Thus, a total of 245 women consented to participate in this study. The institutional review board at UCSF approved the study and all women provided written informed consent at study entry.

### Study protocol

Prior to attending the educational session, each participant was required to identify a referring physician. The referring physician received a short description of the study and agreed to receive the test result in order for the patient to be enrolled. After signing informed consent, the women participated in an educational session conducted by a study physician who used an oral and slideshow presentation to explain genetic testing in general. The study physician also showed slides that included both positive and negative studies regarding *CYP2D6* genotype and breast cancer recurrence. The studies discussed included those published prior to March 2008 when recruitment began. The study physician explicitly told participants that genetic testing remains controversial in the medical literature and that additional studies of the utility of genetic testing on clinical outcome were underway. The presentation was approximately 30 to 45 minutes long, including 30 standardized slides and time for questions and discussion. Participants were asked to complete pre- and post-session questionnaires. *CYP2D6* testing was offered to all participants at the end of the session (see laboratory protocols) and blood was obtained immediately after the educational component concluded. Results were released to the referring clinician 2 to 4 weeks after testing.

Follow-up was performed with a structured phone interview 3 to 6 months after test results were provided to physicians and patients to determine whether a change in medication occurred.

### Demographic, breast cancer risk factors and tamoxifen data collection

The pre- and post-educational session questionnaires collected the following information: demographics, past medical history, breast cancer history (including

pathology and prior treatment), tamoxifen use, other co-medication use, knowledge of genetic testing, and attitudes towards uptaking new technology. Women were classified as pre-menopausal if they indicated having a menstrual period in the prior 3 months and no change in menstrual regularity in the prior year; they were considered post-menopausal if they had no vaginal bleeding (amenorrhea) for at least 6 months without other obvious pathological or physiological cause. Participants were asked if they were experiencing hot flashes, vaginal dryness, sleep problems and any other side effects from tamoxifen. The number, intensity, duration, and severity of hot flashes were reported in the questionnaire. Severity of each side effect was rated on a Likert scale with responses ranging from 1 (mild) to 5 (extremely severe).

#### Laboratory procedures

If the participant agreed to testing, two 10 cc tubes of blood were drawn. One tube of blood was used for genomic DNA extraction that was performed at the UCSF Clinical Pharmacogenomics Laboratory. DNA was extracted from whole blood using the Qiagen QIAamp Blood DNA Kit (Frederick, MD, USA). After extraction, DNA was quantified and stored at  $-20^{\circ}\text{C}$ . A second blood sample was collected in a serum separator tube and stored at  $-20^{\circ}\text{C}$  to measure tamoxifen metabolites, especially endoxifen levels. Tamoxifen metabolite measurements were not reported to patients or clinicians since there were no clinical data on their use at the time the study was conceived and designed.

#### *CYP2D6* genotype

The analysis of *CYP2D6* polymorphisms was performed at the UCSF Clinical Pharmacogenomics Laboratory, a Clinical Laboratory Improvement Amendments Act (CLIA)-certified laboratory, using the AmpliChip CYP450 Test (Roche Molecular Systems, Inc., Branchburg, NJ, USA). This test uses the Affymetrix microarray platform and screens for 27 different alleles of the *CYP2D6* gene (including gene duplications and deletions) and 3 alleles of the *CYP2C19* gene. The AmpliChip CYP450 Data Analysis Software was used to infer the genotype, and to predict the individual's *CYP2D6* enzymatic activity. We classified subjects into four classes: ultra-rapid metabolizers (UMs), extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs). The test and assay conditions for this study followed the manufacturer's instructions [38]. In approximately 1 to 2% of samples, the test results in a 'no genotype' call, presumably because of a rare variant not detected by the chip that interferes with the usual hybridization patterns. In every case of a 'no genotype' result from the AmpliChip, we repeated the

assay at least once to confirm that the result could not be obtained.

#### Reporting of results

Clinicians were informed of test results, including the specific genotype and metabolizing status but no specific treatment recommendation was provided. Results were reported with the specific genotype (for example, \*1/\*4) and the interpretation of the enzymatic activity as classified by the AmpliChip CYP450 Test (for example, 'ultra-rapid metabolizer', 'extensive metabolizer', 'intermediate metabolizer', or 'poor metabolizer'). We used Table 2 from the AmpliChip package insert for the assignment of ultra-rapid, extensive, intermediate and poor *CYP2D6* metabolizers. In addition, information about the effect of metabolizer status on endoxifen levels and the effect of co-medications was provided based on a commonly used reference [39]. Clinicians were not provided specific input about the relationship between genotype or metabolizer status and breast cancer recurrence because of the controversial nature of this association. Clinicians were provided with a form letter to help with informing patients that offered two possible recommendations: (a) to continue current therapy or (b) to call the clinician and schedule an appointment to discuss the results. The *CYP2C19* genotypes from the AmpliChip test and endoxifen levels were not part of the main study and these results were not, therefore, reported to attending oncologists.

#### Clinical follow-up

Three to six months after *CYP2D6* testing, a follow-up questionnaire was administered by a trained research assistant during a structured telephone interview. This questionnaire ascertained whether the patients received the *CYP2D6* test result letter and discussed *CYP2D6* phenotype status (UM, EM, IM, PM) with their clinician, whether the clinician suggested any change in medication based on the test result (tamoxifen, AIs, or any other medication), and what change was suggested. We also determined whether the patients were still taking, started taking, or stopped taking tamoxifen since study participation and what the reason was for any change in hormone therapy.

#### Statistical analysis

To evaluate the effect of *CYP2D6* testing in clinical practice and to determine whether reported *CYP2D6* phenotype affects change in therapy, we compared the rate of medication change among women identified as PM to women identified as UM, EM or IM using Fisher's exact test. In our analysis, data from women with UM and EM phenotype was combined into one category

(UM/EM) since all reports suggest that they have the same clinical outcome. All analyses were conducted with the program STATA (version 10, StataCorp LP, College Station, TX, USA).

## Results

A total of 245 women were enrolled in the study, of whom 235 (96%) participated in the follow-up survey. Ten women (4%) did not return letters or telephone calls and were not included in the analysis of follow-up. The average age of women enrolled in the study was 47 years (range from 23 to 82; Table 1). Most of the participants were Caucasian (68%) and Asian (23%). Thirty-eight percent of women had other chronic health problems. Seventy-two percent of women were married. Educational attainment and income were high; 43% had completed post-graduate degrees and 44% lived in households with > \$100,000 income. At the time of breast cancer diagnosis, 78% (184) were pre-menopausal and 22% (51) were post-menopausal. Nearly all of the women enrolled in the study (97%) had either invasive breast cancer or ductal carcinoma *in situ* (DCIS) with the majority (70%) reporting invasive breast cancer.

Sixty-eight percent (166) of women in the study were taking tamoxifen at the time of enrollment for a median duration of 5 months (range from 1 to 60). The most common side effects attributed to tamoxifen were hot flashes (63%), sleep problems (46%) and vaginal dryness (37%). Approximately 10% of women (24) in the study reported taking selective serotonin reuptake inhibitors (SSRIs), but only one was taking an SSRI considered to be a strong inhibitor of *CYP2D6* (paroxetine). In addition, eight participants (3%) were taking a moderate to potent inhibitor, the norepinephrine-dopamine inhibitor bupropion.

The primary referral method in the study was by a physician or nurse (80%). The rest of the participants were either self-referred or referred by a breast cancer support group (4%) or recruited by the study contact letter (16%). Approximately 50% (122) of the women in the study had previous knowledge of *CYP2D6* testing and the main source of this knowledge was a physician or nurse (38%). Other sources of prior knowledge regarding testing included women who reported reading about *CYP2D6* in the medical literature (20%), the internet (14%), and television or newspapers (5%).

