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CASE REPORT

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Precision medication: An illustrative case series guiding the clinical application of multi-drug interactions and pharmacogenomics

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Abstract

Precision medication entails selecting the precise medication, dose, and timing of administration. Multi-drug interactions and genetics significantly affect precision medication. In this article, we present two simulated cases for real-world applications of precision medication. Clinicians may need to acquire additional skills to apply the principles illustrated by these cases.

KEYWORDS

drug interactions, pharmacogenomics, phenoconversion, precision medication, precision medicine

1 | INTRODUCTION

Precision medicine is the most recent evolution in the field of pharmacogenomics (PGx). According to the foundation started by the field, clinicians use genetic information to guide selection of the "right medication" and "right dose" with the greatest effectiveness and least toxicity for the "right individual" to optimize outcomes.[1] While genetic-guided selection of medication and dose has clinical utility, it likely underestimates true phenotypes of individuals, particularly those who use multiple medications.[1,2] The concomitant use of multiple medications significantly increases the likelihood of drug interactions,[1,3-5] and drug interactions are one of the most important determinants of phenoconversion.[1,3,4,6] Phenoconversion is a process that converts a genotype into a differently expressed phenotype, such as a genotypic normal metabolizer to a phenotypic poor metabolizer, thereby modifying the expected response to a medication.[2,6] This is clinically important because multiple medication use is common in real-life practice, and interindividual differences in medication response, whether genetically determined or due to phenoconversion, can effect outcomes in individuals using multiple medications.[1]

Cytochrome P450 (CYP) is the enzymatic system responsible for phase I metabolism of most medications.[6] Important genetic variations exist for most CYP isoenzymes.[6] Consequently, the CYP system is involved in many drug interactions, including drug-gene interactions (DGIs).[6] Drug-gene interactions can effect interindividual variability in medication pharmacokinetics and response.[6] Moreover, these effects may be amplified, as aforementioned with phenoconversion, in the presence of nongenetic determinants such as drug-drug interactions (DDIs).

Medications interacting with the CYP system are classified as inhibitors, inducers, or substrates. Substrates can be further characterized as having weak, moderate, or strong affinity for a specific CYP isoenzyme. Substrates that share the same isoenzyme metabolic pathway interact when administered at or around the same time of day,[6] in such a manner that a stronger affinity substrate (ie, "perpetrator" of the interaction) competitively inhibits a weaker affinity substrate (ie, "victim" of the interaction), resulting in phenoconversion for the victim substrate. Similarly, substrates sharing the same isoenzyme metabolic pathway with similar affinities also interact when administered at or around the same time of day, whereby the substrate with the higher dose competitively inhibits the substrate with the lower dose, causing phenoconversion for the latter. The same principle applies to substrates interacting with inhibitors or inducers. Therefore, beyond simply considering DDIs and DGIs, we now know that drug-drug-gene interactions, which involve a complex interaction that results from the superimposition of a DDI on a DGI,[5] also influence interindividual variability in medication pharmacokinetics and response.[6]

In this context, selecting the precise medication, dose, and timing of administration for an individual—a term that we coined "precision medication"—is difficult. Clinicians need to understand the influence of DDIs and DGIs—separately and in tandem—on medication pharmacokinetics and response. This article's purpose was to present diverse examples of applying precision medication to complicated patient cases often encountered in clinical practice. The question this article aimed to answer was as follows: How do multi-drug interactions and PGx influence real-world applications of precision medication?

2 | METHODS

To illustrate these applications and provide instructional guidance for clinicians, two simulated cases were described. The cases were intended to demonstrate the impact of genetic variations and concomitant medications on drug interactions and phenoconversion. While the cases were intended to simulate real-world applications, it is worth noting that they were not intended to be prescriptive. In other words, the application of the information that has been provided may vary by clinician and/or by case.

3 | RESULTS

3.1 | Case 1: Warfarin-Rosuvastatin and CYP2C9

Jonathan Bailey was a 72-year-old Caucasian man who presented to his primary care physician for a routine wellness visit. He was a smoker (19 pack-years) and had a history of systolic heart failure (HF) for five years, hypertension, and persistent atrial fibrillation (AF). For the past few years, his baseline exercise capacity would be described as slight limitation of physical activity with some symptoms during normal daily activities but asymptomatic at rest. He had a three-year history of AF, with several attempts of cardioversion and maintenance of sinus rhythm control, that was being effectively managed with a rate control approach and anticoagulation. Prior to initiating anticoagulation, his treating cardiologist ordered a PGx test to guide warfarin dosing. During follow-up, Mr Bailey reported no change since his last visit six months ago, and his blood pressure and ventricular heart rate continued to be well controlled, although slightly irregular. See Figure 1 for additional information captured from his chart review.

