



Article
scientifique

Revue de la
littérature

2024

Published
version

Open
Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Implementing pharmacogenetic testing to optimize proton-pump inhibitors use among Indian population based on CPIC-CYP2C19-PPI dosing guidelines : The need of the hour

Chenchula, Santenna; Atal, Shubham; Jhaj, Ratinder; Uppugunduri Satyanarayana, Chakradhara Rao

How to cite

CHENCHULA, Santenna et al. Implementing pharmacogenetic testing to optimize proton-pump inhibitors use among Indian population based on CPIC-CYP2C19-PPI dosing guidelines : The need of the hour. In: Indian Journal of Pharmacology, 2024, vol. 56, n° 4, p. 277–284. doi: 10.4103/ijp.ijp_198_24

This publication URL: <https://archive-ouverte.unige.ch/unige:187782>

Publication DOI: [10.4103/ijp.ijp_198_24](https://doi.org/10.4103/ijp.ijp_198_24)

Access this article online

Quick Response Code:



Website:

www.ijp-online.com

DOI:

10.4103/ijp.ijp_198_24

Implementing pharmacogenetic testing to optimize proton-pump inhibitors use among Indian population based on CPIC-CYP2C19-PPI dosing guidelines: The need of the hour

Santenna Chenchula, Shubham Atal, Ratinder Jhaj, Chakradhara Rao S. Uppugunduri^{1,2}

Abstract:

Proton-pump inhibitors (PPIs) are widely prescribed to decrease stomach acid and treat various acid-related Gastrointestinal tract (GIT) diseases. However, genetic variations, particularly in the *CYP2C19* gene, affect PPIs metabolism and efficacy. Variants in *CYP2C19* can result in different rates of PPI metabolism, influencing their effectiveness. Personalized medicine strategies, such as genotyping for *CYP2C19*, have the potential to enhance the effectiveness of PPI therapy and patient safety. This review aims to describe the relevance of *CYP2C19* genetic profiling in the Indian population, including normal function (e.g. *CYP2C19**1, *11, *13, *15, *18, *28, and 38), decreased function (e.g., *CYP2C19**9, *10, *16, *19, *25, and 26), loss of function (e.g., *CYP2C19**2, *3, *4, *5, *6, *7, *8, *22, *24, *35, *36, and *37), and increased function (e.g., *CYP2C19**17) variants. This review also examines the clinical pharmacogenomics implementation consortium (CPIC)-*CYP2C19*-PPI guidelines to highlight the importance of pharmacogenomics (PGx)-informed personalized PPI therapy for gastroesophageal reflux disease and peptic ulcer disease treatment. On average, each person in India possesses eight pharmacogenetic (PGx) variants that can be clinically significant, underscoring the need for preemptive testing. Implementing *CYP2C19* genetic testing in India requires expanding laboratory capacity, increasing accessibility in primary care, increasing public awareness, collaboration between pharmacovigilance and PGx programs, investing in advanced sequencing technologies, data management systems, and integration with electronic health records and clinical decision support systems. Addressing challenges such as genetic diversity, socioeconomic factors, health-care access issues, and shortage of trained professionals is essential for implementation. Due to the lack of definitive country-specific policies and PGx guidelines from Indian drug regulatory agencies, guidelines from international consortia such as the Clinical Pharmacogenetics Implementation Consortium and drug labeling offer crucial foundational evidence. This evidence can be used to enhance patient outcomes and ensure the safe and effective use of PPIs in India.

Keywords:

CYP2C19, Indian population, metabolism, omeprazole, personalized medicine, pharmacogenetics, pharmacogenomics, proton-pump inhibitor

Introduction

There is a growing burden of acid peptic diseases (APDs) across the

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

world, particularly in developing countries such as India, due to changing dietary factors and the increasing adoption of a Western-style diet.^[1] In India, the incidence of gastroesophageal reflux disease (GERD)

How to cite this article: Chenchula S, Atal S, Jhaj R, Uppugunduri CR. Implementing pharmacogenetic testing to optimize proton-pump inhibitors use among Indian population based on CPIC-CYP2C19-PPI dosing guidelines: The need of the hour. Indian J Pharmacol 2024;56:277-84.

Department of Pharmacology, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh,
²Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, ¹Pediatric Oncology and Hematology, CANSEARCH Research Platform in Pediatric Oncology and Hematology, University of Geneva, Geneva, Switzerland

Address for correspondence:

Dr. Chakradhara Rao S. Uppugunduri, Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry - 605 006, India.
 E-mail: uscrao@jipmer.ac.in

Submitted: 17-Mar-2024
 Revised: 29-Jul-2024
 Accepted: 12-Aug-2024
 Published: 10-Sep-2024

is 39.2%, that of peptic ulcer disease (PUD) is 37.1%, and that of nonulcer dyspepsia (NUD) is 25.2%, while the lifetime prevalence of PUD ranges from 8% to 12%.^[1,2] Studies have shown that GERD is more common among older people.^[3] Most often, both PUD and its complications are caused by *Helicobacter pylori* infection and the usage of nonsteroidal anti-inflammatory drugs (NSAIDs).^[4] The frequency of *H. pylori* infection in patients with PUD, gastric cancer, and NUD varies in various Indian centers, with rates ranging from 38% to 90%.^[5] The high prevalence of APDs places a substantial burden on health-care systems because both GERD and PUD often require chronic treatment, leading to significant health-care expenditures.^[6] In addition to financial burdens, patients' quality of life is also significantly affected by symptoms such as persistent heartburn, abdominal pain, and nausea, which can interfere with daily activities, work productivity, and social interactions.^[7] Additionally, chronic pain and discomfort can lead to psychological distress, including anxiety and depression. Therefore, optimizing treatment strategies is crucial not only for reducing health-care costs but also for enhancing patients' quality of life.^[7]

Anti-ulcer agents proton-pump inhibitors (PPIs) are the most frequently prescribed medications for treating PUD because they inhibit H⁺-K⁺-ATPase, the final step in the secretion of gastric acid by parietal cells.^[1,4,6] These medications are widely used to treat disorders such as Zollinger–Ellison syndrome, GERD, Barrett's esophagus, erosive esophagitis, and upper gastrointestinal (GI) bleeding.^[6-8] PPIs are more effective than histamine 2 receptor antagonists or H₂-antihistaminics in the treatment and symptomatic alleviation of nonerosive reflux disease and erosive esophagitis.^[6] They also play an important role in stress ulcer prevention and act as gastroprotective drugs when combined with NSAIDs.^[6] In addition, PPIs are a component of several first-line and salvage therapy regimens for eradication of *H. pylori* infection.^[6,9] Currently, several PPIs are available for clinical use in India: first-generation PPIs include lansoprazole, omeprazole, and pantoprazole and second-generation benzimidazole derivatives, such as rabeprazole, esomeprazole, and dexlansoprazole.^[7] Drug utilization studies have shown that pantoprazole is the most commonly prescribed PPI in India.^[8,9] Although PPIs are usually thought to be safe drugs with few short-term side effects, there are increasing amounts of data revealing potential long-term side effects linked to chronic use, including micronutrient deficiencies, pneumonia, type 2 diabetes mellitus, dementia, osteoporosis, bone fractures, spontaneous bacterial peritonitis, kidney disease, and enteric infections.^[8-10]

PPIs undergo hepatic metabolism primarily through the enzymatic action of cytochrome P450 2C19 (CYP2C19),

with a lesser contribution from CYP3A4.^[10,11] However, the degree of CYP2C19 metabolism varies among PPIs.^[10,11] Over 80% of first-generation PPIs, of pantoprazole, omeprazole, and lansoprazole, are subject to CYP2C19 metabolism.^[13] While both omeprazole and esomeprazole are metabolized by CYP2C19, esomeprazole is metabolized to a lesser extent by CYP2C19 than omeprazole, resulting in reduced inter-individual variability in plasma drug concentrations.^[14] In contrast, rabeprazole is primarily metabolized to thioether-rabeprazole through a nonenzymatic path, with limited involvement of CYP2C19.^[15,16] However, dexlansoprazole appears to follow a metabolic pathway similar to that of lansoprazole.^[13,14]

Preliminary studies have shown that nearly 40% of patients with GERD report a limited or complete lack of symptom relief in response to PPI treatment.^[17] While many nongenetic factors, such as age, body mass index, smoking, and concomitant drugs, can influence the response and adverse drug events associated with PPIs, variability due to CYP2C19 genotype is significant and accounts for a large percentage of pharmacokinetic (PK) variability of PPIs.^[11,12,18] In addition to PPIs, CYP2C19 enzyme is essential for the metabolism of several other drugs, such as several antidepressants, sertraline, citalopram, escitalopram, clopidogrel, diazepam, phenytoin, proguanil, voriconazole, nelfinavir, thalidomide, and cyclophosphamide.^[11-13]

Several studies have highlighted that variability in drug clearance is associated with CYP2C19 genetic polymorphisms, which affect the metabolism of certain PPIs.^[10,12,19,20] Significant association between dose, PPI-related adverse events, and CYP2C19 genetic polymorphisms is also known.^[10] Blanco Dorado *et al.* explored potential drug interactions between PPIs and other medications.^[12] Their study showed that omeprazole, due to its greater CYP inhibitory capacity than pantoprazole, significantly decreased the plasma concentration of voriconazole, an antifungal drug, potentially compromising its efficacy. This interaction highlights the significance of considering CYP2C19 polymorphisms in clinical practice to avoid subtherapeutic drug levels and ensure optimal treatment outcomes.^[18] A study involving 110 Indian patients revealed the prevalence of different CYP2C19 genotypes.^[21] A study revealed that 23.64% of patients had a normal metabolizer, 47.23% had a loss-of-function mutation *2 associated with poor metabolizer of PPIs, and 35.45% had a gain-of-function mutation *17 associated with ultra-rapid metabolizer of PPIs.

Personalized treatment through pharmacogenomics (PGx) testing presents a promising approach for safer and more effective therapy of PPIs, considering the

substantial influence of *CYP2C19* genetic variability on PPI pharmacokinetics, therapeutic outcomes, and increased prevalence of *CYP2C19* poor metabolizer (PM) and ultrarapid metabolizer (UM) phenotypes.^[22] By identifying patients' *CYP2C19* genotypes, health-care providers can personalize PPI therapy, optimize drug efficacy, and minimize adverse effects. This tailored approach can enhance symptom relief, improve patient outcomes, and potentially reduce health-care costs allied with ineffective treatments and complications.^[22]

Currently, India is the most populous and one of the most genetically diverse countries in the world, with various ethnic groups and vast cultural, social, and biological diversity.^[23] On average, each person in India possesses at least eight pharmacogenetic (PGx) variants that are clinically significant, highlighting the prominence of preemptive testing for Indian population.^[24] However, PGx testing in India is still in its infancy, with limited integration into clinical practice.^[24] There is an urgent need to promote PGx testing in clinical practice by increasing clinical research to produce data on the prevalence of clinically actionable alleles of genes associated with drug response and adverse effects which may help to initiate the personalized treatment strategies tailored to Indian population.^[24] Currently, there are no definitive country-specific policies or PGx guidelines issued by Indian drug regulatory agencies. As a result, health-care providers and researchers often rely on PGx guidelines from the international consortia of Clinical Pharmacogenetics Implementation Consortium (CPIC), and labeling for approved drugs.^[22] These international guidelines provide foundational proof for prioritizing drug-gene candidates and supporting population-specific PGx initiatives in India.

Pharmacogenetics of the *CYP2C19* Gene

The *CYP2C19* gene, situated on chromosome 10q23.33, is part of the *CYP2C* subfamily.^[14] This gene exhibits high polymorphism, comprising 39 known variant alleles, also rare copy number variants (CNVs).^[14,19] The functionality of the *CYP2C19* gene (phenotype) is commonly influenced by specific genetic variations known as single-nucleotide polymorphisms and rarely by CNVs, resulting in significant variations in drug metabolism rates.^[14,20]

Alleles of *CYP2C19* gene are categorized into: normal function (e.g., *CYP2C19**1, *11, *13, *15, *18, *28, and *38), decreased function (e.g., *CYP2C19**9, *10, *16, *19, *25, and *26), no function (e.g., *CYP2C19**2, *3, *4, *5, *6, *7, *8, *22, *24, *35, *36, and *37), and increased function (e.g., *CYP2C19**17).^[14,20] Therefore, categorizing individual patients based on their specific *CYP2C19* profile is an appropriate approach to tailor PPI treatment

with greater precision. PPI metabolism rates range widely from ultrarapid to poor metabolizers, a diversity that is likely to impact the appropriate and effective dosage of these medications.^[12]

The CPIC guidelines predicted *CYP2C19* phenotypes based on genotypes related to enzymes and corresponding enzyme activities [reproduced in Table 1].^[22] NMs possess 2 fully functional alleles (e.g., *CYP2C19**1/*1), while intermediate metabolizers (IMs) have one normal function allele paired with either a nonfunctional allele (e.g., *CYP2C19**1/*2) or a nonfunctional allele paired with an increased functional allele (e.g., *CYP2C19**2/*17). Poor metabolizers (PMs) exhibit two no-function alleles (e.g. *CYP2C19**2/*2), whereas rapid metabolizers (RMs) possess one normal-function allele and one increased-function allele (i.e., *CYP2C19**1/*17), and ultrarapid metabolizers (MMs) have two increased-function alleles (i.e. *CYP2C19**17/17).^[22] Additionally, there are *CYP2C19* "likely IMs" characterized by the presence of one normal function allele, one reduced function allele, one enhanced function allele, one reduced function allele, two decreased function alleles (e.g., *1/*2, *1/*3, *2/*17, and *3/*17), and "likely PMs" characterized by one no function allele and one decreased function allele (e.g., *2/*9 and *3/*9). In addition, *CYP2C19*-mediated metabolism of PPIs can lead to specific drug interactions in certain individuals.^[10] However, predicting the phenotype of the *CYP2C19* gene in the Indian population faces several limitations and challenges stemming from genetic diversity.^[10] Many genetic studies and databases are based on populations of Caucasian or East Asian descent, and variants specific to the Indian population might be underrepresented, leading to less accurate phenotype predictions.^[23,24]

Furthermore, *CYP2C19* genotype may also predispose these individuals to a greater risk of DDIs when given other putative *CYP2C19* inhibitors or substrates (e.g., voriconazole, fluvoxamine, and omeprazole).^[25] Individuals exhibiting a PM phenotype may experience elevated plasma levels of PPIs. However, once this metabolic pathway reaches its capacity, the isoenzyme can emerge as a significant site for potential interactions with many drugs, including phenytoin, diazepam, clopidogrel, azoles, and warfarin.^[25] Recently, a study evaluating the whole genomes of 1029 Indian individuals for PGx variants, drug-drug interactions (DDIs), and drug-drug-gene interactions (DGIs) associated with 44 noninsulin antidiabetic drugs (NIADs) revealed an increased risk of *CYP2C19*-mediated drug-drug-gene interactions (DDGIs) for certain NIADs, such as saxagliptin, linagliptin, and glyburide, when coadministered with PPIs.^[26]

Table 1: Genotypes and phenotypes of cytochrome P450 2C19 and clinical pharmacogenetics implementation consortium dosing recommendations for lansoprazole, pantoprazole, and omeprazole^[19]

Examples of CYP2C19 diplotypes	CYP2C19 phenotype	Therapeutic recommendation
*1/*1	CYP2C19 normal metabolizer	When treating <i>H. pylori</i> infection and erosive esophagitis, consider increasing the dosage by 50%–100% It is best to administer daily doses in divided increments and monitor their efficacy
*2/*2, *3/*3, *2/*3	CYP2C19 poor metabolizer	When engaging in extended therapy (>12 weeks) and once effectiveness has been attained, contemplate reducing the daily dosage by 50% and maintain vigilant monitoring for sustained efficacy
*17/*17	CYP2C19 ultrarapid metabolizer	Increase the initial daily dose by 100% Daily doses can be administered in divided doses and efficacy can be checked
*1/*17	CYP2C19 rapid metabolizer	When addressing <i>H. pylori</i> infection and erosive esophagitis, contemplate a dose escalation of 50%–100% It is recommended to administer daily doses in divided increments and closely monitor their effectiveness
*2/*9, *3/*9	Intermediate metabolizer of CYP2C19 intermediate metabolizer	After achieving efficacy in chronic therapy (>12 weeks), consider reducing the daily dose by 50% and monitor for sustained effectiveness
*1/*2, *1/*3, *2/*17, *3/*17	CYP2C19 likely an intermediate metabolizer	Once efficacy is established in chronic therapy lasting more than 12 weeks, consider a 50% decrease in daily dose and assess sustained effectiveness
*2/*9, *3/*9	CYP2C19 likely a poor metabolizer	For long-lasting therapy (>12 weeks) and efficacy attained, consider a 50% decline in daily dose and observe for continued efficacy

Taken from the CPIC guidelines publication and reproduced here for the convenience of the reader. CPIC=Clinical pharmacogenetics implementation consortium, CYP2C19=Cytochrome P450 2C19, *H. pylori*=*Helicobacter pylori*

The CPIC-CYP2C19-PPI Dosing Guidelines

As of now, CPIC has released 26 guideline sets covering a broad spectrum of therapeutic fields, such as antidepressants, gastroprotective agents, cardiovascular drugs, anticancer treatments, pain and inflammation medications, immunosuppressants, and anti-infectives (<https://cpicpgx.org>). The main objective of the CPIC guidelines is to help clinicians understand genetic tests to guide drug treatment (<https://cpicpgx.org>).

The current CPIC guidelines for CYP2C19-PPI drugs provide moderate to strong prescribing recommendations for first-generation PPIs (lansoprazole, pantoprazole, and omeprazole) at CPIC level A, but the recommendations for dexlansoprazole are classified as optional (i.e., CPIC level B).^[22] However, due to inconclusive evidence regarding the connection between the CYP2C19 genotype and variability observed in both esomeprazole and rabeprazole plasma concentrations as well as their effectiveness, CPIC presently lacks prescribing guidance for these PPIs, classified as CPIC level C. Furthermore, it is important to note that these endorsements pertain to both oral and intravenous formulations of the PPIs.^[22]

Due to the lack of definitive country-specific policies and PGx guidelines from Indian drug regulatory authorities, guidelines from CPIC and labeling of approved drugs offer essential foundational evidence. This evidence is vital for prioritizing drug–gene candidates to advance population-specific PGx initiatives.^[24]

Frequency of Clinically Important CYP2C19 Alleles in Indian Population

To understand how important it is to carry out genetic testing to prescribe PPI drugs according to the CPIC-CYP2C19-PPI guidelines, it is essential to know the frequency distribution of clinically important CYP2C19 alleles in Indian population.

The frequency of clinically significant annotated CYP2C19 alleles, such as no function and increased function alleles, among the Indian population was found in some preliminary studies and in the comprehensive database “IndiGenomes,” a database of genomic information sequenced from more than 1000 individuals from diverse parts of India containing genetic variants for the Indian population that can be accessed through <http://clingen.igib.res.in/indigen/> [frequency details in Table 2].^[27,28] Studies have shown a high percentage of clinically actionable alleles and genotypes of the CYP2C19 gene in Indian populations, with an increased prevalence of specific CYP2C19 alleles corresponding to altered function of CYP2C19.^[21,27-32]

A real-world study by Deshpande *et al.* among 500 subjects from urban and tribal populations in Telangana revealed distinct metabolizer phenotypes of PPIs based on CYP2C19 genotype profiles and revealed notable differences between the phenotype groups.^[29] This study reported the frequencies of the CYP2C19*2, *3, and *17 alleles as 41%, 1%, and 17%, respectively. The frequencies of normal metabolizers (NM: *1/*1),

Table 2: Frequency of clinically actionable CYP2C19 alleles in the Indian population

Alleles (rs ID)	Frequency (%)
No or Decreased function alleles	
*2 (rs4244285)	36.78
*3 (rs4986893)	0.64
*4 (rs28399504)	0.05
*9 (rs3758581)	88.89
*35 (rs12769205)	36.89
Increased function alleles	
*17 (rs12248560)	14.36

intermediate metabolizers (IM: *1/*2, *1/*3, *2/*17, *3/*17), poor metabolizers (PM: *2/*2, *2/*3), rapid metabolizers (RM: *1/*17), and ultrarapid metabolizers (UM: *17/*17) were 15%, 36.3%, 14.5%, 16.5%, and 3.2% in the urban population, respectively, and 13%, 33%, 28%, 10%, and 1% in the tribal population, respectively.^[22] Urban populations exhibit a greater prevalence of PMs, predominantly due to the CYP2C19*2 allele, whereas tribal populations show a significantly greater proportion of PMs, potentially influencing their response to PPIs such as esomeprazole and pantoprazole, under fasting conditions.

Similarly, a study by Chaudhry *et al.* explored the association between CYP2C19 genetic polymorphisms and *H. pylori* eradication in North Indian gastritis cases ($n = 91$) positive for *H. pylori* who were treated with a regimen including omeprazole, amoxicillin, and tinidazole.^[30] The study findings showed that after initial therapy, CYP2C19 EMs showed only 37% eradication, while PMs demonstrated 92% eradication. However, after retreatment, noneradicated EMs achieved 90% eradication with increased-dose dual therapy.^[22] A possible cause of the increased eradication of PM is the decreased metabolism of omeprazole to 5-OH-OPZ, which increases the intragastric pH and may increase the bioavailability of antibiotics. Hence, it was suggested that, prior to treatment, genotyping of the CYP2C19 gene is essential for determining the phenotype of a patient, which will help optimize the prescribed dose of PPIs in such patients.

Furthermore, a study by Gairolla *et al.*, involving 204 stroke patients and 101 healthy controls, revealed a frequency of poor metabolizer phenotypes, such as CYP2C19*2 homozygous mutant AA (10.8%), IMs, such as heterozygous mutant GA (47.5%), and NM homozygous wild-type GG (41.7%), followed by ultrarapid metabolizer phenotypes, such as CYP2C19*17 homozygous mutant TT (3.4%), RM heterozygous mutant CT (36.3%), and homozygous wild-type CC (60.3%), and the CYP2C19*3 and CYP2C19*4 alleles showed no heterozygous or mutant forms in the population

studied.^[31] Overall, the prevalence of the CYP2C19 IM/PM phenotype was 57.8%, which is higher than that in previous reports from Asia. However, the study did not detect the CYP2C19*3 or *4 alleles in the study population.

Another study by Shetkar *et al.* on CYP2C19 polymorphisms among 110 Indian patients with coronary artery disease who were taking clopidogrel revealed that the frequency of CYP2C19*2 allele, which is related to poor and intermediate metabolic phenotypes (*2/*2; *1/*2), was 40.90%, and the frequency of CYP2C19*17 allele, which is associated with ultrarapid and rapid metabolic activity phenotypes (*17/*17; *1/*17), was 52.70% in the study population. However, the study did not detect the CYP2C19*3, *4, or *5 alleles in the study population.^[21]

Furthermore, Kumar *et al.* investigated the frequency of CYP2C19 genotypes in 109 South Indian individuals who were treated with escitalopram and reported that 17.4% were poor metabolizers (*2/*2 or *2/*3), 8.3% were ultrarapid metabolizers (*1/*17 or *17/*17), 55% were IMs (*1/*2 or *2/*17), and 19.3% were extensive metabolizers (*1/*1). The PM frequency in South Indians (17.4%) was greater than that in Caucasians and Africans but similar to that in other Asian populations.^[32]

Furthermore, a meta-analysis by Koopmans *et al.* on studies providing clinically relevant data on CYP2D6 and CYP2C19 genotype frequencies across global populations and ethnic groups revealed that India has the highest likelihood (80.1%) of possessing a CYP2C19 non-NM-predicted phenotype, primarily due to greater occurrence of the nonfunctional CYP2C19*2 allele and/or the heightened function of the CYP2C19*17 allele.^[33]

Collectively, these studies underscore the critical role of CYP2C19 genotyping in tailoring pharmacotherapy to individual genetic profiles within the Indian population. By identifying specific metabolic phenotypes, clinicians can better predict and optimize treatment responses, thereby improving therapeutic outcomes and minimizing adverse effects. These findings advocate for the routine integration of CYP2C19 genotyping into clinical practice, particularly in settings where diverse genetic backgrounds may influence drug metabolism and treatment efficacy.

Conclusions and Take-home Messages to Clinical Pharmacologists in India

PPIs are the most frequently prescribed medication for treating various acid-related GIT ailments in India, similar to other geographical locations.^[1,6] The significance of CYP2C19 genotyping in the Indian population

is underscored by several studies that elucidate its impact on therapeutic outcomes across various medical conditions.^[21,27-33] The CPIC-CYP2C19-PPI guidelines provide a comprehensive approach to guide PPI dosing adjustments based on individual CYP2C19 phenotypes, allowing optimal therapeutic results while considering the potential risk of both therapeutic failure and adverse effects.^[22] Given the increased and chronic use of first-generation PPIs among patients with GERD and PUDs and due to high frequency of clinically important nonfunction (*2) and increased function (*17) CYP2C19 alleles in the Indian population, preemptive PGx tests for the CYP2C19 gene would allow a physician to select a PPI that is predicted to provide benefit while minimizing the risk for adverse drug reactions, treatment failures, and associated costs.^[21,27-33] The CPIC guidelines recommend reducing the daily dose by 50% for poor metabolizers (PMs), intermediate metabolizers (IMs), likely poor metabolizers, and likely intermediate metabolizers. Conversely, the dose should be increased by 50% to 100% for normal metabolizers (NMs), ultrarapid metabolizers (UMs), and rapid metabolizers (RMs), particularly in patients with chronic use of proton pump inhibitors (PPIs) for more than 12 weeks, to enhance clinical efficacy and safety.^[22]

The US Food and Drug Administration (FDA)'s Table of Pharmacogenomic Biomarkers in Drug Labeling indicates that patients with IM or PM phenotypes taking PPIs such as pantoprazole, dexlansoprazole, or omeprazole and PMs taking esomeprazole, lansoprazole, or rabeprazole may experience higher systemic concentrations of these drugs.^[34] This can potentially lead to higher efficacy or risk of side effects. The FDA's inclusion of PGx biomarkers in drug labeling serves as a guideline for clinicians to tailor drug therapy based on a patient's genetic profile. By incorporating PGx information into drug labeling, the FDA provides health-care providers with the tools needed to make informed decisions that enhance patient care. The FDA's recommendations underscore the importance of considering genetic factors when prescribing medications, especially for drugs with narrow therapeutic indices or significant variability in patient response. This proactive approach helps in identifying patients who might benefit from alternative dosing strategies or different medications that are less affected by genetic variations in drug metabolism. This approach aims to maximize drug efficacy while minimizing the risk of side effects, moving toward a more personalized medicine paradigm.

On the other hand, the 2022 American College of Gastroenterology (ACG) guidelines for GERD therapy recognize that genetic variations in CYP2C19 metabolism can affect response to PPIs.^[35] The guidelines also state that genetic testing to guide PPI therapy is not yet a

standard practice in clinical settings. Despite this, the ACG suggested that when considering a switch to a different PPI, choosing one that is less dependent on CYP2C19 for metabolism, such as rabeprazole, could be a practical alternative. This recommendation is based on the understanding that avoiding CYP2C19-dependent PPIs may help manage the variability in drug response due to genetic differences. Hence, it is also essential to consider the use of rabeprazole, which is not metabolized by CYP2C19 and may not have major DDIs via CYP2C19, while using concomitant drugs with possible metabolism by CYP2C19.

Given that the prevalence of GERD is greater among the elderly population, the genotyping of CYP2C19 will also help individuals personalize other medications that are metabolized by the CYP2C19 enzyme, e.g., clopidogrel.^[36] Therefore, when clopidogrel is used in combination, it may be preferable to choose PPIs with low CYP2C19 inhibition, such as rabeprazole or esomeprazole.^[36] Similarly, drug-food interactions with regard to CYP2C19 should be taken into consideration when prescribing PPIs for chronic therapy.^[37] Strong inhibition of the CYP2C19 enzyme has been reported for food supplements containing berry constituents, resveratrol, and grapefruit juice components.^[38,39] Furthermore, the competitive inhibition of CYP2C19 is mediated by PPIs, which are dependent on the pharmacokinetics of CYP2C19.^[12] The inhibitory effect on CYP2C19 expression is greatest for omeprazole, followed by lansoprazole, pantoprazole, and rabeprazole, and it is least pronounced for ilaprazole.^[39] Furthermore, oral doses, single doses, and racemic mixtures are more likely to be affected by the variability in CYP2C19.^[39] Moreover, omeprazole increased the plasma concentration of voriconazole through CYP2C19 inhibition.^[39] Similarly, omeprazole, a CYP2C19 extensive metabolite, had the lowest eradication rate against *H. pylori*.^[40]

The implementation of genetic testing for CYP2C19 in the Indian health-care system involves several practical considerations, including availability, cost, and necessary infrastructure.^[24] Implementing CYP2C19 genetic testing in India requires an increase in laboratory capacity, increased accessibility in primary care, increased public awareness of the rationale for genetic testing and its potential impact on treatment outcomes, collaboration between pharmacovigilance and PGx programs and the development of advanced sequencing technologies such as next-generation sequencing and microarray data management systems, and integration with electronic health records with inbuilt decision support systems.^[24,41] Additionally, reducing the high costs of genetic testing, which are currently elevated due to limited insurance coverage, is crucial for integrating PGx testing into the Indian health-care system.^[24] Although current costs may

be more in Indian context, it will become more affordable in future. Overcoming other significant barriers, such as the country's genetic diversity, health-care access issues, particularly the urban–rural divide, and a shortage of trained professionals, is essential for successful implementation.^[24]