Table 2 shows the detailed *CYP2D6* genotypes and predicted phenotype frequency distribution of participants in the study by ethnicity. Of the 245 participants, 4% (10) were UMs, 76% (185) were EMs, 13% (32) IMs and 5% (13) were PMs. In addition, in four of the women (2%), we could not ascertain the genotype based on the AmpliChip result (Table 2). Of the 13 PMs, 10 (77%) were Caucasian, 2 (15%) were Latina and 1 (8%)

was Asian. There was no significant difference in the rate of PMs across these racial/ethnic categories. Of the 32 IMs, 15 (47%) were Asian, 15 were Caucasian and 2 (6%) were Latina. Asians were more likely to be classified as IMs compared to Caucasians ( $P = 0.002$ ). Out of 166 women taking tamoxifen at the time of enrollment, 5 were UMs, 125 EMs, 24 IMs, 7 PMs and 5 'no genotype'.

We found a significant association between *CYP2D6* phenotype results and change in therapy (Table 3). Six of the 13 PMs (46%) changed treatment to an AI, compared to 10 out of 186 in the UM/EM group ( $P < 0.001$ ). In contrast, there was no significant difference in treatment change rates between the women classified as IMs, 1 (3%, pre-menopausal) out of 32, and UMs/EMs ( $P = 0.51$ ). In addition, all four women with 'no genotype' call were taking tamoxifen at the time of follow-up, which was no different than the proportion of women taking tamoxifen among UMs/EMs.

Among the subset of pre-menopausal women ( $n = 183$ ), 5 of 11 women with the PM phenotype switched to an AI and OS, which was significantly higher ( $P = 0.001$ ) than the rate of change among the UMs/EMs (5 of 149). There was no difference among women with the UM/EM versus IM phenotype when we analyzed the pre-menopausal women ( $P = 0.54$ ).

A total of 26 women reported that they were not taking hormone therapy at the time of follow-up. Of these women, four (three EMs and one IM, all pre-menopausal) were considering tamoxifen for prevention, seven (six EMs and one IM) were considering tamoxifen for treatment of DCIS and six (five EMs and one IM) for treatment of invasive breast cancer. There was no difference in the probability of being on or off hormone therapy by *CYP2D6* metabolizer status.

Of the 186 UMs/EMs, 21% (38) were taking one or more co-medications at the time of enrollment. Nine of these 38 women (24%) changed or stopped a co-medication at the time of follow-up. Of the women on the most potent inhibitors, two of nine stopped a co-medication. There was no significant difference in the rate of change of co-medication between IMs compared to UMs/EMs ( $P = 0.62$ ). None of the PMs were taking any of the co-medications and *CYP2D6* inhibitors described in Table 1.

We also evaluated whether any factors besides *CYP2D6* genotype predict change in therapy (Table 4). In univariate analyses there was no association between change to AIs and method of referral or previous knowledge of *CYP2D6* testing. Among women who said they had prior knowledge, the source of knowledge (physician versus medical literature versus internet) did not affect choice of therapy. We also found no association between change in therapy and report of interest in

**Table 1 Demographics, breast cancer, tamoxifen use and co-medications use characteristics in the overall population in the study**