The pharmacist working with the cardiology team interpreted Mr Bailey's PGx test results, indicating that he is a normal metabolizer for the CYP2C9 isoenzyme, has no genetic variants for the *VKORC1* or *CYP4F2* genes, is a rapid metabolizer for the CYP2C19 isoenzyme, is a normal metabolizer for the CYP2D6 isoenzyme, is a normal metabolizer for the CYP3A4 isoenzyme, but is lacking functional CYP3A5 isoenzyme activity, and has no genetic variant for the *SLCO1B1* gene, but is homozygous variant for the *ABCG2* gene.

Based on his PGx test results coupled with the PGx-guided dosing information in the FDA-approved product labeling[7] and genomic-based guideline recommendations for the *CYP2C9*, *VKORC1,* and *CYP4F2* genes,[8] Mr Bailey was appropriately anticoagulated with a warfarin dose of 6 mg once daily and a resultant international normalized ratio (INR) of 2.6. Further, his physical examination and self-report at follow-up indicated no signs or symptoms of warfarin toxicity.

At follow-up, Mr Bailey's primary care physician (PCP) decided to start him on a statin because his most recent laboratory results indicated dyslipidemia. The physician gave Mr Bailey a sample supply of rosuvastatin 10 mg and instructed him to begin taking one tablet once daily for five days then two tablets daily thereafter. The physician also gave him a prescription for rosuvastatin 20 mg once daily, to commence when the sample supply was depleted. Mr Bailey began

FIGURE 1 Chart information for Mr Bailey

Objective Findings	66 inches	Total cholesterol 228 mg/dL
	72 kilograms	Triglycerides 220 mg/dL
	Ejection fraction 35%	Low-density lipoprotein 191 mg/dL
	BP 128/76 mmHg	High-density lipoprotein 42 mg/dL
	Heart rate 70-75 bpm	
Medication List	Metoprolol succinate 100 mg by mouth daily	
	Furosemide 40 mg by mouth daily	
	Potassium chloride 20 mEq by mouth daily	
	Lisinopril 20 mg by mouth daily	
	Warfarin 6 mg by mouth daily	
Pharmacogenomic Results	CYP2C9*1/*1	
	VKORC1 (–1639G>A, SNP3673, rs9923231) G/G	
	CYP4F2*1/*1	
	CYP2C19*1/*17	
	CYP2D6*1/*1	
	CYP3A4*1/*1	
	CYP3A5*3/*3	
	SLCO1B1 (c.521T>C, rs4149056) T/T	
	ABCG2 (c.421C>A, rs2231142) A/A	

Medication	F%	CYP1A2 N/A	CYP2C19 *1/*17	CYP2C9 *1/*1	CYP2D6 *1/*1	CYP3A4 *1/*1
Metoprolol	50				80%	
Furosemide	60	NON P450				
Potassium	-	NON P450				
Lisinopril	35	NON P450				
Warfarin	95	15%	10%	45%		30%
Rosuvastatin	15			10%		
Alternative Statins						
Atorvastatin	13					80%
Fluvastatin	24			U/D		
Lovastatin	5					50%
Pitavastatin	-	NON P450				
Pravastatin	17					10%
Simvastatin	5					50%[a]

FIGURE 2 Oral bioavailability and metabolic pathways for Mr Bailey's medication regimen. Abbreviations: F = absolute bioavailability; N/A = not available; U/D = undetermined. The color coding in the cells for CYP450 drug-metabolizing isoenzymes indicates the affinity of the medication for this isoenzyme, as follows: □ = CYP weak affinity substrate, ▒ = CYP moderate affinity substrate, and ■ = CYP strong affinity substrate. The percentages in the cells for CYP450 drug-metabolizing isoenzymes indicate the extent this isoenzyme contributes to the overall metabolic clearance of the medication. [a]Indicates a prodrug

taking rosuvastatin along with his regularly scheduled warfarin dose in the evening.

