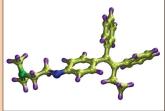
Tamoxifen Benefits and *CYP2D6* Testing in Women With Hormone Receptor—Positive Breast Cancer

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Cancer intervention strategies have been increasingly focused on developing therapies that are personalized and tailored to each individual's unique genetic profile. Evolving understanding of the metabolism and pharmacogenomics of tamoxifen, an early example of targeted therapy for women with hormone receptor—positive breast cancer, has created decision—making challenges for healthcare providers and their patients. This article reviews the pharmacology of tamoxifen, the genetics and physiology of the *CYP2D6* enzyme system that has important effects on tamoxifen metabolism, and subset data analyses from large controlled,

clinical trials that cast new light on previously held beliefs about the utility of *CYP2D6* genotyping for predicting tamoxifen effectiveness and improved breast cancer outcomes in women with early-stage, hormone receptor—positive breast cancer.

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strong focus has been placed in recent years on the development of cancer therapies that are personalized and tailored to each individual's unique genetic profile. Great strides have been made in the area of breast cancer. The use of estrogen- and progesterone-receptor profiling, which began in the 1970s (McGuire, Horowitz, Pearson, & Segaloff, 1977), represents one of the earliest applications of personalized medicine. Evolving understanding of the pharmacogenomics of tamoxifen, an early example of targeted therapy for women with hormone receptor-positive breast cancer, has created decision-making challenges for healthcare providers and their patients. This article will review the pharmacology of tamoxifen, the genetics and physiology of *CYP2D6*, and the clinical implications of both for women with hormone receptor-positive breast cancer.

Pharmacology of Tamoxifen

Adjuvant treatment with tamoxifen therapy over a period of five years has been shown to provide substantial benefit in hormone (estrogen and/or progesterone) receptor-positive breast cancer (stage not specified), reducing disease recurrence by about 50% and breast cancer mortality by about 33% after 15

years of follow-up (Rae et al., 2012). For premenopausal women with hormone-sensitive breast cancer, tamoxifen is the sole choice for adjuvant hormonal therapy (Hertz, McLeod, & Irvin, 2012). As an antiestrogenic agent, tamoxifen has a stronger binding affinity with the estrogen receptor (ER) than does estrogen. However, the tamoxifen compound itself is a relatively weak ER antagonist and is considered a prodrug; the antiestrogenic properties of tamoxifen are derived from its metabolites. The most clinically active metabolite is endoxifen, which has 30-to 100-fold greater affinity for the ER than tamoxifen (Regan et al., 2012; Snozek, O'Kane, & Algeciras-Schimnich, 2009).

The primary mediator in the conversion of tamoxifen to endoxifen is the cytochrome P450 2D6 (CYP2D6) enzyme system (Gaston & Kolesar, 2008; Kelly & Pritchard, 2012; Rae et al., 2012). CYP2D6 activity is genetically coded by a specific gene, but inherited genetic alterations, called CYP2D6 polymorphisms, can result in variations in enzymatic activity (Gaston & Kolesar, 2008). The CYP2D6 system also is involved in the metabolism of many drug classes, including such common drugs as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opioid analgesics, antipsychotic agents, antiarrhythmic agents, and antihistamines (Gaston & Kolesar, 2008).