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Letter to the Editors

CYP2D6 genotyping and tamoxifen in the treatment of post-menopausal breast cancer – a reply

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We appreciate the opportunity to clarify further the issues raised by Damkier [1] related to our recent correspondence [2] in which we summarized the available evidence of the prediction of tamoxifen outcome by genetic variation of CYP2D6 in post-menopausal women with early breast cancer for the purpose of rectifying current controversies. Damkier takes the position that we failed to discuss original findings by others. However we respectfully disagree that the quoted articles [3, 4] can have an impact on our conclusions.

There is no doubt that concordance of genotyping data of germline- and tumour-derived DNA can be achieved in specifically designed studies. However, both quoted studies [3, 4] are irrelevant to the fact in question. In particular, Rae *et al*. [3] fall short of demonstrating such concordance in the very same study population of their previously published pharmacogenetic analyses of BIG1-98 [5] or ATAC [6]. With this regard, it is fair to point the uninitiated reader's attention to the complexity of the CYP2D6 polymorphism for which deviation from Hardy–Weinberg equilibrium (HWE) is possible, particularly when formalin-fixed paraffin-embedded (FFPE) tumour tissue is used for genotyping [2, 7]. The criticism raised by us and others is not a deviation from HWE *per se* but a massive violation in the order of magnitude of 10^{-92} that can only be explained by severe methodological flaws. Thus, Rae *et al*. [3] clearly failed to dispel the doubts on the validity of their previous studies [5, 6]. Schroth *et al*. [8] used updated data sets with regard to *CYP2D6* genotyping and follow-up. Nearly half of the DNA samples were germline-derived and only the remainder was tumour-derived with the observed minor deviation from HWE being limited to the latter. The use of whole tumour sections with an average non-tumour cell content of 51% per section and sample reassured that germline alleles were represented in most cases [7]. Such quality control data have neither been provided [5, 6] nor demanded [9] for the prominent studies claiming no association between *CYP2D6* genotype and tamoxifen outcome, a reason why US researchers may have referred to the study by Schroth *et al*. [8] as the most significant with regard to CYP2D6 tamoxifen pharmacogenetics [10].

On the issue of concomitant treatment we refer to CYP2D6 inhibitors listed in a recent comprehensive review by Zanger & Schwab [11] including paroxetine and fluoxetine. These were shown to inhibit CYP2D6 *in vivo* or in human liver microsomes significantly and their inhibitory constants are known to be different. Although published data with regard to their interaction with tamoxifen may appear inconclusive, attention should be paid to differences in relevant study sizes and designs which may prohibit direct study comparisons. We highly respect the recommendations by the American Society of Clinical Oncology (ASCO) and international regulatory agencies for caution with CYP2D6 inhibitors when using tamoxifen as summarized in our correspondence [2].

Competing Interests

Both authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare HB and MS report scientific collaborations with Roche Molecular Diagnostics and Siemens Healthcare Diagnostics Products GmbH in the previous 3 years. No other relationships or activities exist that could have influenced the submitted work.

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