Characteristics (N = 245)	N/mean	Percent/SD
<b>Mean age (years)<sup>a</sup></b>	47.46	± 9.7
<b>Self-report ethnicity</b>		
Caucasian	166	67.76
Asian/East Asian	56	22.86
African American/Black	2	0.82
Latina/Hispanic	14	5.71
Pacific Islander	1	0.41
Other/mixed	3	1.22
Declined/refused/do not know	3	1.22
<b>Number married (yes)</b>	176	72
<b>Number full-time working</b>	98	40
<b>Education levels</b>		
High school graduated or less	6	2.45
Some college	36	14.69
College graduated	90	36.73
Completed post-graduate degree	105	42.86
Declined/refused	8	3.27
<b>Socio-economic status</b>		
Income < \$50, 000	29	11.84
Income ≥\$50, 000 to < \$100, 000	56	22.86
Income ≥\$100, 000	108	44.07
Declined/refused	52	21.23
<b>Reported other health problems</b>	91	38
<b>Breast cancer characteristics</b>		
Breast cancer (yes)	237	97
Had invasive breast cancer	165	70
Surgery (yes)	231	98
Had lumpectomy	119	52
<b>Menopausal status at diagnosis</b>		
Pre-menopausal	184	78
Post-menopausal	51	22
<b>Mean age at menopause (years)<sup>a</sup></b>	45.61	± 6.79
<b>Had natural menopause</b>	35	22.73
<b>Menopause due to chemotherapy treatment</b>	74	48.05
<b>Previous used of hormone therapy</b>	37	15
<b>Tamoxifen use</b>		
Ever prescribed	191	78
Ever taken	171	70
Currently taking	166	68
<b>Common side effects attributed to tamoxifen</b>		
Hot flashes	154	63
Sleep problems	113	46
Vaginal dryness	90	37
<b>Co-medications/CYP2D6 inhibitors</b>		
<b>Strong inhibitors</b>		
Paroxetine	1	0.41
Bupropion	8	3.26
<b>Moderate inhibitors</b>		
Sertraline	8	3.26
Duloxetine	3	1.22



**Table 1 Demographics, breast cancer, tamoxifen use and co-medications use characteristics in the overall population in the study (Continued)**

<b>All other inhibitors</b>		
Amitriptyline	2	0.82
Amlodipine	2	0.82
Celecoxib	2	0.82
Ceterizine	2	0.82
Citalopram	6	2.45
Diphenhydramine	3	1.22
Escitalopram	6	2.45
Imipramine	1	0.41
Loratadine	3	1.22
Nortriptyline	1	0.41
Ranitidine	1	0.41
<b>Other co-medications</b>		
Gabapentin	10	4.00
Trazodone	2	0.82
Venlafaxine	15	6.12
<b>Referral method</b>		
Physician/nurse referral	196	80
Self-referred or breast cancer support group referral	11	4
Study contact letter	38	16
<b>Previous knowledge of CYP2D6 testing (yes)</b>	122	50
<b>Source of CYP2D6 testing knowledge</b>		
Physician or nurse	46	38
Newspaper	5	4
Television	1	1
Internet	17	14
Medical literature	24	20
Other	27	22
Unknown/missed	2	1

<sup>a</sup>Data presented as mean  $\pm$  SD. N, number of participants in the study; SD, standard deviation.

*CYP2D6* testing ( $P = 0.34$ ) or report of interest in new medical treatments and technology ( $P = 0.59$ ). In addition, age, race/ethnicity and education were not predictive of change in therapy (results not shown). No other significant associations were found. Specifically, age, menopausal status, educational attainment, race/ethnicity and indication for treatment (invasive cancer versus carcinoma *in situ* versus prevention) did not predict change in therapy in univariate analyses. There was no association between change in hormone therapy and reported side effects from tamoxifen.

We used multi-variate models to determine whether any factors may confound the association between *CYP2D6* genotype and change in therapy (Table 4). *CYP2D6* genotype remained the only statistically significant association with change in therapy even after adjustment for age, breast cancer type (invasive breast cancer, DCIS and lobular carcinoma *in situ* (LCIS)), menopausal status (pre-menopausal versus post-menopausal), report of any tamoxifen-induced side effects,

previous knowledge of *CYP2D6* testing, referral method (physician or nurse versus other sources) and interest in *CYP2D6* testing.

## Discussion

We provided *CYP2D6* genotype results to clinicians and patients and evaluated the impact of this information on the proportion of women who changed hormone therapy. Approximately 5% of women were PMs and 6 out of 13 (46%) changed treatment after discussion with their physicians. This was a significantly higher percentage than the rate of therapy change in those with UM, EM or IM phenotypes, suggesting that in this setting phenotype results affected treatment decisions. The association between medication change was not confounded by method of referral to the study or by prior interest in *CYP2D6* testing.