A week and a half later, Mr Bailey contacted his PCP complaining of discoloration of his skin on both forearms. The physician brought Mr Bailey into his office for an urgent visit and confirmed bilateral ecchymosis. A point-of-care test revealed an elevated INR (4.4). The PCP instructed Mr Bailey to hold his warfarin for a day and subsequently lowered his warfarin dose. The day following his PCP visit, Mr Bailey presented to your community

pharmacy with the aforementioned prescription for rosuvastatin 20 mg orally at bedtime and a new prescription for warfarin 3 mg orally once daily.

Knowing Mr Bailey as a customer of your pharmacy for many years, you recognized that he had been appropriately anticoagulated with a relatively stable dose of warfarin (6 mg/d) for more than a year. Upon screening his medication regimen and performing a medication reconciliation, you identified a DDI that likely explained the change in his anticoagulation therapy. After reviewing the metabolic and elimination pathways of the commercially available statins and speaking with Mr Bailey, you contacted his PCP to discuss potential medication options. These options included: (a) continuing high-intensity statin therapy with rosuvastatin and closely monitoring his INR, (b) switching to atorvastatin at an equivalent dose for high-intensity statin therapy and closely monitoring his INR, or (c) switching to an alternative statin that is devoid of a clinically meaningful DDI but is not high-intensity statin therapy per se (eg, pitavastatin and pravastatin) and re-adjusting the warfarin dose based on his INR after the switch.

Both rosuvastatin and warfarin are strong affinity substrates of the CYP2C9 drug-metabolizing isoenzyme, as noted in Figure 2. Although both medications have strong affinity for this isoenzyme, because Mr Bailey's dose of rosuvastatin (20 mg) was higher than his dose of warfarin (6 mg) and both medications were taken at the same time of day, rosuvastatin achieved higher hepatic concentrations than warfarin and, therefore, competitively inhibited warfarin's metabolism by the CYP2C9 isoenzyme. Of note, the *SLCO1B1* gene encodes the organic anion-transporting polypeptide OATP1B1, which facilitates the hepatic uptake (ie, influx) of statins.[9] The *ABCG2* gene encodes the efflux transporter BCRP, which plays an important role in the pharmacokinetics of numerous substrates, including rosuvastatin.[10] Genetic variants in *ABCG2* markedly increase the oral bioavailability and systemic exposure and decrease the hepatic clearance of BCRP substrates such as rosuvastatin.[11-13] Because Mr Bailey had a genetic variant for the *ABCG2* gene that resulted in significantly reduced BCRP transporter function, the hepatic concentrations of rosuvastatin were likely increased, further contributing to competitive inhibition. As a result, warfarin's metabolic clearance was reduced by as much as 45%. Therefore, although Mr Bailey was a normal metabolizer for the CYP2C9 isoenzyme, due to competitive inhibition by rosuvastatin, he underwent phenoconversion to an intermediate or poor metabolizer of warfarin.

Unlike rosuvastatin and with the exception of fluvastatin, the other FDA-approved statins are not metabolized by CYP2C9. Therefore, we would not expect these other statins to competitively inhibit warfarin's metabolism via this enzymatic pathway. Nonetheless, if the goal for Mr Bailey was high-intensity statin therapy, his physician may desire to keep him on rosuvastatin. In doing so, however, because nearly half of warfarin's metabolism is inhibited by rosuvastatin when these two medications are taken at or around the same time of day, it would be prudent to adjust his warfarin dose (downward) and closely monitor his INR. Additionally, to further mitigate the DDI, Mr Bailey could take his rosuvastatin and warfarin at different times of day, namely warfarin in the morning and rosuvastatin at bedtime. If this strategy is employed, then Mr Bailey should be counseled to be consistent with these times of administration each day in order to avoid further INR fluctuations.

By comparison, atorvastatin, lovastatin, and simvastatin are appreciably (≥50%) metabolized by CYP3A4 and they are moderate to strong affinity substrates of this isoenzyme. Similarly, warfarin is appreciably (30%) metabolized by CYP3A4 and it is a strong affinity substrate. While switching rosuvastatin to one of these three alternative statins would have avoided the CYP2C9 isoenzyme-mediated drug interaction, Mr Bailey would still have been at risk for experiencing some CYP3A4 isoenzyme-mediated drug interaction involving warfarin. Nevertheless, it is worth noting that the result of this DDI might be different than the previously described CYP2C9 isoenzyme-mediated drug interaction. Specifically, S-warfarin is much more potent an inhibitor of VKORC1 than R-warfarin, and S-warfarin is predominantly metabolized by the CYP2C9 isoenzyme whereas R-warfarin is predominantly metabolized by the CYP3A4 isoenzyme.[14,15] Therefore, warfarin DDIs involving the CYP2C9 isoenzyme, such as the one that occurred in Mr Bailey, will likely be greater in terms of magnitude of over-anticoagulation and supratherapeutic INR than warfarin DDIs involving the CYP3A4 isoenzyme. Consequently, if the goal for Mr Bailey was high-intensity statin therapy and there was considerable concern about the magnitude of the DDI between rosuvastatin and warfarin, his physician may have desired to switch him to an equivalent dose of atorvastatin (eg, 40-80 mg).

On the other hand, only a small proportion of pravastatin (10%) is metabolized by the CYP3A4 isoenzyme and it is a weak affinity substrate of this isoenzyme. Therefore, we would not expect a clinically meaningful DDI between this statin and warfarin. While pravastatin was a safe option for Mr Bailey, it would not have achieved the goal of high-intensity statin therapy. Pitavastatin also was a safe option for Mr Bailey because it does not undergo CYP-mediated drug metabolism and, therefore, would not have interacted with warfarin via either the CYP2C9 or CYP3A4 isoenzyme. However, like pravastatin, it is considered low- to moderate-intensity statin therapy; and unlike pravastatin, it is only commercially available as a brand-name product and thus comes at a much higher cost. The DDI between warfarin and rosuvastatin that occurred in Mr Bailey was an exemplar case of competitive inhibition resulting in phenoconversion and has been the basis of other reports.[16]

FIGURE 3 Chart information for Mr Howell

Medication List	Aspirin 81 mg by mouth daily Omeprazole 40 mg by mouth daily Hydrochlorothiazide 25 mg by mouth daily Atorvastatin 80 mg by mouth daily Lisinopril 20 mg by mouth daily
Pharmacogenetic Results	Genotype: CYP2C19*1/*17 Phenotype: Rapid Metabolizer Clopidogrel: Increased platelet inhibition

3.2 | Case 2: Clopidogrel-Omeprazole and CYP2C19

Larry Howell was a 66-year-old Asian man with a past medical history of hypertension, hyperlipidemia, and Barrett's esophagus. He presented to the hospital with acute coronary syndrome and underwent percutaneous coronary intervention (PCI), whereby he was given a loading dose (300 mg) of clopidogrel and a stent was placed. See Figure 3 for additional information captured from his chart review.

In accordance with the hospital's PCI protocol, a pharmacogenetic test was ordered to obtain CYP2C19 genotyping in order to guide selection and dosing of future antiplatelet therapy. Five hours after the PCI, the cardiologist received an alert in the electronic health record that Mr Howell's pharmacogenetic test result had been returned (Figure 3). With the result in mind, the cardiologist weighed the benefits (ie, increased activation of clopidogrel resulting in increased platelet inhibition) and risks (ie, increased risk of bleeding but taking a proton pump inhibitor [PPI]), and decided to initiate clopidogrel 75 mg orally daily.

The next day, Mr Howell was discharged from the hospital, with a new prescription for clopidogrel and instructions to resume taking all of his other medications. As the discharging pharmacist with the cardiology team, you followed up with Mr Howell via telephone within 30 days, and noted that, according to his wife, Mr Howell was adherent with his medication regimen and took all of his medications in the morning. She also reported that Mr Howell was regularly exercising, walking 30-60 minutes most days of the week, and eating healthier.

Four months later, though, Mr Howell presented back to the hospital with non-ST-elevation myocardial infarction. He underwent urgent PCI, whereby restenosis of his previously placed stent was discovered. After reviewing the

Medication	F%	CYP2C19 *1/*17	CYP3A4 N/A	CYP2B6 N/A
Omeprazole	35	65%	35%	
Clopidogrel	1	10%[a]	5%[a]	
Atorvastatin	13		80%	
Aspirin	90	NON P450		
Lisinopril	35	NON P450		
Hydrochlorothiazide	70	NON P450		
Alternative Proton Pump Inhibitors				
Rabeprazole	52	80%	20%	
Pantoprazole	77	90%		
Lansoprazole	80	70%	30%	
Esomeprazole	60	65%	35%	
Dexlansoprazole	30	90%		
Alternative Antiplatelets				
Prasugrel	U/D	U/D[a]	U/D[a]	U/D[a]
Ticagrelor	36		86%	

