Incorporating Prior Knowledge into Adverse Drug Reaction Prediction Models: Mechanistic Modeling Approach

Ilia Rattsev[1][0000-0001-6284-3204]

[1] Johns Hopkins University School of Medicine, Baltimore MD 21205, USA
irattse1@jhmi.edu

Abstract. To address the current gaps in the translation of pharmacogenomics (PGx) into clinic, we propose developing a framework for personalized prediction of adverse drug reactions (ADRs) that uses a combination of prior knowledge-based and data-driven approaches to arrive to the predictions. The proposed framework uses mechanistic quantitative systems pharmacology (QSP) model as the backbone and employs machine learning approaches for individualized parameter estimation. The purpose of this framework is to incorporate multiple risk factors into the ADR risk assessment model, while requiring smaller sample size for training and maintaining high interpretability. Furthermore, we will evaluate clinician perspectives on the model usefulness in the clinical setting and inform the design of a clinical decision support (CDS) tool to communicate the model outcome to the clinicians.

Keywords: predictive modeling, pharmacogenomics, precision medicine, knowledge-based reasoning, computational modeling

1 Significance and Innovation

1.1 Genetic risk factors are important predictors of adverse drug reactions that are rarely considered in treatment selection.

Adverse drug reactions (ADRs) represent a major cause or morbidity and mortality worldwide, accounting for up to 8.1% of all hospital admissions in the US and up to 12.4% of admissions in the oncology setting [1, 2]. In the United States alone, it is estimated that ADRs result in more than 100,000 deaths annually and rank among the top 6 leading causes of death [3]. Approximately 30% of ADRs at hospital admissions are caused by drugs with known pharmacogenomic (PGx) annotations, suggesting that they could be predicted based on patient's genotype [1]. Recent advances in statistical genetics and genotyping technology led to the discovery of many novel PGx associations through candidate gene and genome-wide association studies and improved our understanding of genetic contributions to ADRs [4]. Despite this, PGx-guided treatment selection has not been widely implemented in clinic [5].

Lack of clinical validity of basic PGx discoveries has been identified as one of the critical translational gaps halting clinical implementation of PGx [6, 7]. The demonstration of clinical validity of PGx markers has been limited by the small effect size of individual variants, failing to explain sufficient variability to achieve high predictive validity. Instead, several genetic factors may contribute to drug response at the same time, and all of them need to be considered during risk assessment [8–10]. In addition, it is important to acknowledge that it is a complex interplay between genetic, clinical, and environmental risk factors that determines the drug response phenotype [5]. Multimodal algorithms that incorporate the effect of all these variables need to be developed for improved ADR prediction [5, 8].

1.2 Data-driven approaches require large sample sizes and are often not trusted among clinicians.

The most common strategy to incorporate multiple risk factors into ADR prediction models involves using machine learning (ML) approaches [11–13]. However, ML algorithms require large sample sizes for training, which are difficult to obtain for PGx studies. The emergence of large biobanks that combine patient's genomic data with their electronic health records (EHRs) may help overcome this problem in the future. Despite their early promise, biobanks have been of limited use in PGx studies due the lack of clearly recorded drug response phenotype [14]. As biobanks get larger and more complete, and as phenotyping algorithms develop, it may become possible to obtain large samples required for ML tasks. However, limited data availability will always remain a relevant problem for novel drugs, and alternative risk assessment strategies are needed for these cases.

Another challenge associated with data-driven approaches is their poor interpretability, which creates the distrust among clinicians [15–18]. To be successfully implemented in the clinic, the predictive model needs to be able to explain how it arrives to the prediction. Otherwise, the recommendation given by the model is likely to be ignored [18, 19]. In addition to enhancing the trust among physicians, explainable predictions may help providers communicate the decision to the patients more effectively [15, 19–21].

2 Prior Work

We believe that there is an unrealized potential to utilize our extensive knowledge of pharmacology and human physiology in predictive model building. By developing a physiology-based quantitative systems pharmacology (QSP) model, we believe that we can improve ADR risk assessment, while maintaining transparency and interpretability. QSP modeling approaches have been widely used in industry during drug development process [22, 23] and in academia to better understand complex biological phenomena, such as cancer metastasis [24] or immune response to SARS-CoV-2 [25]. However, very few models utilized such approach to predict drug response, and none focused on predicting toxicity [26, 27]. Ultimately, drug response is related to the systemic and

cellular exposure to the drug and its metabolites [28]. In that case, accurate assessment of drug exposure should provide the necessary information for inferring toxicity. Due to physiological differences between individuals, the same systemic exposure to the drug may result in different response. Accounting for these differences comprises the second piece of information required to predict an ADR. Mathematical modeling approaches allow us to mechanistically incorporate the physiological components, including genetic effects, as structural elements of the model, resulting in a more accurate representation of a complex biological system. There is a universal acceptance of dosing guidelines that account for impaired liver and kidney function, which are often developed using pharmacokinetic/pharmacodynamic (PK/PD) modeling. However, the adjustments based on PGx factors that have the same effect on systemic exposure as hepatic or renal impairment are not trusted as much [14, 28].