For pre-menopausal women, change in hormone therapy included both an AI as well as ovarian suppression that leads to significant side effects associated with early

**Table 2 Distribution of CYP2D6 genotype and predicted phenotype by different ethnic groups**

CYP2D6 predicted phenotype/ genotype	Ethnicity							Total N (%)
	Caucasian	Latina/ Hispanic	AA/ Black	Asian	Pacific Islander	Other/ mixed	Declined/ missed	
Ultra-rapid (UM)	<b>8 (5%)</b>	<b>1 (7%)</b>	<b>0</b>	<b>1 (2%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>10 (4%)</b>
*1/*1 × N	5	0	0	0	0	0	0	5
*1/*2 × N	1	1	0	0	0	0	0	2
*2/*1 × N	1	0	0	1	0	0	0	2
*2/*2 × N	1	0	0	0	0	0	0	1
Extensive (EM)	<b>131 (79%)</b>	<b>9 (65%)</b>	<b>2 (100%)</b>	<b>36 (64%)</b>	<b>1 (100%)</b>	<b>3 (100%)</b>	<b>3 (100%)</b>	<b>185 (76%)</b>
*1/*1	19	2	1	2	1	1	0	26
*1/*2	20	0	0	5	0	0	0	25
*1/*3	2	0	0	0	0	0	0	2
*1/*4	23	1	0	1	0	0	1	26
*1/*5	3	0	0	1	0	1	0	5
*1/*6	1	0	0	0	0	0	0	1
*1/*9	4	2	0	0	0	0	0	6
*1/*10	1	0	0	15	0	0	0	16
*1/*17	1	0	1	0	0	0	0	2
*1/*29	0	0	0	0	0	0	1	1
*1/*35	2	0	0	0	0	0	0	2
*1/*41	16	1	0	1	0	0	0	18
*1 × N/*5	1	0	0	0	0	0	0	1
*1 × N/*10	0	0	0	1	0	0	0	1
*2/*2	5	0	0	0	0	0	0	5
*2/*4	11	1	0	0	0	0	1	13
*2/*5	1	0	0	0	0	0	0	1
*2/*9	1	0	0	0	0	0	0	1
*2/*10	0	1	0	10	0	0	0	11
*2/*35	3	0	0	0	0	0	0	3
*2/*41	5	0	0	0	0	0	0	5
*2/*41 × N	1	0	0	0	0	0	0	1
*2 × N/*4	1	0	0	0	0	0	0	1
*2 × N/*9	1	0	0	0	0	0	0	1
*3/*35	1	0	0	0	0	0	0	1
*4/*35	5	0	0	0	0	0	0	5
*5/*35	0	1	0	0	0	0	0	1
*10/*35	1	0	0	0	0	0	0	1
*17/*35	0	0	0	0	0	1	0	1
*35/*41	1	0	0	0	0	0	0	1
*35/*41 × N	1	0	0	0	0	0	0	1
Intermediate (IM)	<b>15 (9%)</b>	<b>2 (14%)</b>	<b>0</b>	<b>15 (27%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>32 (13%)</b>
*4/*9	1	0	0	0	0	0	0	1
*4/*10	2	0	0	0	0	0	0	2
*4/*17	1	0	0	0	0	0	0	1
*4/*41	6	1	0	0	0	0	0	7
*5/*10	1	0	0	2	0	0	0	3
*10/*10	0	0	0	13	0	0	0	13
*10/*41	2	0	0	0	0	0	0	2
*29/*41	0	1	0	0	0	0	0	1



