Department of Epidemiology and Biostatistics

The University of Western Ontario

1151 Richmond Street

London, ON, N6A 3K7

Canada

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Brian J. Zikmund-Fisher, Editor-in-Chief,

Medical Decision Making

Dear Professor Zikmund-Fisher,

My co-authors Rommel Tirona, Simon Bonner, Dan Lizotte and I would like to submit the attached manuscript, entitled “*Developing and Evaluating Pharmacokinetics-Driven Dynamic Personalized Medicine: A Framework and Case Study”* for consideration for publication in Medical Decision Making.

This work uses data previously reported in

*Tirona, Rommel G., et al. "Apixaban and rosuvastatin pharmacokinetics in nonalcoholic fatty liver disease." Drug Metabolism and Disposition 46.5 (2018): 485-492.*

and extends a model initially presented in

*Pananos, A. Demetri, and Daniel J. Lizotte. "Comparisons between Hamiltonian Monte Carlo and maximum a posteriori for a Bayesian model for Apixaban induction dose & dose personalization." Machine Learning for Healthcare Conference. PMLR, 2020.*

to include effects of relevant clinical variables on the pharmacokinetic parameters. Additionally, our work presents a framework for using models similar to ours to decide if additional control over dose selection in personalized medicine vis a vis more complex models is worth the additional burden. Our main contributions are:

* A hierarchical Bayesian model of apixaban pharmacokinetics which can estimate the effects of routinely collected clinical variables, as well as between patient variability in pharmacokinetic parameters.
* A framework for assessing if more complex modes of personalized dosing yield lead to benefits which outweigh the necessary burden to implement said methods.
* A fully worked simulated case study demonstrating our framework.

My co-authors are aware of this submission and consent to its review by Medical Decision Making. We have no conflicts of interest to declare. The funding agreement ensured the authors’ independence in designing the study, interpreting the data, writing, and publishing the report.

Thank you for your time and consideration,

Sincerely

Demetri Pananos