CYP2D6 pharmacogenomics of tamoxifen treatment

BlueCross BlueShield Association

Record Status
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Authors' objectives
This Assessment evaluates the evidence for CYP2D6 genotyping, compared with no testing, to direct treatment regimen choices for patients at high risk for primary breast cancer or breast cancer recurrence, and to improve survival outcomes.

Authors' conclusions
The question examined in this Assessment is whether patients with CYP2D6 gene variants that result in markedly reduced or absent enzyme function have reduced tamoxifen metabolism and lower endoxifen levels compared with genotypic wild-type extensive metabolizers, and as a result have poorer clinical outcomes. This question rests on the assumption, not yet supported by evidence, that some level of endoxifen is sufficient and necessary for tamoxifen efficacy, and that this level is not achieved in patients with markedly reduced or no CYP2D6 enzymatic function. However, because tamoxifen metabolism is complex and CYP2D6 does not appear to account for all variability in endoxifen levels, it is conceivable that polymorphisms in other tamoxifen metabolic pathway enzymes may affect active metabolite levels, and in theory direct measurement of the metabolite(s) itself might be the better predictor of benefit from tamoxifen treatment. However, measuring metabolite levels is not practical for clinical applications. Whether lower endoxifen levels can affect the pharmacodynamics of tamoxifen, the interaction of tamoxifen metabolites with estrogen receptors, and ultimately tamoxifen efficacy, is unclear. Dissociation constants of even the more weakly binding molecules, including tamoxifen itself, are reportedly still sufficient to effectively block estrogen binding. Moreover, it is estimated that at doses used for adjuvant treatment, which are intended to saturate the estrogen receptor, more than 99% of estrogen receptors are bound by tamoxifen and its metabolites. Lacking the appropriate mechanistic evidence, it remains to examine the clinical evidence, the bulk of which addresses clinical validity, the CYP2D6 genotype-tamoxifen treatment outcome association. As noted, heterogeneous results are observed across studies. Heterogeneity in effect estimates, both in magnitude and significance, is likely due to the lack of power in most studies and potential biases. The analysis of archived samples from 2 large completed clinical trials was undertaken to achieve adequate power, to more fully evaluate CYP2D6 genotype, to evaluate aromatase inhibitor-treated control populations in tandem, and to avoid potential sources of bias. That the results of these studies discovered no evidence of association between CYP2D6 genotype and either tamoxifen- or aromatase inhibitor-treated patient outcomes has suggested that using results of CYP2D6 genetic testing to influence decisions about tamoxifen treatment is not currently warranted.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for primary breast cancer or breast cancer recurrence meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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