**Table 2 Distribution of CYP2D6 genotype and predicted phenotype by different ethnic groups (Continued)**

*41/*41	2	0	0	0	0	0	0	2
Poor (PM)	<b>10 (6%)</b>	<b>2 (14%)</b>	<b>0</b>	<b>1 (2%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>13 (5%)</b>
*3/*4	1	0	0	0	0	0	0	1
*4/*4	7	0	0	1	0	0	0	8
*4/*5	0	2	0	0	0	0	0	2
*4/*6	1	0	0	0	0	0	0	1
*4/*7	1	0	0	0	0	0	0	1
No genotype	<b>2 (1%)</b>	<b>0</b>	<b>0</b>	<b>3 (5%)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>5 (2%)</b>
Total	<b>166</b>	<b>14</b>	<b>2</b>	<b>56</b>	<b>1</b>	<b>3</b>	<b>3</b>	<b>245</b>

AA, African American; EM, extensive metabolizer; IM, intermediate metabolizer; N, number of participants in the study; PM, poor metabolizer; UM, ultra-rapid metabolizer.

menopause. Thus, despite the limited evidence and the risk of side effects from an alternative treatment, physicians and patients frequently changed therapy in response to a PM phenotype. Treatment with an AI alone in younger women who have amenorrhea due to chemotherapy may lead to inadequate hormonal suppression [40]. We did not directly make any treatment recommendations. But five of the six women who had changed to an AI also received OS. The only woman who received AI alone was aged 56 years and was known to be post-menopausal prior to breast cancer treatment. Therefore, the physicians who referred to our study appear to be aware of the risks of inadequate hormonal therapy and to have used combination therapy when appropriate.

The association between *CYP2D6* genotype and efficacy of tamoxifen in women with early stage, hormone receptor-positive breast cancer remains unclear. *CYP2D6* activity clearly correlates with endoxifen levels, but the association with outcome has been far more controversial. Several studies have demonstrated an association [11,14-19], but other studies, including the two largest, have failed to confirm an impact of enzyme activity and breast cancer outcome [20-23,25,26]. A recent meta-analysis found a trend towards association between *CYP2D6* genotype and disease free survival but

not overall survival [41]. However, the authors noted considerable heterogeneity among the studies in both the reported associations and in the way subsets of genotypes were grouped. More recently, two large randomized controlled trials, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [25] and the Breast International Group (BIG) 1-98 trial [26], evaluated the impact of *CYP2D6* polymorphisms in patients treated with tamoxifen. Neither study demonstrated an association between the risk of breast cancer recurrence and *CYP2D6* phenotype.

Our study had completed all the enrollment and the follow-up by September 2010, prior to the presentation of the genotyping data from the ATAC and BIG 1-98 trials in December 2010. Thus, at the time that patients and clinicians were deciding how to interpret the genotypes, these results could not be taken into consideration, but could have a significant impact on decisions regarding testing and treatment change. However, as part of our presentation to patients prior to testing, we showed the results of both prior positive and negative studies testing for associations between *CYP2D6* and breast cancer. Since physicians and patients were aware of the controversial results, our study demonstrates that many clinicians and patients are generally willing to make treatment decisions even in the curative setting

**Table 3 Association of CYP2D6 testing and therapeutic decision-making by CYP2D6 phenotypes**

<i>CYP2D6</i> phenotype	Still on tamoxifen	Changed to AIs	No therapy	Total	<i>P</i> <sup>a</sup>	Taking co-medications	Changed co-medication	<i>P</i> <sup>a</sup>
Ultra-rapid (UM)/extensive metabolizer (EM) <sup>b</sup>	156 (84%)	10 (5%)	20 (11%)	<b>186</b>		38 (21%)	9 (5%)	
Intermediate metabolizer (IM)	28 (88%)	1 (3%)	3 (9%)	<b>32</b>	0.51	8 (25%)	2 (3%)	0.62
Poor metabolizer (PM)	4 (31%)	6 (46%)	3 (23%)	<b>13</b>	< 0.001	0	0	-
Total	<b>188</b>	<b>17</b>	<b>26</b>	<b>231</b>		<b>46</b>	<b>11</b>	

<sup>a</sup>*P*-value based on Fisher's exact test of association versus UM/EM. <sup>b</sup>Ultra-rapid metabolizer (UM) data combined with extensive metabolizer (EM) data. AI, aromatase inhibitor.

