Reviewer’s report

Title: Hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites

Version: 3 Date: 19 October 2013

Reviewer: N. Lynn Henry

Reviewer’s report:

The authors report associations between hot flashes and tamoxifen metabolites in 109 subjects.

Major compulsory revisions:

1. It remains difficult to understand how this study was conducted. It appears that patients were treated with tamoxifen as standard of care, and somehow they had blood samples drawn during treatment. In the first paragraph of the Patients and Methods section it states that they were determined as part of routine clinical care. However the first sentence under serum sample handling suggests that they were run in batch (not part of routine care). In the following paragraph it states that DNA was isolated from serum left over from the metabolite analysis, which also suggests the DNA isolation and genotyping was done in batch. The authors state that since this was an observational study with a single questionnaire they were not required to obtain IRB approval, but there is no mention of how they obtained patient consent for the blood draw or the genotyping.

2. Serum samples were collected between July 2008 and December 2011. When were the questionnaires completed? If all completed at one time after December 2011, it is unclear how patients could remember what was going on at the time their serum was drawn, since that could have been more than 3 years before. This would have a serious impact on the quality of the data, which is the key endpoint of the study.

3. What quality assurance was done for the genotyping? Were 10% of genotypes repeated to confirm the assay was working appropriately?

4. How could missing CYP2D6 values be imputed with population medians? Were all of the patients with missing genotype assumed to be EMs? When 20% of the results are missing, and this is critical for the analysis, these assumptions could significantly impact the findings.

5. How were concomitant medications collected? It is difficult to believe that 64% of patients reported moderate-to-severe hot flashes and none was being treated.

6. The final sentence of the conclusion still makes a statement that is not supported by evidence. It was not studied in this analysis and there are insufficient data in the literature to support this conclusion (only a single report,
Minor essential revisions
1. P values should be listed in the tables (especially table 2)

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests