Proton pump inhibitors (PPIs) are widely used for acid suppression in the treatment and prevention of many conditions, including gastroesophageal reflux disease, gastric and duodenal ulcers, erosive esophagitis, *Helicobacter pylori* infection, and pathological hypersecretory conditions. Most PPIs are metabolized primarily by cytochrome P450 2C19 (CYP2C19) into inactive metabolites, and CYP2C19 genotype has been linked to PPI exposure, efficacy, and adverse effects. We summarize the evidence from the literature and provide therapeutic recommendations for PPI prescribing based on CYP2C19 genotype (updates at www.cpicpgx.org). The potential benefits of using CYP2C19 genotype data to guide PPI therapy include (i) identifying patients with genotypes predictive of lower plasma exposure and prescribing them a higher dose that will increase the likelihood of efficacy, and (ii) identifying patients on chronic therapy with genotypes predictive of higher plasma exposure and prescribing them a decreased dose to minimize the risk of toxicity that is associated with long-term PPI use, particularly at higher plasma concentrations.

Proton pump inhibitors (PPIs) are widely used for acid suppression in the treatment and prevention of a variety of conditions, including gastroesophageal reflux disease (GERD), gastric and duodenal ulcers, erosive esophagitis, esoinophilic esophagitis, *Helicobacter pylori* (H. pylori) infection, and pathological hypersecretory conditions in adults and children. Most PPIs are extensively metabolized into inactive metabolites primarily by the hepatic cytochrome P450 2C19 (CYP2C19) enzyme, and CYP2C19 genotypes have been linked to PPI exposure, with lower exposure associated with treatment failure and higher exposure associated with improved efficacy. Higher exposure of PPIs has also been associated with adverse effects, as has long-term use. The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical CYP2C19 genotyping test results to guide PPI prescribing. Detailed guidelines for the use of PPIs, cost effectiveness of CYP2C19 genotyping, and whether to order a CYP2C19 genotype test prior to PPI prescribing are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at www.cpicpgx.org/guidelines/.

**FOCUSED LITERATURE REVIEW**

A systematic literature review focused on the link between CYP2C19 genotypes and PPI metabolism, exposure, efficacy, and adverse effects was conducted (details in Supplemental Material).

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GENE: CYP2C19

Background
The CYP2C19 gene is highly polymorphic with 37 known variant stars (*) alleles, including rare copy number variants (i.e., gene deletions) (https://www.pharmvar.org/gene/CYP2C19; see CYP2C19 Allele Definition Table online3,4). The frequencies of these alleles significantly differ across ancestry diverse populations (see CYP2C19 Frequency Table online3,4). Alleles are categorized into functional groups as follows: normal function (e.g., CYP2C19*1), decreased function (e.g., CYP2C19*9), no function (e.g., CYP2C19*2 and *3), and increased function (e.g., CYP2C19*17). Clinical allele function, as described in the CYP2C19 Allele Functionality Table, was determined based on reported in vitro and/or in vivo data when available.3,4 The most common CYP2C19 no function allele, CYP2C19*2 (c.681G > A; rs4244285), has an allele frequency of ~15% in Europeans and Africans, ~25–30% in Asians, and ~60% in Oceanians. Other CYP2C19 variant alleles with decreased or no function (e.g., *3–*8) typically have allele frequencies below 1%, with the exception of CYP2C19*9 (c.636G > A; rs4986893) in Asians (allele frequency of 2–7%) and Oceanians (allele frequency of 15%). The increased function allele CYP2C19*17 (c.-806C > T; rs12248560) is most common in African, European, and Near Eastern populations, with an allele frequency of ~20%.

