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Predicting Pharmacokinetic Variability and Drug Interaction Risk Using Omics-Based Biomarkers

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ABSTRACT

Interindividual variability in drug pharmacokinetics and susceptibility to drug–drug interactions remain major barriers in precision dosing, particularly for narrow therapeutic index drugs. While genetic factors contribute, much variability arises from dynamic influences such as physiology, disease, age, diet, microbiome, and concomitant medications. Conventional approaches provide limited retrospective insight. Emerging phenotypic biomarkers offer a proactive, mechanism-based strategy to quantify variability, improve exposure prediction, assess drug interaction risk, and individualize dosing beyond pharmacogenomics.

Interindividual variability in drug pharmacokinetics (PK) and drug–drug interactions (DDIs) remain some of the most pressing challenges in translational and clinical pharmacology. For many drugs, particularly those with a narrow therapeutic index such as tacrolimus, warfarin, carbamazepine, and digoxin, small differences in systemic exposure can determine whether a therapy is effective, ineffective or toxic. Multiple intrinsic and extrinsic factors contribute to variability, including genetics, liver or kidney dysfunction, other disease states (e.g., inflammation), age, sex, diet, microbiome, and concomitant medications. Established tools such as pharmacogenomics (PGx), population pharmacokinetic (popPK) modeling, and therapeutic drug monitoring (TDM) have advanced precision dosing but have important limitations as they do not capture the mechanistic basis of variability.

Over the past two decades, PGx has been a cornerstone of precision medicine. Genotype-guided prescribing strategies for CYP2D6, CYP2C19, and HLA-B*57:01 exemplify the clinical utility of PGx in stratifying patients into risk categories. However, PGx primarily captures inherited genetic variability and does not account for dynamic physiological and environmental influences. For instance, while CYP3A5 genotype is a major determinant of tacrolimus clearance, it explains only a fraction of observed variability [1]. Consideration of CYP3A4 variability, particularly among CYP3A5 non-expressors, is critical in predicting tacrolimus exposure. Moreover, PGx provides largely categorical classifications (e.g., poor, intermediate, or ultrarapid metabolizers) that do not fully capture the continuous and context-dependent nature of enzyme activity, particularly in the presence of DDIs, environmental factors, or disease progression. While population PK models incorporate demographic and clinical covariates to explain variability, they often rely on indirect surrogates of biological mechanisms and may have limited ability to predict individual-level changes. TDM remains valuable for select drugs but is retrospective and offers limited prospective or mechanistic insight. In contrast, omics-based biomarkers provide a complementary, mechanism-driven approach by directly quantifying enzyme and transporter abundance or activity, enabling dynamic in vivo phenotyping. When integrated with phydiologically-based pharamcokinetic (PBPK) or hybrid modeling frameworks, omics data can enhance prediction of clearance, DDIs, and interindividual variability, supporting early-phase clinical pharmacology studies, prospective DDI assessment, and patient-specific dose optimization.

1 | Emergence of Omics-Based Biomarkers

Omics-based biomarkers, derived particularly from proteomics and metabolomics, offer a mechanistic approach for drug exposure prediction. Relying on advances in high-throughput

TABLE 1 | Representative metabolomics-based biomarkers of drug disposition.

Biomarker (enzyme/transporter)	Clinical relevance	Clinical acceptance
4β-Hydroxycholesterol (CYP3A4)	CYP3A induction marker; predicts DDIs with inducers/inhibitors	Extensively studied; limitation of selectivity and sensitivity
Solanidine (CYP2D6)	Probe for CYP2D6 phenotype	An exogenous compound; not validated to Phase I studied
Testosterone glucuronide to androsterone glucuronide (UGT2B17)	Marker of UGT2B17 glucuronidation activity; sex hormone metabolism	Evaluated in pediatric and adult patients and healthy volunteers. Limited reports
Coproporphyrin I/III (OATP1B1/1B3)	Endogenous biomarker of hepatic uptake	Routinely used for DDI prediction during Phase I studies. Useful in predicting pharmacogenomics variability
N1-Methylnicotinamide and N1-methyladenosine (OCT2)	Biomarker of renal OAT transporter activity	Well studied, but requires renal clearance data for clinical applications
Indole-3-carboxylic acid glucuronide (OAT1/3)	Biomarker of renal OAT transporter activity	Promising, but limited data

LC–MS/MS methods, these biomarkers provide quantitative and dynamic measurements of drug disposition pathways in vivo. Just as serum creatinine serves as a surrogate marker of glomerular filtration rate and guides renal dosing, omics-based biomarkers can be developed for individual enzymes and transporters to inform renal secretion, hepatic metabolism, and systemic exposure, thereby informing dose selection, DDI study design, and risk mitigation strategies during drug development and clinical use. Integrating such biomarkers into PBPK models can help predict drug clearance, optimize dosing strategies, and predict DDIs in a manner that transcends the limitations of PGx.

Quantitative proteomics provides direct measurements of protein abundance of drug-metabolizing enzymes, such as CYPs and UGTs, and transporters including OATP1B1, OCT2, and P-glycoprotein, in biofluids and tissues. Techniques such as targeted LC–MS/MS with stable isotope–labeled standards allow for precise quantification. Metabolomics captures small-molecule metabolites that reflect enzymatic activity or pathway perturbations, with untargeted metabolomics enabling the discovery of novel endogenous biomarkers of enzyme or transporter function. Transcriptomics, using RNA-seq or quantitative PCR, quantifies mRNA levels of drug-metabolizing enzymes and transporters. While transcript abundance does not always correlate directly with protein function, peripheral tissues such as the peripheral blood mononuclear cells (PBMC) can serve as accessible surrogates for hepatic expression. Together, these approaches enable systems-level characterization of drug disposition capacity, effectively bridging genotype to phenotype. The use of quantitative proteomics and metabolomics in predicting PK variability is summarized below.

1.1 | Quantitative Proteomics-Based Approaches to Predict PK Variability

One of the most powerful applications of quantitative proteomics is in PBPK modeling. Proteomics-derived abundances of enzymes and transporters can be used as biomarkers and integrated into PBPK models to predict drug clearance and distribution across populations, supporting first-in-human dose selection, scenario testing for DDIs, and extrapolation across age and disease states [2].

This approach has proven particularly valuable in accounting for age-dependent expression differences through proteomics-informed PBPK modeling, where abundance data refine predictions of drug disposition in neonates, children, and elderly populations. Proteomics data also enables relative expression factor (REF)-based scaling, in which abundances measured in human tissues are used to scale in vitro activity from recombinant systems or cell lines to clinically relevant values. Moreover, quantitative proteomics allows estimation of the fraction metabolized (f_m) by individual pathways, thereby improving predictions of DDI liability. These approaches have been successfully applied to CYP3A substrates, UGT2B7-mediated pathways, and OATP1B1 transporter substrates, demonstrating the translational utility of proteomics-informed PBPK modeling in drug development and clinical practice. Another particularly exciting frontier is the use of extracellular vesicles (EVs) and circulating cells as circulating surrogates of tissue-specific protein expression. EVs are secreted by virtually all cell types and carry membrane proteins, mRNA, and metabolites reflective of their tissue of origin. Quantitative proteomics of EVs enables non-invasive monitoring of enzyme and transporter abundances in patients, with potential application in longitudinal phenotyping, dose adjustment over time, and assessment of enzyme or transporter induction or suppression during polypharmacy. For example, CYP3A4 protein abundance in plasma-derived EVs has been correlated with metabolism capacity [3], while CYP3A4 transcript levels in PBMCs have been used as surrogates for hepatic activity [4]. EV-based proteomics has also revealed transporter expression signatures such as OATP1B1 and P-glycoprotein, providing biomarkers for hepatic and renal clearance pathways [5]. Such strategies extend the application of omics beyond static tissue data to dynamic, patient-specific monitoring, making dynamic phenotyping feasible in

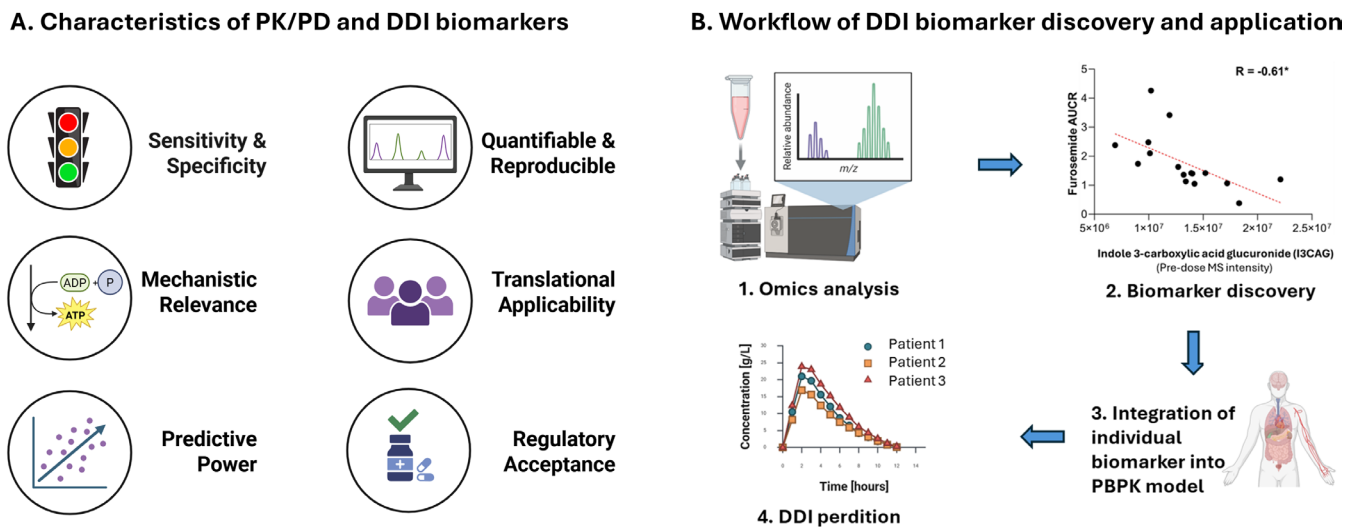

FIGURE 1 | Conceptual framework highlighting ideal characteristics of pharmacokinetic (PK) and drug–drug interaction (DDI) biomarkers (A) and representative visual representation of biomarker discovery and application in DDI prediction (B). Figure A depicts the essential characteristics that define an optimal biomarker for PK assessment and DDI evaluation. An ideal biomarker should exhibit high sensitivity and selectivity, which can enable accurate detection of drug-related changes without interference from unrelated factors. It must demonstrate mechanistic relevance, reflecting a direct connection to the biological or pharmacological processes underlying drug action or interaction. Equally important is predictive power, ensuring that the biomarker can reliably forecast clinical outcomes, including efficacy and safety, across diverse patient populations. Robust quantifiability and reproducibility are critical, allowing consistent measurement through validated analytical methods across different laboratories and studies. The biomarker should also possess translational applicability, bridging preclinical findings to clinical practice and supporting decision-making throughout drug development. Finally, regulatory acceptance is essential, aligning with established guidelines and gaining endorsement from regulatory authorities to facilitate its integration into clinical and labeling recommendations. The regression plot presented in Figure B shows correlation of indole 3-carboxylic acid (OAT biomarker) with DDI potential between probenecid-furosemide from study by Thakur et al. [9].

clinical settings. However, despite their strong translational appeal, EV-based and PBMC-derived surrogate biomarkers face important biological and analytical limitations, including heterogeneity in vesicle origin, incomplete representation of tissue-specific expression, and sensitivity to disease- and context-dependent confounders. In addition, variability in isolation methods, assay standardization, and quantitative reproducibility across platforms remains a key challenge that must be addressed before broad investigational clinical settings.

The emerging application of proteomics in transforming biosimilar development by enabling PD biomarker-based equivalence assessments is also noteworthy. Traditional biosimilar approval requires costly and time-consuming clinical efficacy trials because biological products cannot be exact molecular copies of the reference drug. In this recent proof-of-concept approach, proteomic analysis of longitudinal plasma samples identified candidate proteins linked to interferon β-1a and its pegylated form. From hundreds of differentially expressed proteins, three biomarkers, LAG3, GRN, and I-TAC, were prioritized based on FDA criteria such as dose–response, mechanistic relevance, sensitivity, and reproducibility. These findings illustrate that proteomics-driven PD biomarkers can reduce reliance on comparative clinical studies, streamline regulatory pathways, and accelerate biosimilar approval. This approach represents a major innovation in clinical pharmacology, paving the way for more efficient, cost-effective biosimilar development and broader patient access.

1.2 | Metabolomics-Based Biomarker Approaches for PK and DDI Prediction

Metabolomics offers unique opportunities for biomarker discovery through untargeted approaches. The use of endogenous biomarkers offers a non-invasive and scalable strategy for evaluating enzyme and transporter activity as well as predicting DDIs (Table 1). Coproporphyrin I and III are validated metabolomic biomarkers for OATP1B1 and OATP1B3 function and have been recommended by the International Transporter Consortium as clinically useful probes. For instance, co-administration of rifampicin reduces OATP1B1 activity as reflected by reduced coproporphyrin clearance, enabling early detection of transporter-mediated interactions. The 4β-hydroxycholesterol is an established endogenous biomarker of CYP3A activity and is particularly useful in evaluating induction effects in vivo [6]. Endogenous metabolites reflecting CYP2D6 activity, including urinary solanidine, have long been applied in clinical phenotyping studies [7]. UGT2B17 activity can be monitored by quantifying testosterone glucuronide to androsterone glucuronide ratios, providing insights into androgen metabolism and drug clearance [8]. Indole-3-carboxylic acid glucuronide has been recently identified as an endogenous biomarker of OAT1 and OAT3 activity using a systematic biomarker discovery approach [9]. Similarly, N1-methylnicotinamide and 1-methyladenosine, have been used in confirming clinical OCT2/MATEs DDIs, especially when renal clearance is used as an endpoint [10].

Figure 1 illustrates key attributes of an optimal biomarker for PK/PD assessment and DDI evaluation: high sensitivity and selectivity for accurate detection, mechanistic relevance to drug action, predictive power for clinical outcomes, robust quantifiability and reproducibility across studies, translational applicability from preclinical to clinical settings, and regulatory acceptance to support integration into drug development and labeling. Once validated, omics-based biomarkers can be used as practical tools in clinical pharmacology for patient-centric PK and DDI prediction.

Integrating machine learning (ML) with metabolomics offers a powerful extension to population PK modeling. By combining high-dimensional metabolomic data with clinical and demographic information, ML can capture nonlinear drivers of drug disposition and interindividual variability that traditional approaches may overlook, enabling improved prediction and personalized dosing with less intensive sampling. As omics and computational methods advance, such hybrid approaches can effectively link data-driven insights with mechanistic PBPK and QSP models. Importantly, ML should complement, not replace, mechanistic understanding, while challenges such as external validation, interpretability, and overfitting must be addressed through transparent, biologically informed modeling frameworks.

