Title: Gene-expression signatures predicting therapeutic response of breast tumors to tamoxifen
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Abstract #292: Two thirds of breast tumors express estrogen receptor and are candidates for treatment with antiestrogens such as tamoxifen. However, tamoxifen treatment is effective only in 30-40% of cases [EBCTCG, 1998], and histopathological characteristics of the tumors are insufficient to predict tumor evolution upon tamoxifen treatment.
In this study, a top-down approach was adopted in order to identify putative biomarkers of tamoxifen response for ER positive breast cancer patients. Individual markers of tamoxifen-response were identified in combined analysis on three publically available datasets using a Cox PH regression model testing the significance of an interaction term between treatment and the prognostic value of a gene. ~400 univariate markers were derived from the meta-analysis, which can predict cancer relapse following adjuvant tamoxifen therapy. These biomarkers are contained into four clusters of genes that whose expression levels co-vary across tumors. Grouped, these genes are better predictors of recurrence than previously published prognostic markers. Furthermore, co-variation would suggest that these clusters of genes are regulated by common pathways/transcription factors. Pathway enrichment analysis and network inference of the derived marker clusters has identified genes related to the ubiquitin-proteosome pathway, associated with intracellular protein degradation, and the cholesterol synthesis pathway, which can regulate local estrogen production and/or cellular membrane integrity. These pathways may represent targets for the development of combined therapies tailored to patients with a high risk of relapse on tamoxifen alone.
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