1521-009X/51/12/1547–1550$35.00
DRUG METABOLISM AND DISPOSITION

dx.doi.org/10.1124/dmd.123.001453
Drug Metab Dispos 51:1547–1550, December 2023

50th Anniversary Celebration Collection—Commentary

Innovations, Opportunities, and Challenges for Predicting Alteration in Drug-Metabolizing Enzyme and Transporter Activity in Specific Populations

Paresh P. Chothe, Vikram Arya,[1] Bhagwat Prasad, Diane Ramsden, and Kunal Taskar

Drug Metabolism and Pharmacokinetics, Oncology Research and Development, AstraZeneca, Waltham, Massachusetts (P.P.C., D.R.); Division of Infectious Disease Pharmacology, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland (V.A.); Department of Pharmaceutical Sciences, Washington State University, Spokane, Washington (B.P.); and Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, R&D, Stevenage, United Kingdom (K.T.)

Received September 7, 2023; accepted September 28, 2023

ABSTRACT

Drug-metabolizing enzymes and transporters (DMETs) are key regulators of the pharmacokinetics, efficacy, and toxicity of therapeutics. Over the past two decades, significant advancements in in vitro methodologies, targeted proteomics, in vitro to in vivo extrapolation methods, and integrated computational approaches such as physiologically based pharmacokinetic modeling have unequivocally contributed to improving our ability to quantitatively predict the role of DMETs in absorption, distribution, metabolism, and excretion and drug-drug interactions. However, the paucity of data regarding alterations in DMET activity in specific populations such as pregnant individuals, lactation, pediatrics, geriatrics, organ impairment, and disease states such as, cancer, kidney, and liver diseases and inflammation has restricted our ability to realize the full potential of these recent advancements. We envision that a series of carefully curated articles in a special supplementary issue of *Drug Metabolism and Disposition* will summarize the latest progress in in silico, in vitro, and in vivo approaches to characterize alteration in DMET activity and quantitatively predict drug disposition in specific populations. In addition, the supplementary issue will underscore the current scientific knowledge gaps that present formidable barriers to fully understand the clinical implications of altered DMET activity in specific populations and highlight opportunities for multistakeholder collaboration to advance our collective understanding of this rapidly emerging area.

SIGNIFICANCE STATEMENT

This commentary highlights current knowledge and identifies gaps and key challenges in understanding the role of drug-metabolizing enzymes and transporters (DMETs) in drug disposition in specific populations. With this commentary for the special issue in *Drug Metabolism and Disposition*, the authors intend to increase interest and invite potential contributors whose research is focused or has aided in expanding the understanding around the role and impact of DMETs in drug disposition in specific populations.

Commentary

Early clinical drug development generally involves evaluation of a new drug in healthy individuals (Karakunnel et al., 2018). In the majority of the cases, other critically important specific populations such as pregnant individuals, pediatrics, and patients with the underlying disease condition are excluded. Although in some instances late-stage clinical trials enroll a diverse patient population with respect to age, ethnicity, hepatic and kidney dysfunction, pediatrics (primarily adolescents), and varying body mass index, information related to determining a safe and effective dosing regimen in specific populations is mostly derived from data collected in otherwise healthy individuals. Below are a few selected examples to illustrate how altered expression and/or activities of drug-metabolizing enzymes and transporters (DMETs), along with ontogeny related changes, can alter the pharmacokinetics (PK) and/or pharmacodynamics profile of drugs in various specific populations and may potentially result in suboptimal efficacy and/or unknown risk of adverse effects.

Sex. In recent years, sex-related differences in the PK of drugs have been widely attributed to differences in body weight, plasma volume, gastric emptying time, plasma protein levels, and the activities of key DMETs. Available data suggests that men appear to have higher activities of some phase I and phase II enzymes and efflux drug transporters such as P-glycoprotein compared with women (Schwartz, 2003; Gandhi et al., 2004; Soldin and Mattison, 2009; Yang et al., 2012). Furthermore,

The authors received no financial support for this work.

Paresh P. Chothe and Diane Ramsden hold common stocks in AstraZeneca. Bhagwat Prasad is the founder of Precision Quantomics Inc., and his laboratory is funded by Genentech, Gilead, Merck, and Takeda.

