Tamoxifen Metabolite Testing

Tamoxifen (Tam) , the anti-estrogen used to treat estrogen receptor (ER)-positive breast cancer, is a pro-drug that is converted to its therapeutically active metabolites, Z- and Z'-endoxifen isomers and Z- and Z'-4-hydroxy-tamoxifen (Z-4-OH-Tam) isomers by several metabolic enzymes. Both Z-endoxifen and Z-4-OH-Tam have an ~100-fold greater affinity towards the ER and a 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than Tam, whereas the Z' isomers of endoxifen and 4-OH-Tam have ~10% of their respective Z isomer activity levels[1]. Effective treatment depends on adequate Tam conversion to its active metabolite isomers. The plasma active metabolite concentrations vary due to several factors: common genetic variants in genes encoding the biotransformation enzymes (e.g., CYP2D6), environmental factors that inhibit these enzymes (e.g., concomitant drugs), and compliance to the medication. The polymorphic CYP2D6 enzyme is critical in the Tam conversion to Z-endoxifen; however, CYP2D6 genotype can only account for 30% – 40% of the variability seen in active metabolites. The Anti-estrogenic activity score (ASS) was developed, based on the plasma active isomer concentrations and their respective antiestrogenic activities, to arrive at a more accurate estimate of the biologic effectiveness of Tam treatment[2]. Both Tam metabolite testing and CYP2D6 genotyping are offerred together at Mount Sinai Genetic Testing Laboratory for personalized Tam treatment.

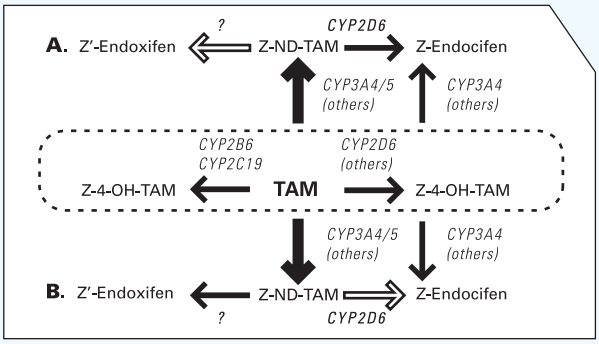

Figure: *Schema of tamoxifen biotransformation in (a) CYP2D6 extensive and ultra-rapid metabolizers and (b) CYP2D6 poor metabolizers.*

Testing Methods, Sensitivity and Turnaround Time:

Biochemical analysis: Mount Sinai Genetic Testing Laboratory is the only clinical lab that offers Tam metabolite testing service. The levels of Tamoxifen and its active metabolite isomers Z- and Z'-endoxifen, Z- and Z'-4-OH-Tam, and N-desmethyltamoxifen are measured by liquid chromatography and tandem mass spectrometry (LC-MS/MS)[1]. The analytical performance and metabolite ranges are established on steady-state levels with standard dose (20 mg/day). The ASS score is calculated from all active metabolite concentrations and is reported to predict the effectiveness of Tam therapy. Importantly, ASS scores in the 0-20th percentile are indicative of increased risks for recurrence. Our metabolite testing is approved by New York State and results are reported to the referring physician within 3-5 days of receipt of the sample.

Molecular analysis: For optimal interpretation of Tam metabolite testing, genotyping of 15 important CYP2D6 variants (*2-*11, *15, *17, *29, *35, *41) plus gene duplication is available at Mount Sinai Genetic Testing Laboratory and should be ordered the first time blood is drawn for metabolite testing. Based on the identified CYP2D6 genotype, patients will be reported as ultrarapid, extensive, intermediate or poor metabolizers, and results are reported to the referring physician within 7 days from the receipt of the specimen.

Specimen and Shipping Requirements:

Biochemical analysis: 1 green-top (Sodium Heparin) 5-10 ml tubes of blood drawn before the patient takes their daily dose of Tam. Separate plasma immediately and freeze. Ship frozen specimen on dry ice. Protect from light by wrapping tubes of blood in tin foil. Note that the patient must be on standard dose (20 mg/day) of Tam for at least 3 months prior to testing.

Molecular analysis: 1 lavender-top (EDTA) 5-10 ml tube of blood shipped refrigerated or at room temperature *(do NOT freeze)*.

1. *Jaremko M, et al. Tamoxifen metabolite isomer separation and quantification by liquid chromatography-tandem mass spectrometry. Anal Chem 2010; 82:10186-93.*
2. *Barginear MF, et al. Increasing tamoxien dose in breast cancer patients based on CYP2D6 genotypes and endoxifen levels: effect on active metabolite isomers and the antiestrogenic activity score. Clin Pharmacol Ther 2011; 90 (4): 605-611*
3. *Madlensky L, et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, a nd breast cancer outcomes. Clin Pharmacol Ther 2011. 89 (5): 718-725.*

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