

Dear Health Care Provider,

This Tamoxitest™ tamoxifen resistance information package contains the following:

- **Research Summary** - A brief summary of the relevant research pointing out the utility of tamoxifen resistance testing in improving patient care and outcomes.
- **Annotated Bibliography**
- **Frequently Asked Questions**
- **Prescription Form** - A prescription form is included that is simply completed and handed to the patient. We know you are busy, so we handle the rest.

Research Summary – The Effects of CYP2D6 Genotypes & Co-medication on Tamoxifen Efficacy

Recent pharmacogenetic and drug interaction research provides an important explanation for why one-third of women with ER (estrogen receptor) positive breast cancer fail tamoxifen treatment. The ability of these women to convert tamoxifen to the active compound, endoxifen, is compromised, resulting in greatly increased risk of relapse. DNA testing and careful analysis of overall drug regimens in these patients provides evidence that can be used to improve their chance of survival by changing co-medications or to aromatase inhibitors.

The Research

Cytochrome P450 2D6 (CYP2D6) activity is the rate limiting step in the conversion of tamoxifen to endoxifen, which has a 100 X greater affinity for the estrogen receptor than tamoxifen and is 30-100 times more effective at preventing ER positive tumor growth. CYP2D6 genetic PMs (poor metabolizers -- homozygous for null or low activity alleles *3,*4, *5, and/or *6 and comprising 7-10% of the population) have endoxifen levels 26% of normal. CYP2D6*4/*4 PMs had a 3.12 hazard ratio for breast cancer relapse. CYP2D6 genetically normal metabolizers also taking a CYP2D6 inhibitor such as SSRIs had 58% lower endoxifen levels. Two year relapse free survival is 68% in patients with the CYP2D6 PM phenotype and 98% in normal metabolizers.

Predicted Outcomes

Widespread genotyping and metabolism based drug interaction monitoring could result in successful outcomes for the majority of the 35% of ER positive breast cancer patients who currently fail tamoxifen treatment. Out of the ~120,000 new patients diagnosed with ER positive breast cancer each year, 42,000 are predicted to fail tamoxifen treatment, approximately the same number predicted to have a CYP2D6 variant phenotype.

Annotated Bibliography

On October 18, 2006, an FDA Advisory Subcommittee was convened to review the tamoxifen research findings to date and to make a recommendation regarding a label change. The consensus of the Subcommittee was that the label should be updated to reflect the fact that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizers treated with tamoxifen (by genotype or drug interaction) are at increased risk for breast cancer recurrence.

Key Points

- Evidence exists to suggest phenotyping for CYP2D6 when administering tamoxifen therapy in post-menopausal ER- positive breast cancer patients.
- CYP2D6 Poor Metabolizers have been shown to have lower endoxifen plasma levels and higher recurrence of breast cancer.
- Co-administered CYP2D6- metabolized SSRI's to control hot flashes as a side effect of tamoxifen can further reduce conversion of tamoxifen to endoxifen.
- Alternative therapies exist for treatment of post-menopausal ER-positive breast cancer patients who have variant alleles that interfere with 2D6 metabolism of tamoxifen.

CYP2D6 and Tamoxifen Peer-reviewed Publications

- ❏ Schroth W et al. 2009. Association Between CYP2D6 Polymorphisms and Outcomes Among Women With Early Stage Breast Cancer Treated With Tamoxifen. *JAMA* 302(13):1429-1436.

Conclusion: Among women with breast cancer treated with tamoxifen, there was an association between CYP2D6 variation and clinical outcomes, such that the presence of 2 functional *CYP2D6* alleles was associated with better clinical outcomes and the presence of nonfunctional or reduced-function alleles with worse outcomes. The recurrence rates were 14.9% for extensive metabolizers, 20.9% for intermediate metabolizers, and 29.0% for poor metabolizers.

- ❏ Goetz MP et al. 2007. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat* 101:113-21.