We hope that using a PK/PD approach at the backbone of the predictive algorithm will promote higher confidence in using PGx-guided recommendations among clinicians. By extensively using prior knowledge to infer parameter values, we reduce the sample size required to build the model, overcoming a major limitation of data-driven approaches. We hypothesize that the QSP model developed in this work will improve the prediction of aromatase inhibitor toxicity and provide functionality for clinical use. We have chosen the case study of aromatase inhibitor-induced bone toxicity due to the high prevalence of the reaction, unknown mechanism underlying toxicity and an unresolved need for personalized risk assessment in the clinic [29, 30].

3 Objective

To facilitate the translation of PGx into clinical care, we propose developing a novel framework for ADR prediction that incorporates prior knowledge of human physiology and drug pharmacology into the model backbone. Using the case study of aromatase inhibitor-induced bone toxicity, this thesis will demonstrate how such framework can be used to overcome the challenges associated with data-driven methods.

In Aim 1 we will develop a mechanistic model of aromatase inhibitor-induced bone toxicity. We will first build a mathematical model of bone remodeling and combine it with a physiologically-based PK/PD (PBPK/PD) model of exemestane. We will then use the prior knowledge of how PGx variants affect biological processes to mechanistically incorporate their effect.

In Aim 2 we will enable our model to make personalized predictions of aromatase inhibitor-induced bone toxicity and simulate the effect of interventions to manage the symptoms. We will use data-driven approaches to incorporate interindividual variability into the model and use patient-specific parameters to make personalized predictions. We will then simulate the effect of interventions commonly employed to manage the toxicity and determine the subgroups of individuals that many differentially benefit from these interventions.

In Aim 3 we will evaluate physician perspectives on clinical usefulness of the model. Via qualitative interviews and surveys, we will evaluate clinicians' acceptance and per-

ceived trustworthiness of the model, determine the most effective way of communicating model predictions to the physician, and inform the design of a clinical decision support (CDS) tool.

4 Methods

4.1 Aim 1: Developing a QSP model.

Several mathematical models of bone remodeling exist in the literature [31-34]. After conducting a comprehensive review, we have adapted the models developed by Farhat et al. [33] and Jörg et al. [34] and incorporated the effect of estrogen on bone dynamics, as estrogen deprivation is a direct physiological effect of aromatase inhibitor therapy. When possible, the parameters describing the system were transferred from the adapted models, while the parameters describing the newly added terms were obtained from the literature. For model validation clinical and pharmacokinetic data for women enrolled in clinical trials of the medications that alter the activity of the molecular and cellular factors included in our bone remodeling network.

We will then develop a PBPK/PD model of exemestane to describe the drug distribution throughout the body. To avoid unnecessary complexity of the model and aid in parameter estimation, we will retain only the tissues relevant to drug absorption (stomach and small intestine), metabolism (small intestine and liver), site of action (adipose) and site of toxicity (bone). Next, we will model endogenous estrogen production by aromatase in the absence of the inhibitor. To model the PD component, we will mechanistically incorporate the interaction of exemestane with aromatase and relate it to estrogen suppression. The genes known to affect PK of exemestane, such as those encoding metabolizing enzymes and transporters, will be included in the model explicitly via introducing an interaction term between the drug and the specific protein. Physiological parameters, such as tissue volumes and blood flows, will be individualized and calculated based on body weight. Physicochemical properties of the drug and its active metabolite will be obtained from the Food and Drug Administration (FDA) reports, published literature, and in silico predictions. Metabolic rates extracted from in vitro studies will be scaled to represent human physiology. Initial conditions, such as endogenous molecule concentrations will be obtained from prior literature. Finally, the PBPK/PD model will be merged with the mathematical model of bone remodeling to constitute the complete QSP model.

4.2 Aim 2: Building personalized prediction model.

After we define the structure of the model and obtain the parameters values, we will investigate the effect of interindividual variability on drug exposure and estrogen suppression by selecting a subset of parameters, for which high variability is expected between individuals. We will then create a virtual population of 1,000 patients that will be randomly sampled from the population distribution of parameter values. Based on the simulations in virtual patients, we will be able to determine highly influential parameters and obtain 90% confidence intervals for the population concentration-time

profiles for exemestane, estrogen and bone turnover metabolites. We will then use publicly available clinical, pharmacokinetic, and aggregated genetic data for women enrolled in clinical trials of aromatase inhibitors and osteoporosis medications to estimate the individual-level parameter values with ML approaches. By using ML to estimate the parameters values describing actual physiological processes, such as enzyme kinetics and protein expression, we can use a wider variety of data sources than for the specific drug response prediction tasks.

To evaluate our model, we will obtain the individual-level clinical, genetic, pharmacokinetic and laboratory data for 244 women with hormone receptor-positive breast cancer enrolled in an Exemestane and Letrozole Pharmacogenetics (ELPh) trial and taking exemestane [35]. Using the QSP model developed in Aim 1 and the individualized parameter values obtained in Aim 2, we will simulate administration of 25 mg of exemestane once daily for three months for each individual. make personalized predictions of bone toxicity for the trial participants. The predicted concentrations of bone turnover metabolites and bone mineral density (BMD) values will then be compared to the observed measurements at 3 months. In addition, we will evaluate the ability of our model to predict a binary outcome of bone toxicity, such as bone loss and osteoporosis, by calculating its sensitivity, specificity, and positive predictive value.

The mechanistic nature of our model enables us to introduce perturbations into the system and simulate its behavior. There exist several interventional strategies that aim to prevent or mitigate the severity of aromatase inhibitor-induced bone toxicity, including dose adjustment, bisphosphonate therapy, and switch to tamoxifen or to a non-steroidal aromatase inhibitor [36]. The subset of individuals from the ELPh cohort experiencing exemestane-induced bone toxicity will be selected, and all 4 interventions will be simulated for each individual. To illustrate how such simulations may be useful for clinical decision-making, we will model the patient trajectory with and without preventative interventions. Based on the outcome of the simulation, each intervention will be classified as either successful or unsuccessful for the individual, according to its ability to resolve the symptoms quickly without sacrificing efficacy beyond acceptable level. To determine whether there exist subgroups of individuals that are more likely to benefit from the intervention than others, we will stratify the subjects by their demographics, genetics, and clinical characteristics, and calculate the proportion of individuals predicted to benefit from the intervention in each subgroup. The statistically significant differences between the groups will be detected using the chi-squared test.

4.3 Aim 3: Evaluating clinician perspectives.

Once the model is developed, it is important to assess clinicians' perspectives on its usefulness and their willingness to use it in practice. Therefore, the goals of Aim 3 are to evaluate the perceived usefulness of the model in the clinical setting and to inform the design of the initial prototype for the CDS tool. First, we will determine, via discussions with our clinical collaborators, how the proposed predictive model may fit within the existing clinical workflow. Second, we will interview 10 clinical fellows to evaluate physician preferences regarding the desired features of a CDS tool designed

to help clinicians choose an appropriate intervention and enhance patient-provider communication. Based on physicians' feedback, we will develop a low-fidelity prototype of the tool and evaluate clinician acceptance of the model via a web-based survey. Clinician acceptance will be calculated as a composite score consisting of 6 previously validated constructs [37]: intention to use, perceived usefulness, perceived service benefits, perceived service risks, perceived thread to professional autonomy, and trusting believes. We are hoping that accomplishing this aim will help us gain a better understanding of the clinical utility of the model and identify potential areas for improvement to ensure successful clinical implementation in the future.

5 Expected Results

By accomplishing the aims, we will deliver a framework for explainable personalized predictions of treatment response that integrates prior knowledge in the model backbone and is accepted by clinicians. This strategy holds promise to enable personalized medicine for patients undergoing aromatase inhibitor therapy with potential to generalize to other treatments for which there is a balance between therapeutic benefit and risk for ADRs.

6 Questions for the Consortium

We would greatly appreciate consortium's feedback regarding:

- whether there are any natural language processing approaches to extract the parameter values for the mathematical model from existing literature they would recommend;
- how to separate the uncertainty in parameter estimates from natural interindividual variability in parameter values during parameter identification process;
- how to choose whether to use Markov chain Monte Carlo simulations or ML methods for parameter estimation during individualization of the model;
- the potential publication venues for different parts of the thesis.

Acknowledgments. I would like to thank my thesis advisor, Casey Overby Taylor, for her mentorship and guidance along the way. We would also like to thank Dr. Vered Stearns, Dr. Feilim Mac Gabhann, Dr. Daniel Hertz and Dr. Ciprian Crainiceanu for serving on thesis committee and providing valuable feedback regarding the problem scope and proposed research plan. This study is supported by an NIH NHGRI Genomic Innovator award [R35 HG010714 to C.O.T.].

Disclosure of Interests. The authors have no competing interests to declare.

References

1. Chan SL, Ang X, Sani LL, et al. Prevalence and characteristics of adverse drug reactions at admission to hospital: a prospective observational study. *Br J Clin Pharmacol*. 2016;82(6):1636-1646. doi:10.1111/BCP.13081

2. Chan A, Soh D, Ko Y, Huang YC, Chiang J. Characteristics of unplanned hospital admissions due to drug-related problems in cancer patients. *Support Care Cancer*. 2014;22(7):1875-1881. doi:10.1007/S00520-014-2160-0
3. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200-1205. doi:10.1001/JAMA.279.15.1200
4. McInnes G, Yee SW, Pershad Y, Altman RB. Genomewide Association Studies in Pharmacogenomics. *Clin Pharmacol Ther*. 2021;110(3):637-648. doi:10.1002/CPT.2349
5. Giri J, Moyer AM, Bielinski SJ, Caraballo PJ. Concepts Driving Pharmacogenomics Implementation Into Everyday Healthcare. *Pharmgenomics Pers Med*. 2019;12:305. doi:10.2147/PGPM.S193185
6. Pirmohamed M. Acceptance of Biomarker-Based Tests for Application in Clinical Practice: Criteria and Obstacles. *Clin Pharmacol Ther*. 2010;88(6):862-866. doi:10.1038/CLPT.2010.245
7. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. *Annu Rev Genomics Hum Genet*. 2014;15:349-370. doi:10.1146/annurev-genom-090413-025419
8. Nelson MR, Johnson T, Warren L, et al. The genetics of drug efficacy: opportunities and challenges. *Nat Rev Genet*. 2016;17(4):197-206. doi:10.1038/NRG.2016.12
9. Chhibber A, Kroetz DL, Tantisira KG, et al. Genomic architecture of pharmacological efficacy and adverse events. *Pharmacogenomics*. 2014;15(16):2025-2048. doi:10.2217/pgs.14.144
10. Relling M V., Evans WE. Pharmacogenomics in the clinic. *Nature*. 2015;526(7573):343. doi:10.1038/NATURE15817
11. Duong SQ, Crowson CS, Athreya A, et al. Clinical predictors of response to methotrexate in patients with rheumatoid arthritis: a machine learning approach using clinical trial data. *Arthritis Res Ther*. 2022;24(1). doi:10.1186/S13075-022-02851-5
12. Juan-Salvadores P, Veiga C, Díaz VAJ, et al. Using Machine Learning Techniques to Predict MACE in Very Young Acute Coronary Syndrome Patients. *Diagnostics (Basel)*. 2022;12(2). doi:10.3390/DIAGNOSTICS12020422
13. Huang C, Clayton EA, Matyunina L V., et al. Machine learning predicts individual cancer patient responses to therapeutic drugs with high accuracy. *Sci Rep*. 2018;8(1). doi:10.1038/S41598-018-34753-5
14. Pirmohamed M. Pharmacogenomics: current status and future perspectives. *Nat Rev Genet*. 2023;24(6):350-362. doi:10.1038/S41576-022-00572-8
15. Diprose WK, Buist N, Hua N, Thurier Q, Shand G, Robinson R. Physician understanding, explainability, and trust in a hypothetical machine learning risk calculator. *J Am Med Inform Assoc*. 2020;27(4):592-600. doi:10.1093/JAMIA/OCZ229
16. Moss L, Corsar D, Shaw M, Piper I, Hawthorne C. Demystifying the Black Box: The Importance of Interpretability of Predictive Models in Neurocritical Care. *Neurocrit Care*. 2022;37(Suppl 2):185-191. doi:10.1007/S12028-022-01504-4
17. Payrovnaziri SN, Chen Z, Rengifo-Moreno P, et al. Explainable artificial intelligence models using real-world electronic health record data: a systematic scoping review. *J Am Med Inform Assoc*. 2020;27(7):1173. doi:10.1093/JAMIA/OCAA053
18. Petkus H, Hoogewerf J, Wyatt JC. What do senior physicians think about AI and clinical decision support systems: Quantitative and qualitative analysis of data from specialty societies. *Clinical Medicine*. 2020;20(3):324. doi:10.7861/CLINMED.2019-0317

