Quantitative Methods for Prediction of the Effect of Cytochrome P450 Gene Polymorphisms on Substrate Drug Exposure: Authors' Reply

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We would like to thank Goutelle and Tod for their interest in our study and for bringing their previous publication on cytochrome P450 2C19 (*CYP2C19*) polymorphisms to our attention [1]. First, we would like to clarify that we have not claimed our study to be the first to provide precise estimates of the influence of *CYP2C19* genotypes on (es)citalopram exposure, but the first to quantify this influence by means of a systematic review and meta-analysis [2]. We still believe this holds true and would like to point out a few pivotal differences between our meta-analysis and the study by Goutelle et al. Most importantly, our analysis was based on a comprehensive literature review to assure that the estimates took into account all available pharmacokinetic data, while their analysis was based on a limited number of studies assembled in a fashion that was not described in detail. In addition, we restricted our scope to studies on (es)citalopram, accounting for the possibility that the impact of *CYP2C19* polymorphisms may differ between different *CYP2C19* substrates. In contrast, the analysis by Goutelle and co-workers was based on studies of a large number of *CYP2C19* substrates, implicitly assuming that the clearance attributable to *CYP2C19* would be affected equally

for all substrates. Only two of these studies provided data specifically concerning citalopram, as compared with the 14 publications included in our meta-analysis. The fact that both methods produced similar results is reassuring, because it confirms both the robustness of the pharmacogenetic effect estimates and the usefulness of the unified modeling approach proposed by Ohno et al. [3] and Tod et al. [4].

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