FIGURE 4 Oral bioavailability and metabolic pathways for Mr Howell's Medication Regimen. Abbreviations: F = absolute bioavailability; N/A = not available; U/D = undetermined. The color coding in the cells for CYP450 drug-metabolizing isoenzymes indicates the affinity of the medication for this isoenzyme, as follows: □ = CYP weak affinity substrate, ■ = CYP moderate affinity substrate, and ■ = CYP strong affinity substrate. The percentages in the cells for CYP450 drug-metabolizing isoenzymes indicate the extent this isoenzyme contributes to the overall metabolic clearance of the medication. [a]Indicates a prodrug

notes in Mr Howell's chart and carefully scrutinizing his medication regimen, you contacted the cardiologist with a plausible explanation of the restenosis and a plan for prophylaxis.

Both clopidogrel and omeprazole are substrates of the CYP2C19 drug-metabolizing isoenzyme, but they have different affinities (see Figure 4).[17,18] Specifically, omeprazole is a strong affinity substrate, whereas clopidogrel is a weak affinity substrate. Moreover, CYP2C19 predominantly catalyzes the biotransformation of clopidogrel, which is a prodrug, to an active metabolite that selectively and irreversibly inhibits platelet aggregation.[19]

Because omeprazole has a stronger affinity for the CYP2C19 isoenzyme than clopidogrel and because both medications were taken at the same time of day, omeprazole competitively inhibited clopidogrel's metabolism by this isoenzyme.[17,18] Even though only a small proportion (about 10%) of clopidogrel is metabolized by CYP2C19, competitive inhibition markedly interferes with its activation. Therefore, although Mr Howell was a genotypic rapid metabolizer for the CYP2C19 isoenzyme, due to competitive inhibition by omeprazole, he underwent phenoconversion to an intermediate or possibly even poor metabolizer of clopidogrel.

Additionally, both omeprazole and atorvastatin have moderate affinities for CYP3A4, which also is partly responsible for clopidogrel's bioactivation.[18,20,21] Because these medications have stronger affinities for this isoenzyme than clopidogrel and Mr Howell was taking all of them at the same time of day, both omeprazole and atorvastatin competitively inhibited clopidogrel's CYP3A4-mediated metabolism. Although Mr Howell's *CYP3A4* genotype was unknown, he was inevitably a poor metabolizer of clopidogrel by the CYP3A4 isoenzyme due to competitive inhibition. Collectively, these DDIs and DGIs likely contributed to, or potentially caused, the restenosis.

Next, look at the bottom portion of Figure 4 for a visual representation of alternative medications that could have been used in place of either omeprazole or clopidogrel. Because of his bleeding risk (ie, age, dual antiplatelet therapy, and history of Barrett's esophagus), therapy with a PPI rather than an H_2-receptor antagonist (eg, famotidine) was deemed medically necessary for Mr Howell. Yet to mitigate the DDI between omeprazole and clopidogrel, the vexing question is as follows: Which PPI would have been safest for Mr Howell?

First, there is a plethora of evidence demonstrating an omeprazole-clopidogrel DDI and major adverse cardiovascular events associated with this interaction.[22-27] There is comparatively less evidence for the other PPIs, with the exception of esomeprazole.[25-28] Secondly, although all of the PPIs are CYP2C19 substrates, they have varying degrees of affinity for this isoenzyme. Omeprazole has the strongest affinity, followed by esomeprazole with moderate affinity, followed by the other PPIs, which have comparatively weaker affinity for CYP2C19. Still, even among the weaker affinity PPIs, some data indicate that pantoprazole and rabeprazole have the lowest affinity for the CYP2C19 isoenzyme.[17,25,26,29,30]

Our choice was to select a PPI with a weak affinity for CYP2C19 in order to minimize the competitive interaction with clopidogrel. In Mr Howell's case, if he took clopidogrel 75 mg with one of the weak affinity PPIs (eg, pantoprazole 40 mg and rabeprazole 20 mg) then clopidogrel's bioactivation would not have been competitively inhibited. Notwithstanding, to mitigate this less egregious DDI, Mr Howell should take one of the other PPIs at least two to four hours before taking clopidogrel.

Alternatively, if Mr Howell's cardiologist and/or PCP decided that omeprazole was the PPI of choice, then another option to prevent the DDI and possibly restenosis was to replace clopidogrel with alternative antiplatelet therapy. According to evidence-based PGx guidelines, prasugrel or ticagrelor should be used as alternatives to clopidogrel for individuals who are CYP2C19 poor metabolizers.[19] Since Mr Howell "behaved" like a CYP2C19 poor metabolizer for clopidogrel, due to phenoconversion by omeprazole, then it would have been prudent to follow the PGx-based recommendation.

