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

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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 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)

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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 metabolization 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 *H. pylori* 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 *H. pylori* 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.

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Conflicts of interest

There are no conflicts of interest.

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