Genetic Test Interpretation
The combination of inherited alleles determines a person’s diplotype (also referred to as genotype). Table 1 defines each predicted phenotype based on allele function combinations and provides example diplotypes. CYP2C19 normal metabolizers (NMs) are characterized by the presence of two normal function alleles (e.g., CYP2C19 *1/*1). CYP2C19 intermediate metabolizers (IMs) are characterized by the presence of one normal function allele and one no function allele (e.g., CYP2C19 *1/*2), or one no function allele and one increased function allele (e.g., CYP2C19 *2/*17). Limited data suggest that the increased function allele CYP2C19*17 may not compensate for no function alleles such as CYP2C19*2.3 CYP2C19 poor metabolizers (PMs) are characterized by the presence of two no function alleles (e.g., CYP2C19 *2/*2). Diplotypes characterized by one normal function allele and one increased function allele (i.e., CYP2C19 *1/*17) are classified as rapid metabolizers (RMs), and diplotypes characterized by two increased function alleles (i.e., CYP2C19 *17/*17) are classified as ultrarapid metabolizers (UMs). There are limited data available for decreased function alleles (e.g., CYP2C19*9); therefore, individuals who have one normal function and one decreased function allele, or one increased function and one decreased function allele, or two decreased function alleles, are currently classified as “likely IM.” Individuals with one no function and one decreased function allele are currently classified as “likely PM.” The “indeterminate” phenotype is assigned when the individual carries one or two uncertain function alleles. See the CYP2C19 Diplotype-Phenotype Table online for a complete list of possible diplotypes and the corresponding predicted phenotype assignments.3,4

Clinical laboratories report CYP2C19 genotype results using star (*) allele nomenclature. The star (*) allele nomenclature for CYP2C19 is found at the Pharmacogene Variation (PharmVar) Consortium website (https://www.pharmvar.org/gene/CYP2C19). Tables on the CPIC website contain a list of CYP2C19 alleles, the combinations of variants that define each allele, allele clinical functional status, and reported allele frequencies across major ancestral populations.3

Available Genetic Test Options
See the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

Table 1 Assignment of predicted CYP2C19 phenotype based on genotype

<table>
<thead>
<tr>
<th>Predicted phenotype</th>
<th>Genotype</th>
<th>Examples of CYP2C19 diplotypes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultrarapid metabolizer</td>
<td>An individual carrying two increased function alleles</td>
<td>*17/*17</td>
</tr>
<tr>
<td>CYP2C19 rapid metabolizer</td>
<td>An individual carrying one normal function allele and one increased function allele</td>
<td>*1/*17</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>An individual carrying two normal function alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP2C19 likely intermediate metabolizer</td>
<td>An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles</td>
<td>*1/*9, *9/*17, *9/*9</td>
</tr>
<tr>
<td>CYP2C19 intermediate metabolizer</td>
<td>An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele</td>
<td>*1/*2, *1/*3, *2/*17, *3/*17</td>
</tr>
<tr>
<td>CYP2C19 likely poor metabolizer</td>
<td>An individual carrying one decreased function allele and one no function allele</td>
<td>*2/*9, *3/*9</td>
</tr>
<tr>
<td>CYP2C19 poor metabolizer</td>
<td>An individual carrying two no function alleles</td>
<td>*2/*2, *3/*3, *2/*3</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>An individual carrying one or two uncertain function alleles</td>
<td>*1/*12, *2/*12, *12/*14</td>
</tr>
</tbody>
</table>

CYP2C19, cytochrome P450 2C19.

*Please refer to the CYP2C19 Diplotype-Phenotype Table online for a complete list.3,4 bThere are limited data to characterize the function of decreased function alleles.
Incidental Findings
No inherited diseases or conditions have been consistently or strongly linked to germline genetic variants in *CYP2C19* independent of drug metabolism and response.

Other Considerations
Not applicable.

**DRUGS: PROTON PUMP INHIBITORS**

**Background**
PPIs are substituted benzimidazoles that inhibit the final pathway of acid production in gastric parietal cells by covalently binding to the hydrogen/potassium adenosine triphosphatase proton pump, which leads to inhibition of gastric acid secretion that lasts for 24–48 hours despite short PPI half-lives. This irreversible inhibition is only overcome by synthesis of new hydrogen/potassium adenosine triphosphatase proton pumps, which may take ~54 hours to fully regenerate. Six PPIs are currently used in clinical practice, including the first-generation inhibitors omeprazole, lansoprazole, and pantoprazole, and the second-generation inhibitors esomeprazole, rabeprazole, and dexlansoprazole. *CYP2C19* is a major metabolic pathway for the clearance of first-generation PPIs (~80%) with a lesser contribution by CYP3A4. Dexlansoprazole (R-lansoprazole) appears to share a similar metabolic pathway to lansoprazole. In contrast, the second-generation PPIs esomeprazole and rabeprazole are less dependent on *CYP2C19* in their metabolism, suggesting that they may be less influenced by genetic variability in *CYP2C19* compared with first-generation PPIs. Specifically, rabeprazole is primarily cleared by nonenzymatic mechanisms. Omeprazole and esomeprazole exhibit nonlinear pharmacokinetics due to *CYP2C19* autoinhibition leading to an increased area under the serum concentration-time curve (AUC) with repeated administration. The elevation in AUC that results from autoinhibition is greater for esomeprazole (1.45–1.74 fold) than omeprazole.