Conclusion: CYP2D6 metabolism, as measured by genetic variation and enzyme inhibition, is an independent predictor of breast cancer outcome in post-menopausal women receiving tamoxifen for early breast cancer. Determination of CYP2D6 genotype may be of value in selecting adjuvant hormonal therapy and it appears CYP2D6 inhibitors should be avoided in tamoxifen-treated women.

- ❏ Grabinski et al. 2006. Relationship between CYP2D6 and estrogen receptor alpha polymorphisms on tamoxifen metabolism in adjuvant breast cancer treatment. *Proceedings of The American Society of Clinical Oncology*.

Conclusion: Tamoxifen (TAM) and its metabolites display large inter-individual variation with profound implications for breast cancer outcomes. Tamoxifen is hydroxylated to the potent metabolites, 4-hydroxytamoxifen (4-OH TAM) and endoxifen, by various cytochrome P450 (CYP450) genes including CYP2C9 and CYP2D6. The *SULT1A1* gene is involved in the conjugation of 4-OH TAM. Tamoxifen's binding site is the estrogen receptor (ER). Genotype and ethnicity are significantly associated with levels of TAM and 4-OH TAM and may explain clinical variation in response to TAM treatment.

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- Goetz et al. 2005. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 23(36):9312-8.

Conclusion: In tamoxifen-treated patients, women with the CYP2D6 *4/*4 genotype tend to have a higher risk of disease relapse and a lower incidence of hot flashes, which is consistent with our previous observation that CYP2D6 is responsible for the metabolic activation of tamoxifen to endoxifen.

- Hyeong-Seok Lim et al. 2007. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. *J Clin Oncol* 25(25):3837-45.

Conclusion: CYP2D6*10/*10 is associated with lower steady-state plasma concentrations of active tamoxifen metabolites, which could possibly influence the clinical outcome by tamoxifen in Asian breast cancer patients.

- Jin Y et al. 2005. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 97(1):30-9.

Conclusion: Interactions between CYP2D6 polymorphisms and co administered antidepressants and other drugs that are CYP2D6 inhibitors may be associated with altered tamoxifen activity.

- Schroth W et al. 2007. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. *J Clin Oncol* 25(33):5187-93.

Conclusion: Because genetically determined, impaired tamoxifen metabolism results in worse treatment outcomes, genotyping for CYP2D6 alleles *4, *5, *10, and *41 can identify patients who will have little benefit from adjuvant tamoxifen therapy. In addition to functional CYP2D6 alleles, the CYP2C19 *17 variant identifies patients likely to benefit from tamoxifen.

Frequently Asked Questions

Who Should Be Tested?

The CYP2D6 test for tamoxifen is considered appropriate for postmenopausal women who are taking or considering taking tamoxifen to prevent the recurrence of breast cancer. It is especially important if the patient is also taking or considering co-administration with SSRIs (Selective Serotonin Reuptake Inhibitor) such as fluoxetine, paroxetine and high doses of sertraline or any of the more than 200 other medicines that inhibit CYP2D6 activity.

Does Insurance cover the testing?

Most insurers including Medicare are now consistently covering pharmacogenetic testing in many diagnostic situations including history of adverse drug reactions or lack of response to medication, pain management, cancer management, and management of many co-morbid conditions. We are currently only able to bill insurance for CYP2D6, CYP2C9, and CYP2C19. Testing of CYP1A2, 5HTT, NAT2, UGT1A1, DPD, and VKOR are also available, but only at a self-pay rate. CPT codes and preauthorization instructions are provided on the Physician Referral Prescription form if you would like to confirm eligibility in advance. For self-pay rates, call 800 TEST-DNA (800-837-8362). A patient safeguard program is available for patients without insurance or whose insurance will not cover the testing.

How do I order testing?

Simply complete the required prescription information on the enclosed Physician Referral Prescription form, hand it to the patient, and tell them to follow the instructions at the top of the page. When the patient contacts us, we will send the cheek swab collection kit with prepaid shipping directly to them. Alternatively, you can fax the form to 206-219-4000 with the patient's insurance information, mailing address, and phone number, and we will handle the rest. Additional forms can be printed at <http://www.Tamoxitest.com/Documents/Rxform.pdf>. Buccal swab or blood collection kits with return shipping can be supplied on request at 800 TEST-DNA (800-837-8362).

How do I interpret test results?

For every test ordered, we provide 90-days access to GeneMedRx Drug and Gene Interaction software with the patient's genotypes already entered so you can determine the impact of genetics in the context of their overall medication regimen. GeneMedRx was primarily authored by Dr. Jessica Oesterheld, a recognized expert in drug interactions and coauthor of the top selling book, *Clinical Manual of Drug Interaction Principles for Medical Practice*. A short demo of the software and a free 30-day trial is available at www.GeneMedRx.com/demo.

How long does testing take?

Results are typically available within 6 business days.



Physician Referral Prescription for Tamoxitest™ CYP2D6 Tamoxifen Resistance DNA Test

Your physician thinks that you will benefit from having the Tamoxitest™, and has included a prescription for this testing below. Tamoxitest™ determines your genetic ability to convert tamoxifen to endoxifen; endoxifen is responsible for helping to prevent breast cancer recurrence in the body. About 10% of patients cannot convert tamoxifen to endoxifen and need an alternative therapy. Another 35% have a reduced ability to convert tamoxifen to endoxifen and may require higher doses and need to be very careful about taking other medications, over-the-counters and herbals that can interfere with this conversion. Testing is covered by many insurance plans. Preauthorization instructions are on the back of the form if you would like to confirm coverage in advance.

Please call a DNA Testing Consultant at 800 TEST-DNA (800-837-8362) with this prescription in hand to obtain the cheek swab collection kit for the Tamoxitest™. The consultant can also answer any questions you may have at that time. Alternatively, you can fax this form with a copy of both sides of your insurance card, and your mailing address and phone number to 206-219-4000 and your kit will be mailed.

<p>Patient's Name: _____</p> <p>Date of Prescription: _____ Phone: _____ DOB: _____</p> <p>To: Genelex Corporation 3000 First Ave., Suite One Seattle, WA 98121 Phone: 800-523-3080 Fax: 206-219-4000</p> <p>From (Referring Physician): Name: _____ Address: _____ City, State, Zip: _____ Phone: _____ Fax: _____ Email: _____</p> <p>TESTING IS MEDICALLY NECESSARY. Please perform the TamoxiTest™ on this patient to determine tamoxifen resistance for the diagnosis codes noted below.</p> <p>Physician Signature: _____ License #: _____ UPIN: _____</p> <hr/> <p>Diagnosis Codes: <input type="checkbox"/> 174.9 <input type="checkbox"/> 174.8 _____</p>

Is the testing covered by insurance?

Genelex has seen pharmacogenetic testing coverage by the insurers listed below however coverage benefits can vary by plan. To confirm coverage prior to submitting a sample, see preauthorization instructions at the bottom of this page. Alternatively, we have a patient safeguard program that limits patient out of pocket expense to \$295.00. This option allows the patient to submit for reimbursement directly to their own insurance company. Genelex will provide a detailed invoice to the patient and will not submit a claim. This is also the option available for patients with no insurance or who do not want their insurance to be billed. For patients with financial hardship, please call 800-523-6487 to request a financial consideration form.

Medicare	Blue Cross	Aetna	Cigna
Humana	United Healthcare	DWI Holding	Group Health
Farm Bureau	Tricare	Oxford HMO	

Optional Preauthorization Instructions

Call the number on your insurance card and provide them with:

1. The CPT codes for requested testing:
1 x 83891, 2 x 83892, 1 x 83900, 14 x 83914, 1 x 83909, 1 x 83912, 1 x 83912-26
2. The ICD-9 diagnosis codes provided by your physician.
3. Your physician's name and other requested information.

Record the following information about your insurance company call(s):

1. Date of phone call _____ Phone number with extension _____
2. Name of person you spoke with _____
3. Preauthorization number _____ Valid dates: _____

If preauthorization is denied, Genelex encourages patients to appeal. Contact Jennifer Rustan at jennifer@genelex.com or call 800 TEST-DNA (800 837-8362) for help with this process. We have successfully handled appeals before and have materials we can provide on your behalf.