

Submitted by: Sanford Health Pharmacogenomics Committee

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NCCN Guidelines panel: Breast Cancer Panel

On behalf of the Sanford Health Pharmacogenetics Committee, I respectfully request the NCCN Breast Cancer Panel to review the enclosed material from the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and Tamoxifen Therapy in reference to a change in Tamoxifen for breast cancer in patients with CYP2D6 poor metabolizer status.

Specific change: Change Tamoxifen guidelines to state recommendation of alternate hormonal therapy such as Aromatase inhibitors (plus or minus ovarian suppression) for poor metabolizers of CYP2D6.

FDA Clearance: Tamoxifen and Aromatase inhibitors are FDA approved for breast cancer treatment.

Rationale: In support of the proposed change, CPIC guidelines state a strong recommendation for CYP2D6 poor metabolizers to use alternative hormonal therapy such as an aromatase inhibitor plus or minus ovarian suppression due to lower endoxifen concentrations compared to normal metabolizers; higher risk of breast cancer recurrence, event-free and recurrence free survival compared to normal metabolizers.

The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors to some of these publications.

1. Madlensky, L. et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. Clinical pharmacology and therapeutics 89, 718-25 (2011).
2. Ruddy, K.J. et al. Personalized medicine in breast cancer: tamoxifen, endoxifen, and CYP2D6 in clinical practice. Breast Cancer Res Treat 141, 421-7 (2013).
3. Rangel, L.B., Taraba, J.L., Frei, C.R., Smith, L., Rodriguez, G. & Kuhn, J.G. Pharmacogenomic diversity of tamoxifen metabolites and estrogen receptor genes in Hispanics and non-Hispanic whites with breast cancer. Breast Cancer Res Treat 148, 571-80 (2014).
4. Hennig, E.E. et al. Limited predictive value of achieving beneficial plasma (Z)-endoxifen threshold level by CYP2D6 genotyping in tamoxifen-treated Polish women with breast cancer. BMC Cancer 15, 570 (2015)
5. Schroth, W. et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. Jama 302, 1429-36 (2009)

Sincerely,

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