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Response to “ Methodological Considerations on CYP2D6 Phenoconversion Due to Drug-Drug Interaction”

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Keywords

CYP2D6; dextromethorphan; metoprolol; phenotyping; precision medicine

We thank doctors Ziesenitz and Mikus for their detailed reading our work, *CYP2D6 Genotype Phenotype Discordance Due to Drug-Drug Interaction*.⁽¹⁾ We agree that the concept of phenoconversion is important and understudied, though few studies have been performed to demonstrate this concept.

The authors raise concern about the use of the term “microdose” and have referenced a document developed by the FDA for use in “exploratory IND studies” (though the reference provided is inactive). Clearly this study was not an exploratory IND study and we would argue that the definition is not as standardized as the authors have suggested. We acknowledge that a more appropriate term may have been “low-dose” though the term “microdose” has been used for this dose of dextromethorphan by other authors in the field. (2) Regardless, we believe this point is largely semantic and does not have a bearing on the conclusions of our study.

We also agree that the number of subjects examined in this study is not enough to change clinical practice; a much larger prospective study is necessary to make a definitive conclusion, as we noted in the limitations and discussion. This work demonstrates the need for such a study. A detailed reading of our manuscripts explains the discrepancy in CYP2D6 subjects to which the authors have referred. The outlined numbers of 2, 10, 23, and 4 refer to the numbers of *CYP2D6* genotypes while the abstract refers to the phenotype of these subjects. The authors should note that the standard nomenclature for writing human genotypes are italics, as above, while phenotype and enzyme function non-italicized, as we had reported in the abstract. Thus, it should be clear that the abstract refers to phenotype, not genotype.

We appreciate the request for more data and had not included the AUC data due to the length of the manuscript and our reliance our outcome being based upon the 3 hour ratio. We

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actually had four data points, the first was time zero, not a blank sample. However, we have provided these data below to satisfy their request.

Mikus and Zlesenitz raise a concern about lack of a 3 hour blood draw time point. We believe, as has been demonstrated by other investigators examining this phenotyping probe drug and other drug metabolizing enzymes, the 3 hour time point most accurately represents enzyme phenotype and that constructing a kinetic curve more accurately reflects the 3 hour value than a single blood draw at this time point.(3–5) A single blood draw may be prone to more variability than the data points we have outlined in our methods, and is far better modeled than a single ratio.

The derived interaction term was developed in an attempt to summarize the effects of all CYP2D6 dependent drugs in a single term, and thus, allow integration into predictive models. The authors will note that this term did not perform as we had hoped, though we felt that providing these data may spark other investigators to explore this concept further. In the age of electronic medical records with statistical modeling, a unified term that predicts drug metabolizing enzyme phenotype in the setting of phenoconversion would benefit clinicians and patients.

Finally, we disagree that the sample size was insufficient, as was outlined by the a-priori power calculation. As acknowledged above and in the manuscript, population level studies are necessary in order for clinicians to confidently change dose or therapy due to concern of phenoconversion.

In summary, our power was adequate to examine this question, a close reading of the manuscript, with attention to standard nomenclature answers the majority of the questions outlined, and we have provided further data to support our findings. In the near future, we hope to see a robust study on this topic from doctors Ziesenitz and Mikus to add to knowledge we have provided.

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Dextromethorphan					
Phenotype	Median AUC ng/ml*hour	PM 38.59	IM 7.10	NM 0.80	UM -