While PPIs have been among the most commonly prescribed medications due in part to the perception that they have a high safety-to-risk profile, a large body of evidence is emerging that links adverse events with long-term PPI use. PPI use has been associated with numerous adverse events, including electrolyte imbalances (e.g., hypomagnesemia), infections, kidney disease, and bone fractures.

**Linking Genetic Variability to Variability in Drug-Related Phenotypes**

**First-Generation PPIs: Omeprazole, Lansoprazole, and Pantoprazole.** There is a substantial body of evidence linking *CYP2C19* genotype with variability in plasma concentrations and efficacy of first-generation PPIs (omeprazole, lansoprazole, and pantoprazole). As outlined in Tables S1–S3, the evidence associating *CYP2C19* genotype with omeprazole, lansoprazole, and pantoprazole plasma concentrations was graded as high. Multiple studies have shown that the *CYP2C19* IM and PM phenotypes are associated with decreased clearance and increased plasma concentrations of these PPIs leading to increased treatment success compared with *CYP2C19* NM genotypes, including for *H. pylori* infection and erosive esophagitis.

In contrast, *CYP2C19* RMs and UMs have increased PPI clearance and decreased plasma concentrations compared with *CYP2C19* NM genotypes, which may increase risk of treatment failure compared with *CYP2C19* NM genotypes, IMs, and PMs. It is important to note that most *CYP2C19* studies evaluating PPIs were conducted in Asian populations, in whom the frequency of the increased function *CYP2C19*17 allele is low compared with non-Asians; therefore, few studies including *CYP2C19* RMs and UMs have been published to date. Prescribing recommendations for *CYP2C19* RMs and UMs in this guideline were based on pharmacokinetic differences vs. NM genotypes and differences in PPI effectiveness between NMs and IMs/PMs. This body of literature provides the basis for the prescribing recommendations presented in Table 2.

**Second-Generation PPIs: Esomeprazole, Rabeprazole, and Dexlansoprazole.** There is less evidence linking *CYP2C19* genotype variability in plasma concentrations and effectiveness of second-generation PPIs (esomeprazole, rabeprazole, and dexlansoprazole), both in terms of number of studies and strength of the association. As outlined in Table S4–S6, the evidence associating *CYP2C19* genotype with esomeprazole, rabeprazole, and dexlansoprazole plasma concentrations, efficacy, and toxicity was graded as moderate or weak. While fewer data exist on the influence of *CYP2C19* genotype on dexlansoprazole compared with first-generation PPIs, similar effects of *CYP2C19* genotype on dexlansoprazole pharmacokinetics and effectiveness are expected given its similar metabolic pathway to lansoprazole.

Inconsistent findings regarding the effect of *CYP2C19* genotype on the pharmacokinetics and therapeutic response to esomeprazole and rabeprazole preclude making recommendations for these second-generation PPIs (i.e., CPIC level C; no recommendation).

**Therapeutic Recommendations**

Table 2 summarizes therapeutic recommendations for PPI prescribing in adults and pediatric patients based on *CYP2C19* phenotype, specifically for the first-generation PPIs (omeprazole, lansoprazole, and pantoprazole) and dexlansoprazole. These recommendations apply to both oral and intravenous PPI use. While *CYP2C19* NMs are expected to have normal PPI metabolism and clearance, a large body of literature from studies in Asian populations reported an association between *CYP2C19* NMs and decreased therapeutic effectiveness with these PPIs (e.g., failure to eradicate *H. pylori* infection and lower healing rates of erosive esophagitis) compared with *CYP2C19* IMs and PMs (Tables S1–S4). Therefore, for *CYP2C19* NMs, initiating these PPIs at standard daily doses (e.g., label-recommended doses) is generally recommended; however, for *H. pylori* infection or erosive esophagitis, clinicians may consider increasing the recommended dose for these indications by 50–100% to optimize therapeutic efficacy.