19. Alam L, Mueller S. Examining the effect of explanation on satisfaction and trust in AI diagnostic systems. *BMC Med Inform Decis Mak*. 2021;21(1). doi:10.1186/S12911-021-01542-6
20. Arbelaez Ossa L, Starke G, Lorenzini G, Vogt JE, Shaw DM, Elger BS. Re-focusing explainability in medicine. *Digit Health*. 2022;8. doi:10.1177/20552076221074488
21. Squassina A, Manchia M, Manolopoulos VG, et al. Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice. *Pharmacogenomics*. 2010;11(8):1149-1167. doi:10.2217/PGS.10.97
22. Lu D, Yadav R, Holder P, et al. Complex PK-PD of an engineered IL-15/IL-15Rα-Fc fusion protein in cynomolgus monkeys: QSP modeling of lymphocyte dynamics. *Eur J Pharm Sci.* 2023;186:106450. doi:10.1016/j.ejps.2023.106450
23. Scheuher B, Ghusinga KR, McGirr K, et al. Towards a platform quantitative systems pharmacology (QSP) model for preclinical to clinical translation of antibody drug conjugates (ADCs). *J Pharmacokinet Pharmacodyn.* Published online October 3, 2023. doi:10.1007/s10928-023-09884-6
24. Norton KA, Gong C, Jamalian S, Popel AS. Multiscale Agent-Based and Hybrid Modeling of the Tumor Immune Microenvironment. *Processes (Basel).* 2019;7(1):37. doi:10.3390/pr7010037
25. Dai W, Rao R, Sher A, Tania N, Musante CJ, Allen R. A Prototype QSP Model of the Immune Response to SARS-CoV-2 for Community Development. *CPT Pharmacometrics Syst Pharmacol.* 2021;10(1):18-29. doi:10.1002/psp4.12574
26. Arulraj T, Wang H, Emens LA, Santa-Maria CA, Popel AS. A transcriptome-informed QSP model of metastatic triple-negative breast cancer identifies predictive biomarkers for PD-1 inhibition. *Sci Adv.* 2023;9(26):eadg0289. doi:10.1126/sciadv.adg0289
27. Coletti R, Leonardelli L, Parolo S, Marchetti L. A QSP model of prostate cancer immunotherapy to identify effective combination therapies. *Sci Rep.* 2020;10(1):9063. doi:10.1038/s41598-020-65590-0
28. Pirmohamed M, Hughes DA. Pharmacogenetic tests: the need for a level playing field. *Nature Reviews Drug Discovery 2013 12:1*. 2012;12(1):3-4. doi:10.1038/nrd3921
29. Hyder T, Marino CC, Ahmad S, Nasrazadani A, Brufsky AM. Aromatase Inhibitor-Associated Musculoskeletal Syndrome: Understanding Mechanisms and Management. *Front Endocrinol (Lausanne)*. 2021;12. doi:10.3389/FENDO.2021.713700
30. Rattsev I, Stearns V, Blackford AL, et al. Incorporation of emergent symptoms and genetic covariates improves prediction of aromatase inhibitor therapy discontinuation. *JAMIA Open.* 2024;7(1):ooae006. doi:10.1093/jamiaopen/ooae006
31. Ait Oumghar I, Barkaoui A, Chabrand P. Toward a Mathematical Modeling of Diseases' Impact on Bone Remodeling: Technical Review. *Front Bioeng Biotechnol.* 2020;8:584198. Published 2020 Nov 2. doi:10.3389/fbioe.2020.584198
32. Pivonka P, Zimak J, Smith DW, et al. Model structure and control of bone remodeling: a theoretical study. *Bone.* 2008;43(2):249-263. doi:10.1016/j.bone.2008.03.025
33. Farhat A, Jiang D, Cui D, Keller ET, Jackson TL. An integrative model of prostate cancer interaction with the bone microenvironment. *Math Biosci.* 2017;294:1-14. doi:10.1016/j.mbs.2017.09.005
34. Jörg DJ, Fuertinger DH, Cherif A, et al. Modeling osteoporosis to design and optimize pharmacological therapies comprising multiple drug types. *Elife.* 2022;11:e76228. doi:10.7554/eLife.76228
35. Hertz DL, Douglas JA, Miller RM, et al. Genome-wide association study of aromatase inhibitor discontinuation due to musculoskeletal symptoms. *Support Care Cancer.* 2022;30(10):8059-8067. doi:10.1007/s00520-022-07243-8

36. Gupta A, Henry NL, Loprinzi CL. Management of Aromatase Inhibitor–Induced Musculoskeletal Symptoms. *JCO Oncol Pract*. 2020;16(11):733-739. doi:10.1200/op.20.00113
37. Jansen-Kosterink S, van Velsen L, Cabrita M. Clinician acceptance of complex clinical decision support systems for treatment allocation of patients with chronic low back pain. BMC Med Inform Decis Mak. 2021;21(1):137. doi:10.1186/s12911-021-01502-0