2 | Future Directions and Conclusion

Despite significant progress, clinical implementation of omics-based biomarkers remains limited by analytical complexity, dynamic biological variability, and the need for large-scale prospective validation. Standardized, high-throughput assays and earlier integration into Phase I studies are needed to fully realize their translational potential. Looking ahead, incorporation of metabolomics and multi-omics data into early drug development, supported by machine learning, offers a path to improved prediction of exposure, efficacy, toxicity, and DDI risk, while collaboration across academia, industry, and regulators will be essential for biomarker qualification. Overall, omics-based biomarkers complement PGx, popPK, and TDM by providing dynamic, mechanistic insights into enzyme and transporter activity, enabling improved precision dosing in complex and variable clinical settings.

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Conflicts of Interest

Bhagwat Prasad is cofounder of Precision Quantomics Inc. and recipient of research funding from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Generation Bio, Gilead Sciences, Johnson & Johnson, Merck, Novartis, and Takeda.

References

1. M. Déri, Z. Szakál-Tóth, F. Fekete, et al., "CYP3A-Status Is Associated With Blood Concentration and Dose-Requirement of Tacrolimus in Heart Transplant Recipients," *Scientific Reports* 11 (2021): 21389.

2. S. Neuhoff, M. D. Harwood, A. Rostami-Hodjegan, and B. Achour, "Application of Proteomic Data in the Translation of In Vitro Observations to Associated Clinical Outcomes," *Drug Discovery Today: Technologies* 39 (2021): 13–22.

3. A. D. Rodrigues, L. S. Wood, M. Vourvahis, and A. Rowland, "Leveraging Human Plasma-Derived Small Extracellular Vesicles as Liquid Biopsy to Study the Induction of Cytochrome P450 3A4 by Modafinil," *Clinical Pharmacology and Therapeutics* 111 (2022): 425–434.

4. M. Ferraresso, S. Turolo, M. Belingheri, et al., "Relationship Between mRNA Expression Levels of CYP3A4, CYP3A5 and SXR in Peripheral Mononuclear Blood Cells and Aging in Young Kidney Transplant Recipients Under Tacrolimus Treatment," *Pharmacogenomics* 16 (2015): 483–491.

5. B. Achour, Z. M. al-Majdoub, A. Grybos-Gajniak, et al., "Liquid Biopsy Enables Quantification of the Abundance and Interindividual Variability of Hepatic Enzymes and Transporters," *Clinical Pharmacology and Therapeutics* 109 (2021): 222–232.

6. U. Diczfalusy, K. P. Kanebratt, E. Bredberg, T. B. Andersson, Y. Böttiger, and L. Bertilsson, "4β-Hydroxycholesterol as an Endogenous Marker for CYP3A4/5 Activity. Stability and Half-Life of Elimination After Induction With Rifampicin," *British Journal of Clinical Pharmacology* 67 (2009): 38–43.

7. J. I. Kiiski, M. Neuvonen, M. Kurkela, et al., "Solanidine Is a Sensitive and Specific Dietary Biomarker for CYP2D6 Activity," *Human Genomics* 18 (2024): 11.

8. H. Zhang, A. Basit, C. Wolford, et al., "Normalized Testosterone Glucuronide as a Potential Urinary Biomarker for Highly Variable UGT2B17 in Children 7–18 Years," *Clinical Pharmacology and Therapeutics* 107 (2020): 1149–1158.

9. A. Thakur, D. K. Singh, K. D. Hart, et al., "From Discovery to Translation: Endogenous Substrates of OAT1 and OAT3 as Clinical Biomarkers for Renal Secretory Function," *Clinical Pharmacology and Therapeutics* 118 (2025): 693–704.

10. S. Asano, A. Galetin, Y. Tomita, et al., "Predicting OCT2/MATEs-Mediated Drug Interactions in Healthy Volunteers and Patients With Chronic Kidney Disease: Insights From Extended Clearance Concept, Endogenous Biomarkers, and In Vitro Inhibition Studies (Perspectives From the International Transporter Consortium)," *Clinical Pharmacology and Therapeutics* 118 (2025): 994–1014, https://doi.org/10.1002/cpt.3727.