**Table 4 Association of therapeutic decision-making by clinical and breast cancer characteristics, *CYP2D6* phenotype, previous knowledge of *CYP2D6* testing, referral method, and interest in *CYP2D6* testing**

Characteristics	Change to aromatase inhibitors			
	Unadjusted		Adjusted <sup>a</sup>	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.03 (0.98, 1.08)	0.23	1.02 (0.95, 1.10)	0.50
Breast cancer type				
Invasive breast cancer	-	-	-	-
Ductal carcinoma <i>in situ</i> (DCIS)	1.07 (0.32, 3.48)	0.90	1.33 (0.34, 5.11)	0.67
Lobular carcinoma <i>in situ</i> (LCIS)	0.82 (0.09, 6.76)	0.85	0.44 (0.03, 5.59)	0.53
Post-menopausal status	1.54 (0.51, 4.62)	0.43	1.78 (0.35, 9.08)	0.48
Report of any tamoxifen side effects (yes)	1.09 (0.34, 3.50)	0.87	0.61 (0.16, 2.31)	0.47
<i>CYP2D6</i> phenotype				
UM/EM <sup>b</sup>	-	-	-	-
IM	0.56 (0.07, 4.59)	0.59	0.38 (0.04, 3.38)	0.38
PM	<b>15.08 (4.26, 53.33)</b>	<b>0.0001</b>	<b>22.85 (5.28, 98.74)</b>	<b>0.0001</b>
Previous knowledge of <i>CYP2D6</i> testing (yes)	0.88 (0.33, 2.38)	0.81	0.91 (0.29, 2.84)	0.87
Referred by physician or nurse (yes)	0.60 (0.20, 1.81)	0.37	0.36 (0.09, 1.37)	0.13
Very interested in <i>CYP2D6</i> testing before attending the educational session (versus somewhat and not really interested)	1.77 (0.49, 6.38)	0.38	3.01 (0.66, 13.65)	0.15

The number of participants followed up was 235. <sup>a</sup>Odd ratios adjusted for age, breast cancer type, menopausal status, report of any tamoxifen side effects, *CYP2D6* phenotype, previous knowledge of *CYP2D6* testing, referral method, and interest in *CYP2D6* testing. *P*-value  $\leq$  0.05. <sup>b</sup>Ultra-rapid metabolizer (UM) data combined with extensive metabolizer (EM) data. CI, confidence interval; DCIS, ductal carcinoma *in situ*; EM, extensive metabolizer; IM, intermediate metabolizer; LCIS, lobular carcinoma *in situ*; N, number of participants; OR, odds ratio; PM, poor metabolizer; UM, ultra-rapid metabolizer.

based on non-definitive and retrospective pharmacogenetic information when accompanied by a reasonable hypothesis.

The prevalence of *CYP2D6* polymorphisms varies across ethnic groups. The frequency of *CYP2D6* PMs in our study is consistent with previous reports [15,19]. Like other investigators [14,24,42], we found that the most frequent variant present in Asians was *CYP2D6*\*10, an allele with reduced activity. Results examining the association between the \*10 allele and clinical outcomes have also been mixed [14,16,19,20,24,42]. The rate of medication change among patients with the IM *CYP2D6* phenotype, including patients homozygous for this allele, was similar to that in patients with the UM/EM phenotype, suggesting that physicians do not consider these patients at significantly increased risk of recurrence.