Following administration of standard doses of first-generation PPIs, *CYP2C19* IMs and PMs experience higher PPI AUC (3–14-fold) and maximum plasma drug concentration (2–6-fold) compared with *CYP2C19* NMs as a result of reduced PPI clearance via the *CYP2C19* pathway. The
increased PPI exposure in CYP2C19 IMs and PMs has been linked to improved acid suppression (i.e., higher intragastric pH and longer time with pH > 4.0) and improved therapeutic benefits. Thus, CYP2C19 IMs and PMs are considered to be “therapeutically advantaged” compared with NMs in terms of efficacy.19–23 However, it has been suggested that continued inhibition of acid secretion in individuals taking PPIs chronically who are genotyped as CYP2C19 IMs or PMs may have a higher risk of PPI-related adverse events compared with NM, RM, or UM phenotypes.1 While the current data are insufficient to make strong dosing recommendations, potential associations of CYP2C19 phenotype and incidence of adverse events (e.g., infections) are emerging.24 Therefore, for CYP2C19 IMs and PMs, it is recommended to initiate standard daily dosing to maximize the likelihood of efficacy and, once efficacy is achieved, consider a 50% reduction in the daily dose in the setting of chronic PPI therapy (beyond 12 weeks) to minimize the risk of adverse events from prolonged acid suppression. If a dose

<table>
<thead>
<tr>
<th>CYP2C19 phenotype&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Implications for phenotypic measures</th>
<th>Therapeutic recommendation</th>
<th>Classification of recommendation&lt;sup&gt;b&lt;/sup&gt; – omeprazole, lansoprazole, and pantoprazole</th>
<th>Classification of recommendation&lt;sup&gt;b&lt;/sup&gt; – dexlansoprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 ultrarapid metabolizer</td>
<td>Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure</td>
<td>Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy</td>
<td>Optional</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2C19 rapid metabolizer</td>
<td>Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure</td>
<td>Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of Helicobacter pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.</td>
<td>Moderate</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2C19 normal metabolizer</td>
<td>Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs</td>
<td>Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.</td>
<td>Moderate</td>
<td>Optional</td>
</tr>
<tr>
<td>CYP2C19 likely intermediate metabolizer</td>
<td>Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity</td>
<td>Initiate standard starting daily dose. For chronic therapy (&gt; 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy</td>
<td>Optional&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Optional&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td>Initiate standard starting daily dose. For chronic therapy (&gt; 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy</td>
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<td>Moderate</td>
<td>Optional</td>
</tr>
</tbody>
</table>

<sup>a</sup>CYP2C19, cytochrome P450 2C19; IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; PPI, proton pump inhibitor.
<sup>b</sup>The online CYP2C19 Frequency Table provides phenotype frequencies for major race/ethnic groups, and the online CYP2C19 Diplotype-Phenotype Table provides a complete list of possible diplotypes and phenotype assignments. 3,4 <sup>c</sup>Rating scheme described in the Supplemental Material. <sup>c</sup>The strength of recommendation for “likely” phenotypes is the same as for their respective confirmed phenotypes. “Likely” indicates the uncertainty in the phenotype assignment, but it is reasonable to apply the recommendation for the confirmed phenotype to the corresponding “likely” phenotype.
reduction is made, monitoring for continued efficacy is recommended. Additional studies that investigate the relationship between CYP2C19 genotype and incidence of PPI-related adverse events are needed.

The RM and UM phenotypes are driven by the presence of the increased function CYP2C19*17 allele. Due to the relatively recent discovery of this variant and because the majority of studies describing associations between CYP2C19 genotype, pharmacokinetics, and pharmacodynamics of PPIs were conducted in Asian populations in whom the CYP2C19*17 allele occurs less frequently, there are limited data on the relationship between CYP2C19*17, pharmacokinetic parameters, acid secretion indices, and therapeutic outcomes in CYP2C19 RM and UMs. Additional studies with CYP2C19 RM and UM phenotypes are needed. Nevertheless, the low PPI exposure documented in patients who are CYP2C19 UMs compared with NMs, IMs, and PMs suggests that these individuals may benefit from higher-than-standard daily doses of PPIs (Tables S1–S3). Therefore, it is recommended to increase the starting daily dose by 100% in CYP2C19 UM phenotypes. For RM phenotypes, standard dosing should be initiated, but a 50–100% dose increase could be considered for the treatment of H. pylori infection and erosive esophagitis to maximize the likelihood of therapeutic plasma concentrations and therapeutic effect. These patients should be monitored for efficacy.