[1]The views expressed in this article are those of the author. No official support or endorsement by the United States Food and Drug Administration (USFDA) is provided or should be inferred.

dx.doi.org/10.1124/dmd.123.001453.

ABBREVIATIONS: ALD, alcoholic liver disease; CYP3A4, cytochrome P450 3A4; DMET, drug-metabolizing enzyme and transporter; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic.

sex differences in the PK of drugs have been shown to correlate with sex-dependent adverse drug reactions in women (Zucker and Prendergast, 2020). A well known example is the sedative-hypnotic drug zolpidem, indicated for the treatment of insomnia. A decade after its approval, postmarketing reports highlighted cognitive deficits in women, with this adverse event directly associated with higher systemic exposure of zolpidem in women compared with men (Zucker and Prendergast, 2020). Subsequently, a drug safety communication issued by the US Food and Drug Administration recommended that the initial dose of zolpidem be reduced in women because of slower elimination relative to men (https://wayback.archive-it.org/7993/20170111080036/http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm).

Pregnancy. Several studies have reported significant changes in the PK of drugs during pregnancy due to physiologic changes that lead to altered activities of DMETs (Hebert et al., 2008; Zhang et al., 2020). For example, the systemic exposure of metoprolol and lamotrigine is decreased by up to fivefold due to increased metabolic clearance during pregnancy (Hogstedt et al., 1985; Pennell et al., 2004). Another study by Mlugu et al. (2022) demonstrated that the 4β-hydroxycholesterol/cholesterol ratio was significantly higher in pregnant women compared with nonpregnant women. Further, in pregnant women, the authors reported a significant increase in 4β-hydroxycholesterol/cholesterol ratio from the second trimester to the third trimester of pregnancy. The increased cytochrome P450 3A4 (CYP3A4) activity is also evident in the study by Mlugu et al. (2022). In this study, systemic exposure of midazolam (CYP3A4 substrate) was significantly decreased (1.9-fold) during pregnancy (28–32 weeks gestation) compared with that during postpartum (6–10 weeks). In the same study, increased renal P-glycoprotein activity was also evident as digoxin (P-gp substrate) renal secretion was twofold higher during pregnancy compared with that during postpartum (Hebert et al., 2008).

Age. Most clinically relevant DMETs show unique developmental patterns (Shi and Klotz, 2011; Brouwer et al., 2015; Elmorsi et al., 2016; Chapron et al., 2022), thus presenting uncertainties in quantitative PK predictions, especially in the pediatric population for whom understanding of DMET abundance across the age continuum is inadequate. For example, Liu et al. (2021) proposed a physiologically based pharmacokinetic modeling framework to predict neonatal PK. The sensitivity analysis conducted by the authors showed that the OCT2 activity in term newborns is 25%–50% of the value implemented in the model and highlighted the need for additional evaluation to investigate OCT2 ontogeny in the newborns. Further, changes in key physiologic processes in the elderly population can also significantly alter drug disposition (McLachlan and Pont, 2012). For example, reduced phase I and II metabolism and reduced renal clearance is reported in elderly population, which may have a substantial effect on drug disposition. Recently published data have indicated a 2.3-fold increase in the systemic exposure of midazolam in healthy elderly population compared with healthy adults, and this was attributed to reduced activity of CYP3A4 (Rattanacheeworn et al., 2021).

Disease State. Disease-associated changes in the activity of DMETs can have a significant impact on the PK and/or toxicity of drugs (Staudinger, 2013; Cheng et al., 2016; Evers et al., 2018). The effect of liver diseases such as alcoholic liver disease (ALD) and nonalcoholic fatty liver disease such as nonalcoholic steatohepatitis (NASH) on DMET activity has been widely evaluated, and it has been demonstrated that the severity of the disease state is directly linked to its impact on the activities of various DMETs that are implicated in the ADME of drugs (Vildhede et al., 2020; Ladumor et al., 2023; Lin et al., 2023). In chronic liver diseases, the abundance of hepatic CYP3A4 and organic anion transporting polypeptide (OATP) transporters is substantially reduced, which can lead to drug accumulation, thus requiring dose adjustment (Verbeeck, 2008; Lin et al., 2023). To this end, a study by Weersink et al. (2018) systematically evaluated the safety of 209 drugs in liver cirrhosis patients. Based on their analysis, the authors recommended avoiding all nonsteroidal anti-inflammatory drugs in the setting of liver cirrhosis (due to altered pharmacodynamics) as these patients are at higher risk of renal insufficiency with nonsteroidal anti-inflammatory drug use compared with the healthy population. Further, the authors also indicated that several calcium channel blockers are also deemed either unsafe or require dose adjustment in liver cirrhosis patients due to altered pharmacokinetics as most calcium channel blockers are primarily cleared by the liver.

Severe liver diseases may also alter kidney function and renal transporter activity. A recent study by Frost et al. (2023) indicated a significant decrease in the abundance of organic anion transporter (OAT)-3 in NASH, ALD, and viral hepatitis C, decrease in the abundance of OAT4 in NASH and that of urate transporter 1 (URAT1) in ALD and viral hepatitis C. Therefore, it is important to consider renal transporter changes in addition to hepatic DMETs for potential dose adjustment in the chronic liver disease patient population. Like liver diseases, chronic kidney diseases have also been shown to significantly alter the PK of a

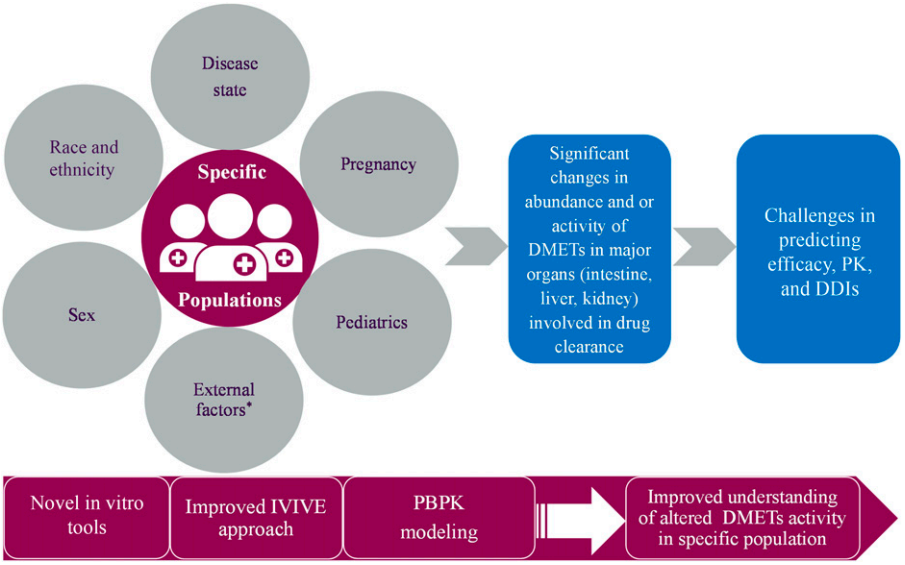

Fig. 1. Illustration of challenges (top part of the figure) in predicting PK, pharmacodynamics, and drug-drug interactions due to alteration in DMETs in various specific populations. Newer approaches and advanced methodologies including in vitro tools, in vitro to in vivo extrapolation (IVIVE) methods, and physiologically based pharmacokinetic (PBPK) modeling will enable us to improve the understanding of DMETs in specific populations to achieve clinical success of therapeutic drugs (bottom part of the figure). *External factors, including diet, concomitant medication use, and smoking.

TABLE 1

Key challenges, innovation, and opportunities in various areas important for understanding the role of DMETs in drug disposition in specific populations

Area	Challenges	Innovation and Opportunities
In vitro methods	• Lack of in vitro assays representing specific populations • Limited access to human reagent from specific populations (e.g. hepatocytes, microsomes) • Poor viability of primary cells from specific populations (e.g. hepatocytes)	• Novel 3D or microphysiological systems models representing special population (Freag et al., 2020; Teng et al., 2021) • Crossindustry, academia, and research effort to source primary tissue from patient populations • Integration of iPS cells from patients and healthy volunteers • Technologies (i.e., CRISPR) to recapitulate or model disease progression (Ramakrishna et al., 2021)
In vivo nonclinical models	• Species differences in the abundance, zonation, and activity of DMETs • Lack of knowledge on age special maturation of DMETs in different organs • Scarcity of appropriate disease models • Poor translation of drug PK to humans	• Appropriate selection of animal models that closely mimic target human population in relation to abundance and activity of DMETs (Zhu et al., 2023) • Building disease special animal models (Hayashi et al., 2023)
In vitro in vivo extrapolation	• Lack of evidence on protein abundance and activity of DMETs • Uncertainty in using extrapolation methods in transporter-based clearance predictions	• Tissue procurement and large-scale targeted proteomics in special populations • Tissue special exosome analysis • Biomarker incorporation
PBPK modeling	• Unknown physiologic and genetic differences (systems parameters) that can modulate activity of DMETs • Lack of understanding in ontogeny of DMETs • Lack of tissue-specific data in PK studies • Lack of clinical data for reverse translation and model verification	• Technology development • Bigger efforts for collaboration among scientific communities in obtaining and sharing information • Development of open databases and promotion of professional training

3D, three-dimensional; iPS, induced pluripotent stem; PBPK, physiologically based pharmacokinetic.

drug or its metabolites due to decreased renal excretion. Changes in the expression/activity of DMETs in the liver and gut of patients with chronic kidney disease can further impact the disposition of drugs (Sun et al., 2006; Nolin et al., 2008; Yeung et al., 2014).

Altered expression and/or activities of clinically relevant DMETs have also been identified as key drivers in PK variability across diverse populations (Yang et al., 2013) (Fig. 1). Over the last few years, biomarkers, exosome analysis, and targeted proteomics have emerged as powerful tools to quantitatively evaluate or measure the protein levels or activity of DMETs in key organs involved in drug disposition (liver, intestine, kidney, and brain) and have led to improvements in in vitro to in vivo extrapolation and the prediction of interindividual variability in the PK of drugs through coupling with physiologically based pharmacokinetic modeling (Prasad et al., 2019; Ahire et al., 2023). However, there are still considerable knowledge gaps in our understanding of the modulation of the abundance and activity of DMETs in specific populations and the subsequent impact on drug disposition (Table 1).

To shine light on the recent advancements in our understanding of the changes in DMET expression and/or activity in various specific populations and stimulate discussions for future research to address the current knowledge gaps, the overarching goals of this special supplementary issue in *Drug Metabolism and Disposition* are to 1) summarize the latest advancements in in silico, in vitro, and in vivo approaches to characterize alteration in DMET activity and quantitatively predict drug disposition in specific populations; 2) underscore the current scientific knowledge gaps that present formidable barriers to fully understanding the clinical implications of altered DMET activity in specific populations; and 3) highlight opportunities for multistakeholder collaboration to advance our collective understanding of this rapidly emerging area.

Data Availability

The authors declare that all the data supporting the findings of this study are contained within the paper.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Chothe, Arya, Prasad, Ramsden, Taskar.

References

Ahire D, Heyward S, and Prasad B (2023) Intestinal Metabolism of Diclofenac by Polymorphic UGT2B17 Correlates with its Highly Variable Pharmacokinetics and Safety across Populations. *Clin Pharmacol Ther* **114**:161–172.

Brouwer KL, Aleksunes LM, Brandys B, Giacoia GP, Knipp G, Lukacova V, Meibohm B, Nigam SK, Rieder M, and de Wildt SN; Pediatric Transporter Working Group (2015) Human Ontogeny of Drug Transporters: Review and Recommendations of the Pediatric Transporter Working Group. *Clin Pharmacol Ther* **98**:266–287.

Chapron BD, Chapron A, and Leeder JS (2022) Recent advances in the ontogeny of drug disposition. *Br J Clin Pharmacol* **88**:4267–4284.

Cheng Y, El-Kattan A, Zhang Y, Ray AS, and Lai Y (2016) Involvement of Drug Transporters in Organ Toxicity: The Fundamental Basis of Drug Discovery and Development. *Chem Res Toxicol* **29**:545–563.

Elmorsi Y, Barber J, and Rostami-Hodjegan A (2016) Ontogeny of Hepatic Drug Transporters and Relevance to Drugs Used in Pediatrics. *Drug Metab Dispos* **44**:992–998.

Evers R, Piquette-Miller M, Polli JW, Russel FGM, Sprowl JA, Tohyama K, Ware JA, de Wildt SN, Xie W, and Brouwer KLR; International Transporter Consortium (2018) Disease-Associated Changes in Drug Transporters May Impact the Pharmacokinetics and/or Toxicity of Drugs: A White Paper From the International Transporter Consortium. *Clin Pharmacol Ther* **104**:900–915.

Freag MS, Namgung B, Reyna Fernandez ME, Gherardi E, Sengupta S, and Jang HL (2020) Human Nonalcoholic Steatohepatitis on a Chip. *Hepatol Commun* **5**:217–233.

Frost KL, Jilek JL, Sinari S, Klein RR, Billheimer D, Wright SH, and Cherrington NJ (2023) Renal Transporter Alterations in Patients with Chronic Liver Diseases: Nonalcoholic Steatohepatitis, Alcohol-Associated, Viral Hepatitis, and Alcohol-Viral Combination. *Drug Metab Dispos* **51**:155–164.

Gandhi M, Aweeka F, Greenblatt RM, and Blaschke TF (2004) Sex differences in pharmacokinetics and pharmacodynamics. *Annu Rev Pharmacol Toxicol* **44**:499–523.

Hayashi M, Kuwabara Y, Ito K, Hojo Y, Arai F, Kamijima K, Takeiri M, Wang X, Diao P, Nakayama J, et al. (2023) Development of the Rabbit NASH Model Resembling Human NASH and Atherosclerosis. *Biomedicines* **11**:384.

Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, Thummel KE, Fishbein DP, and Unadkat JD (2008) Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. *Clin Pharmacol Ther* **84**:248–253.

Högstedt S, Lindberg B, Peng DR, Regårdh CG, and Rane A (1985) Pregnancy-induced increase in metoprolol metabolism. *Clin Pharmacol Ther* **37**:688–692.

Karakunnel JJ, Bui N, Palaniappan L, Schmidt KT, Mahaffey KW, Morrison B, Figg WD, and Kummar S (2018) Reviewing the role of healthy volunteer studies in drug development. *J Transl Med* **16**:336.

Ladumor MK, Storelli F, Liang X, Lai Y, Enogieru OJ, Chothe PP, Evers R, and Unadkat JD (2023) Predicting changes in the pharmacokinetics of CYP3A-metabolized drugs in hepatic impairment and insights into factors driving these changes. *CPT Pharmacometrics Syst Pharmacol* **12**:261–273.

Lin J, Kimoto E, Yamazaki S, Vourvahis M, Bergman A, Rodrigues AD, Costales C, Li R, and Varma MVS (2023) Effect of Hepatic Impairment on OATP1B Activity: Quantitative