Therefore, given the increased and chronic use of first-generation PPIs among patients with GERD and PUDs and due to the high frequency of clinically important nonfunction and increased function CYP2C19 genotypes in the Indian population, we recommend the widespread implementation of preemptive PGx testing for CYP2C19 genotyping in health-care facilities across India, which would allow health-care professionals to select a PPI that is predicted to provide benefit while minimizing the risk for adverse drug reactions, treatment failures, and associated costs. This personalized approach is a crucial step toward achieving precision medicine in the management of GI and related conditions. This integration can enhance personalized medicine and improve patient outcomes. Furthermore, improved symptom control and reduced adverse effects can contribute to better quality of life and increased adherence to prescribed PPI therapy. By adopting PGx-informed PPI therapy, clinical pharmacologists can significantly improve patient outcomes, improve treatment success, and ensure the safe and effective use of PPIs among the Indian population. Notably, the Asian Institute of Gastroenterology, a prestigious gastroenterology institute in India, has already implemented PGx testing-based PPI treatment for patients requiring chronic use (source: organization web page). Clinical pharmacologists across the country should also adopt this approach in their health-care institutions, which will benefit the safe and effective use of PPIs in the Indian population. This personalized approach is essential for achieving precision medicine in the management of GI and other conditions, ultimately contributing to improved patient outcomes and overall treatment success.

Author contributions

All authors contributed to the conceptualization, drafting, and revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

CRS UPPUGUNDURI is supported by the CANSEARCH Foundation. CRS UPPUGUNDURI's work in PGx is supported by SNSF (Grant Number: IZLIZ3_200243). We also thank Dr. Anitha K, Assistant Professor, Department of Pharmacology, NMIMSU, Shirpur, India, and Dr. Suresh Kumar, Associate Professor, RAKMSHU,

United Arab Emirates, for their feedback while revising the article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Bhatia S, Shukla A, Johnson D, Thatte U, Lawate P, Babu S, *et al.* An expert review and recommendations on the rational use of proton pump inhibitors: Indian perspective. *J Assoc Physicians India* 2019;67:88-96.
- Singh V, Trikha B, Nain CK, Singh K, Vaiphei K. Epidemiology of *Helicobacter pylori* and peptic ulcer in India. *J Gastroenterol Hepatol* 2002;17:659-65.
- Wang HY, Leena KB, Plymoth A, Hergens MP, Yin L, Shenoy KT, *et al.* Prevalence of gastro-esophageal reflux disease and its risk factors in a community-based population in Southern India. *BMC Gastroenterol* 2016;16:36.
- Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: A meta-analysis. *Lancet* 2002;359:14-22.
- Dhawal OP, Dhawal M. Prevalence of *Helicobacter pylori* infection & pattern of gastrointestinal involvement in patients undergoing upper gastrointestinal endoscopy in Sikkim. *Indian J Med Res* 2018;147:517-20.
- Mejia A, Kraft WK. Acid peptic diseases: Pharmacological approach to treatment. *Expert Rev Clin Pharmacol* 2009;2:295-314.
- Barkun A, Leontiadis G. Systematic review of the symptom burden, quality of life impairment and costs associated with peptic ulcer disease. *Am J Med* 2010;123:358-66.e2.
- Chenchula S, Gupta R, Gupta SK, Padmavathi R, Pathan S. Assessment of WHO core drug use indicators at a tertiary care Institute of National Importance in India. *Bioinformatics* 2022;18:888-93.
- Chenchula S, Sharma P, Ghanta MK, Amerneni KC, Rajakarunakaran P, Saggurthi P, *et al.* Association and mechanisms of proton pump inhibitors use with type-2diabetes mellitus incidence in adults: A systemic review and meta-analysis. *Curr Diabetes Rev* 2024;20:e120124225581.
- Xia B, He Q, Smith FG, Gkoutos VG, Nirantharakumar K, Kuo ZC, *et al.* Individualized prevention of proton pump inhibitor related adverse events by risk stratification. *Nat Commun* 2024;15:3591.
- Yadlapati R, DeLay K. Proton pump inhibitor-refractory gastroesophageal reflux disease. *Med Clin North Am* 2019;103:15-27.
- El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: From CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol* 2018;14:447-60.
- Gawrońska-Szklarz B, Adamiak-Giera U, Wyska E, Kurzawski M, Gornik W, Kaldonska M, *et al.* CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. *Eur J Clin Pharmacol* 2012;68:1267-74.
- Botton MR, Whirl-Carrillo M, Del Tredici AL, Sangkuhl K, Cavallari LH, Agúndez JA, *et al.* *PharmVar GeneFocus: CYP2C19*. *Clin Pharmacol Ther* 2021;109:352-66.
- Abelö A, Andersson TB, Antonsson M, Naudot AK, Skånberg I, Weidolf L. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos* 2000;28:966-72.
- Marelli S, Pace F. Rabeprazole for the treatment of acid-related disorders. *Expert Rev Gastroenterol Hepatol* 2012;6:423-35.
- Furuta T, Ohashi K, Kamata T, Takashima M, Kosuge K,