Endoxifen concentration varies not only according to the number of functional *CYP2D6* alleles [43] but also in the presence of potent *CYP2D6* enzyme inhibitors. Agents such as the SSRIs paroxetine or fluoxetine, and

the anti-arrhythmic quinidine are among the most potent inhibitors [9,44]. When these medications are co-administered with tamoxifen to women with an EM phenotype, endoxifen concentrations are similar to those observed in PM and have the potential, therefore, to reduce tamoxifen efficacy [9,43,44]. Other commonly used medications such as bupropion, duloxetine, clomipramine, thioridazine, pherphenazine, and pimozide exhibit inhibition close to that of paroxetine, fluoxetine and quinidine [44-46]. While we found that some women did change their co-medications, this was unrelated to *CYP2D6* genotype. Our study did not collect enough information from physicians to distinguish between those two possibilities.

Our study is unique in that, to our knowledge, no prior pharmacogenetic studies on change in therapy for *CYP2D6* have been previously published. Several studies have examined the issue of incorporating pharmacogenetic data in dosing warfarin [47,48]; however, genetic testing for warfarin dosing does not involve a change to a different medication. Several studies have also shown

that genetic testing for *BRCA1/2* leads to selection of risk-reducing surgeries [49-51], the use of post-menopausal hormone therapy [52], and pre-implantation genetic diagnosis [53].

Our study also has several important limitations. First, the evidence for the association between *CYP2D6* polymorphisms and outcomes remains mixed in the literature and the availability of the most recent results may have changed the decisions that patients and providers in our study made. Second, our sample may have been biased by referral patterns and by patient participation. Physicians and patients who are interested in testing and in changing therapy based on test results may have been more likely to participate in our study. However, we found no association between prior knowledge or interest in *CYP2D6* genotype testing and choice of therapy at follow-up. In addition, there were no other significant predictors within our data. Third, our sample may not be universally generalizable. Our patients tended to be mostly Caucasians and Asians, highly educated on average, with a relatively high income level, and most were already being followed at a University medical center for breast cancer. Furthermore, our study used patient self-report of medication use rather than chart review or physician report. However, both patient report and physician report may have limitations. More studies should be conducted to determine how genotyping results would be used in community settings.

## Conclusions

Our study demonstrates that *CYP2D6* pharmacogenetic testing led to change in therapy among patients with genotypes that predicted no *CYP2D6* activity. Thus, clinicians and patients do use pharmacogenetic results to change therapy, even in the absence of definitive knowledge about the utility of the pharmacogenetic result. Ultimately, prospective randomized trials will be required to demonstrate the impact of treatment change based on pharmacogenetic testing.

## Abbreviations

AI: aromatase inhibitor; ATAC: Arimidex, Tamoxifen, Alone or in Combination; BIG: Breast International Group; *CYP2C19*: cytochrome P450 2C19; *CYP2D6*: cytochrome P450 2D6; DCIS: ductal carcinoma *in situ*; EM: extensive metabolizer; IM: intermediate metabolizer; OS: ovarian suppression; PM: poor metabolizer; SSRI: selective serotonin reuptake inhibitor; UCSF: University of California San Francisco; UM: ultra-rapid metabolizer.

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## Authors' contributions

WL and EZ participated in the conception, design and implementation of the study, acquisition of data, performed the statistical analysis and interpretation of data, and participated in drafting and preparation of the manuscript. HR, MSB, and MM participated in the conception of the study, acquisition of data and drafting the manuscript. TM provided administrative and institutional support, and participated in drafting the manuscript. ST and AHBW carried out the DNA extraction, *CYP2D6* genotype assay and interpretation, and participated in drafting the manuscript. HJL and MN provided technical support and interpretation for the AmpliChip CYP450 Test and Data Analysis Software. All authors read and approved the final version of the manuscript.

## Competing interests

HJL and MN are full-time employees of Roche Molecular Systems, Inc., which manufactures the AmpliChip CYP450 Test. These authors were not involved in any of the presentations of information to patients regarding the assay either prior to or after testing. They were involved in assisting the UCSF investigators with technical questions regarding the assay, and were involved in critical revisions of the manuscript. The rest of the authors declare that they have no competing interests.

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