Pharmacokinetic Analysis of Endogenous Biomarker and Substrate Drugs. *Clin Pharmacol Ther* **113**:1058–1069.
Liu XI, Momper JD, Rakhmanina NY, Green DJ, Burckart GJ, Cressey TR, Mirochnick M, Best BM, van den Anker JN, and Dallmann A (2021) Physiologically Based Pharmacokinetic Modeling Framework to Predict Neonatal Pharmacokinetics of Transplacentally Acquired Emtricitabine, Dolutegravir, and Raltegravir. *Clin Pharmacokinet* **60**:795–809.
McLachlan AJ and Pont LG (2012) Drug metabolism in older people–a key consideration in achieving optimal outcomes with medicines. *J Gerontol A Biol Sci Med Sci* **67**:175–180.
Mlugu EM, Minzi OM, Kamuhabwa AAR, Diczfalusy U, and Aklillu E (2022) Pregnancy Increases CYP3A Enzymes Activity as Measured by the 4β-Hydroxycholesterol/Cholesterol Ratio. *Int J Mol Sci* **23**:15168.
Nolin TD, Naud J, Leblond FA, and Pichette V (2008) Emerging evidence of the impact of kidney disease on drug metabolism and transport. *Clin Pharmacol Ther* **83**:898–903.
Pennell PB, Newport DJ, Stowe ZN, Helmers SL, Montgomery JQ, and Henry TR (2004) The impact of pregnancy and childbirth on the metabolism of lamotrigine. *Neurology* **62**:292–295.
Prasad B, Achour B, Artursson P, Hop CECA, Lai Y, Smith PC, Barber J, Wisniewski JR, Spellman D, Uchida Y, et al. (2019) Toward a Consensus on Applying Quantitative Liquid Chromatography-Tandem Mass Spectrometry Proteomics in Translational Pharmacology Research: A White Paper. *Clin Pharmacol Ther* **106**:525–543.
Ramakrishna G, Babu PE, Singh R, and Trehanpati N (2021) Application of CRISPR-Cas9 based gene editing to study the pathogenesis of colon and liver cancer using organoids. *Hepatol Int* **15**:1309–1317.
Rattanacheeworn P, Kerr SJ, Kittanamongkolchai W, Townamchai N, Udomkarnjananun S, Praditpornsilpa K, Thanusuwannasak T, Udomnilobol U, Jianmongkol S, Ongpipattanakul B, et al. (2021) Quantification of CYP3A and Drug Transporters Activity in Healthy Young, Healthy Elderly and Chronic Kidney Disease Elderly Patients by a Microdose Cocktail Approach. *Front Pharmacol* **12**:726669.
Schwartz JB (2003) The influence of sex on pharmacokinetics. *Clin Pharmacokinet* **42**:107–121.
Shi S and Klotz U (2011) Age-related changes in pharmacokinetics. *Curr Drug Metab* **12**:601–610.
Soldin OP and Mattison DR (2009) Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* **48**:143–157.
Staudinger JL (2013) Disease, drug metabolism, and transporter interactions. *Pharm Res* **30**:2171–2173.
Sun H, Frassetto L, and Benet LZ (2006) Effects of renal failure on drug transport and metabolism. *Pharmacol Ther* **109**:1–11.
Teng Y, Zhao Z, Tasnim F, Huang X, and Yu H (2021) A scalable and sensitive steatosis chip with long-term perfusion of in situ differentiated HepaRG organoids. *Biomaterials* **275**:120904.
Verbeeck RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol* **64**:1147–1161.
Vildhede A, Kimoto E, Pelis RM, Rodrigues AD, and Varma MVS (2020) Quantitative Proteomics and Mechanistic Modeling of Transporter-Mediated Disposition in Nonalcoholic Fatty Liver Disease. *Clin Pharmacol Ther* **107**:1128–1137.
Weersink RA, Bouma M, Burger DM, Drenth JPH, Harkes-Idzinga SF, Hunfeld NGM, Metselaar HJ, Monster-Simons MH, Taxis K, and Borgsteede SD (2018) Evidence-Based Recommendations to Improve the Safe Use of Drugs in Patients with Liver Cirrhosis. *Drug Saf* **41**:603–613.
Yang L, Li Y, Hong H, Chang CW, Guo LW, Lyn-Cook B, Shi L, and Ning B (2012) Sex Differences in the Expression of Drug-Metabolizing and Transporter Genes in Human Liver. *J Drug Metab Toxicol* **3**:1000119.
Yang L, Price ET, Chang CW, Li Y, Huang Y, Guo LW, Guo Y, Kaput J, Shi L, and Ning B (2013) Gene expression variability in human hepatic drug metabolizing enzymes and transporters. *PLoS One* **8**:e60368.
Yeung CK, Shen DD, Thummel KE, and Himmelfarb J (2014) Effects of chronic kidney disease and uremia on hepatic drug metabolism and transport. *Kidney Int* **85**:522–528.
Zhang H, Bastian JR, Zhao W, Chen H, Shaik IH, Chaphekar N, Caritis SN, and Venkataramanan R (2020) Pregnancy Alters CYP- and UGT-Mediated Metabolism of Buprenorphine. *Ther Drug Monit* **42**:264–270.
Zhu Y, Chen L, He Y, Qin L, Tan D, Bai Z, Song Y, and Wang YH (2023) The alteration of drug metabolism enzymes and pharmacokinetic parameters in nonalcoholic fatty liver disease: current animal models and clinical practice. *Drug Metab Rev* **55**:163–180.
Zucker I and Prendergast BJ (2020) Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol Sex Differ* **11**:32.

Address correspondence to: Dr. Paresh P. Chothe, Oncology R&D Early Research & Development, 35 Gatehouse Drive, Waltham, MA 02451. E-mail: paresh.chothe@astrazeneca.com