- Kawasaki T, *et al.* Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* 1998;129:1027-30.
18. El-Serag H, Becher A, Jones R. Systematic review: Persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. *Aliment Pharmacol Ther* 2010;32:720-37.
 19. Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br J Clin Pharmacol* 2001;52:349-55.
 20. Blanco Dorado S, Maroñas Amigo O, Latorre-Pellicer A, Rodríguez Jato MT, López-Vizcaíno A, Gómez Márquez A, *et al.* A multicentre prospective study evaluating the impact of proton-pump inhibitors omeprazole and pantoprazole on voriconazole plasma concentrations. *Br J Clin Pharmacol* 2020;86:1661-6.
 21. Shetkar SS, Ramakrishnan S, Seth S, Chandna P, Verma SK, Bhargava B, *et al.* CYP 450 2C19 polymorphisms in Indian patients with coronary artery disease. *Indian Heart J* 2014;66:16-24.
 22. Lima JJ, Thomas CD, Barbarino J, Desta Z, Van Driest SL, El Rouby N, *et al.* Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2C19 and proton pump inhibitor dosing. *Clin Pharmacol Ther* 2021;109:1417-23.
 23. Mastana SS. Unity in diversity: An overview of the genomic anthropology of India. *Ann Hum Biol* 2014;41:287-99.
 24. Sahana S, Bhoyar RC, Sivasdas A, Jain A, Imran M, Rophina M, *et al.* Pharmacogenomic landscape of Indian population using whole genomes. *Clin Transl Sci* 2022;15:866-77.
 25. de Jong LM, Boussallami S, Sánchez-López E, Giera M, Tushuizen ME, Hoekstra M, *et al.* The impact of CYP2C19 genotype on phenoconversion by concomitant medication. *Front Pharmacol* 2023;14:1201906.
 26. Sivasdas A, Sahana S, Jolly B, Bhoyar RC, Jain A, Sharma D, *et al.* Landscape of pharmacogenetic variants associated with non-insulin antidiabetic drugs in the Indian population. *BMJ Open Diabetes Res Care* 2024;12:e003769.
 27. Jain A, Bhoyar RC, Pandhare K, Mishra A, Sharma D, Imran M, *et al.* IndiGenomes: A comprehensive resource of genetic variants from over 1000 Indian genomes. *Nucleic Acids Res* 2021;49:D1225-32.
 28. Umamaheswaran G, Kumar DK, Adithan C. Distribution of genetic polymorphisms of genes encoding drug metabolizing enzymes and drug transporters – A review with Indian perspective. *Indian J Med Res* 2014;139:27-65.
 29. Deshpande N, Sharanya V, Ravi Kanth VV, Murthy HV, Sasikala M, Banerjee R, *et al.* Rapid and ultra-rapid metabolizers with CYP2C19*17 polymorphism do not respond to standard therapy with proton pump inhibitors. *Meta Gene* 2016;9:159-64.
 30. Chaudhry AS, Kochhar R, Kohli KK. Importance of CYP2C19 genetic polymorphism in the eradication of *Helicobacter pylori* in North Indians. *Indian J Med Res* 2009;130:437-43.
 31. Gairolla J, Khurana D, Sarma P, Kler R, Medhi B, Khullar M, *et al.* Association between CYP2C19 genotypes with clinical phenotypes and adipokine levels among ischemic stroke patients: A prospective observational study. *Cureus* 2023;15:e39265.
 32. Kumar BJ, Thangavel Mahalingam V, Kumar MG. The impact of CYP2C19 genotypes on steady-state plasma concentration of escitalopram in South Indian population with major depressive disorder. *Pharmacia* 2024;71:1-6.
 33. Koopmans AB, Braakman MH, Vinkers DJ, Hoek HW, van Harten PN. Meta-analysis of probability estimates of worldwide variation of CYP2D6 and CYP2C19. *Transl Psychiatry* 2021;11:141.
 34. Food and Drug Administration. FDA Table of Pharmacogenetics Association; 2022. Available from: <https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>. [Last accessed on 2024 Apr 09].
 35. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2022;117:27-56.
 36. Ben Ghezala I, Luu M, Bardou M. An update on drug-drug interactions associated with proton pump inhibitors. *Expert Opin Drug Metab Toxicol* 2022;18:337-46.
 37. Ochoa D, Román M, Cabaleiro T, Saiz-Rodríguez M, Mejía G, Abad-Santos F. Effect of food on the pharmacokinetics of omeprazole, pantoprazole and rabeprazole. *BMC Pharmacol Toxicol* 2020;21:54.
 38. Seki H, Akiyoshi T, Imaoka A, Ohtani H. Inhibitory kinetics of fruit components on CYP2C19 activity. *Drug Metab Pharmacokin* 2019;34:181-6.
 39. Sand PG, Dreiseitel A, Stang M, Schreier P, Oehme A, Locher S, *et al.* Cytochrome P450 2C19 inhibitory activity of common berry constituents. *Phytother Res* 2010;24:304-7.
 40. Dean L, Kane M. Omeprazole therapy and CYP2C19 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. *Medical Genetics Summaries*. Bethesda (MD): National Center for Biotechnology Information (US); 2021.
 41. Chenchula S, Atal S, Uppugunduri CR. A review of real-world evidence on preemptive pharmacogenomic testing for preventing adverse drug reactions: A reality for future health care. *Pharmacogenomics J* 2024;24:9.