Similar to clopidogrel, prasugrel also is a prodrug but is mainly bioactivated by the CYP2B6 and CYP3A4 isoenzymes, and to a lesser extent by the CYP2C19 isoenzyme. On the other hand, ticagrelor is not a prodrug nor a substrate of the CYP2C19 isoenzyme, rather is it mostly metabolized by the CYP3A4 isoenzyme; albeit both the parent drug and the active metabolite inhibit platelet aggregation.[31] Therefore, for reasons previously explained, prasugrel in combination with omeprazole may not have been the precise medication regimen for Mr Howell.

Conversely, ticagrelor has moderate affinity for the CYP3A4 isoenzyme, similar to omeprazole and atorvastatin. However, because the dose of ticagrelor (ie, 90 mg) was expected to be higher than the dose of either omeprazole (ie, 20 mg) or atorvastatin (ie, 80 mg), when administered at the same time of day, ticagrelor would be the "perpetrator" of the DDI and omeprazole and atorvastatin would be the "victims" of the interaction. Therefore, ticagrelor was the precise medication for antiplatelet therapy for Mr Howell. However, it would have been prudent to separate the time of administration of both omeprazole and atorvastatin from ticagrelor.

The DDI between clopidogrel and omeprazole that occurred in Mr Howell not only reiterated the mechanism and consequence of the interaction that has been previously reported,[22,23] and is the basis of warnings in the FDA-approved product labeling for clopidogrel,[32] but it also demonstrated how a drug interaction can change an individual's phenotype,

thereby completely altering medication response. This case also retold the consequence of the DGI between clopidogrel and variations of the *CYP2C19* gene, which also have been extensively reported in the literature[23,33-35] and included in the warnings in the FDA-approved product labeling for clopidogrel.[32]

4 | DISCUSSION

In real-world applications, whereby individuals presenting to the healthcare system commonly take multiple medications, precision medication entails selecting the right combination and doses of medications and administering them at the right times of day. While PGx enables precision medication, the leading misconception is that genotyping results provide the "answers," when in fact this is not often the case. As illustrated by these simulated cases, genotyping may significantly underestimate phenoconversion. For prodrugs, phenoconversion to a reduced metabolic capacity inhibits or, at least substantially reduces, an individual's ability to convert the medication to an active metabolite, thereby increasing the risk for therapeutic failure. For most other drugs, though, this reduces an individual's ability to metabolize an active medication to inactive metabolites for clearance from the body, thereby increasing the risk for toxicity. While not illustrated by these cases, it is worth noting that phenoconversion also has the capability to increase metabolic capacity in certain clinical scenarios, such as when an inducer (eg, primidone) is concomitantly used with substrates sharing the same isoenzyme metabolic pathway.

5 | CONCLUSIONS

Multi-drug interactions and genetics can profoundly influence real-world applications of precision medication. Clinicians that use PGx and apply precision medication within their practice need to understand the nuances illustrated by the cases presented in this article. This may require additional trainings and competencies in the medical and pharmacy fields.

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CONFLICT OF INTEREST

The authors disclose that they performed this work as employees of Tabula Rasa HealthCare and that they possess shares and/or stock options in the aforementioned company.

AUTHOR CONTRIBUTIONS

KTB, EJC, VM, and JT contributed to conceptualization; KTB, DM, and EJC contributed to methodology; KTB, DM, EJC, VM, and JT contributed to case development; CHK, VM, and JT contributed to case interpretation; KTB and EJC contributed to writing—original draft; KTB, DM, EJC, CHK, VM, and JT contributed to writing—review & editing; CHK, VM, and JT contributed to resources; CHK and JT contributed to supervision. No funded writing assistance was used in the creation of this manuscript. Each author provided substantial contributions to research concept and design, acquisition of data/information, and analysis and interpretation of data/information. Additionally, each author contributed significantly to the preparation of the manuscript and revised it critically for important intellectual content. All authors gave final approval of the version of the manuscript to be considered for publication, and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVALS

This article did not require ethical approval because it presents simulated, rather than actual, patient cases. Although the cases were formulated from real-world applications, no patient-specific information was used in this article. The cases were intended to demonstrate the impact of genetic variations and concomitant medications on drug interactions and phenoconversion in order to provide instructional guidance for pharmacists.

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