The plasma half-life of PPIs is short (~30 minutes to 5 hours), but the biological effects they exert are much longer, as it takes ~54 hours to regenerate new acid pumps after inactivation by PPIs. Studies have documented that daily doses administered two to four times daily may result in improved efficacy compared with the same total daily dose given once daily. Although adherence to PPI dosing three to four times per day to overcome the short half-life may be challenging, it is recommended that increased PPI doses (50–100%) be administered as twice daily dosing, and more frequent dosing intervals could be considered for increased benefit, with the caveat that this dosing regimen may compromise compliance.

There are fewer data available investigating the association between dexlansoprazole and CYP2C19 metabolizer status compared with the first-generation PPIs. However, reported pharmacokinetic data support the association between CYP2C19 IMs and PMs and increased dexlansoprazole exposure. Additionally, CYP2C19 PMs were reported to have greater acid suppression compared with NMs. Given the similarity in metabolism between lansoprazole and dexlansoprazole, it is reasonable to extrapolate the recommendations from the first-generation PPIs (Table 2). These recommendations are considered “optional” due to the limited data with dexlansoprazole and CYP2C19.

**Recommendations for Incidental Findings**

Not applicable.

**Other Considerations**

**Drug-Drug-Gene Interactions.** In addition to CYP2C19, most PPIs are metabolized to some extent by CYP3A, and the fraction of metabolism by this alternative pathway increases in CYP2C19 IM and PM phenotypes. Due to drug-drug-gene interactions, concomitant administration of strong inhibitors of CYP3A may increase the risk for adverse effects during chronic dosing with PPIs in CYP2C19 IMs and PMs. In addition, strong inhibitors of CYP2C19 (e.g., fluvoxamine) can lead to phenocconversion that substantially increases systemic exposure to PPIs (except in CYP2C19 PMs), while inducers of CYP2C19 and CYP3A (e.g., rifampin) can lead to reduced exposure and treatment failure. Therefore, assessment of drug interactions may be needed when a PPI and a perpetrator drug are coadministered chronically.

**Implementation of This Guideline.** The guideline supplement and CPIC website (https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/) contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support in the Supplemental Material).

**Potential Benefits and Risks for the Patient**

The potential benefit of using CYP2C19 genotype data to guide PPI therapy is that patients with genotypes predictive of lower plasma exposure may be identified and prescribed an increased dose that will increase the likelihood of efficacy. Patients on chronic therapy with genotypes predictive of higher plasma exposure may consider a dose reduction to minimize the risk of toxicity that is associated with long-term PPI use.
(overexposure), particularly at higher plasma concentrations. The potential risks of genotype-guided PPI therapy include therapeutic failure in patients for whom a dose decrease was recommended and increased risk of toxicity in patients for whom a dose increase was recommended. As with any laboratory test, a possible risk to patients is an error in genotyping or phenotype prediction, which could have long-term adverse health implications for patients.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

There are some important limitations to CYP2C19 genetic tests. Targeted genotyping tests focus on interrogating previously described star (*) alleles and therefore are not designed to detect novel variants. Furthermore, rare allelic variants may not be included in the genotype test used, and patients with these rare variants may be assigned an NM phenotype (CYP2C19*1/*1) by default. As such, an assigned *1 allele could potentially harbor an undetected CYP2C19 genetic variant that results in altered metabolism and drug exposure. In addition, rare alleles with gene deletions at the CYP2C19 locus have recently been reported (‘36 and ‘37); however, most clinical laboratories do not currently test for CYP2C19 copy number variants or deletions. Therefore, it is important that clinical providers appreciate the limitations of targeted genotyping tests and understand which CYP2C19 variant alleles were genotyped when interpreting results. As with any diagnostic test, CYP2C19 genotype is just one factor that clinicians should consider when prescribing PPIs.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC’s guidelines, or for any errors or omissions.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

J.A.J. is a consultant to United Health Group for their plans to begin implementing pharmacogenomics in clinical practice. S.A.S. is a paid employee of Sema4, which is a for-profit genetic testing company that offers pharmacogenetic testing. D.L.T. is a paid employee of Translational Software, which is a for-profit genetic testing company that offers pharmacogenetic testing. All other authors declared no competing interests for this work. As an Associate Editor for Clinical Pharmacology & Therapeutics, S.L.V.D. was not involved in the review or decision process for this paper.

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11. Sim, S.C. et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to...