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Title*: Revisit Tamoxifen Pharmacogenomics for TAILORx Breast Cancer Patients*

Tamoxifen is used as adjuvant endocrine therapy in hormone sensitive breast cancer patients to prevent recurrence after primary treatment. Without prophylactic treatment with endocrine therapy (for example, tamoxifen) or chemotherapy, 15% of these patients do have recurrent breast cancer in 10 years. Current National Comprehensive Cancer Network (NCCN) guidelines recommend both adjuvant chemo- and endocrine therapies for most of the carcinoma in situ (CIS) patients for the reduction of mortality. However, stratification of patients based on their risk of recurrence has led to a reevaluation of the need for adjuvant chemotherapy. Research using the 21-gene Oncotype DX strategy identified cancer genomic risk factors and stratified risk levels of breast cancer patients based on Recurrence Scores (RS). The TAILORx (Trial Assigning Individualized Options for Treatment) used the 21-gene Oncotype DX assay to categorize hormone receptor (HR) positive breast cancer population and concluded that patients with mid-range RS using adjuvant endocrine therapy alone is as effective as chemo-endocrine treatment1, suggesting that tamoxifen treatment alone would have comparative efficacy as with chemotherapy. Consequently, without chemotherapy, survival of these patients depends on safe and effective tamoxifen treatment. The evolving understanding of the metabolism and pharmacogenomics of tamoxifen has challenged healthcare providers and patients. Tamoxifen is activated by liver CYP450 enzymes. Among the tamoxifen metabolites, endoxifen is the most potent estrogen receptor inhibitor. Inactivation of tamoxifen metabolites also involves multiple enzymes. In addition, activity levels of these metabolizing enzymes can be affected by other medications, especially antidepressants that are often co-prescribed to the breast cancer patients. Furthermore, considering individual patient factors, clinical trials have historically relied on various criteria that were not all ideal for monitoring tamoxifen therapy, and hence reported conflicting results. Based on current knowledge, decision on mid-range breast cancer treatment may require individualized considerations rather than single risk group-based decision.