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Genetic Variations and Drug Response in GERD: The Role of Pharmacogenomic Testing in Optimizing PPI Therapy

Muhammad Hassan[1*], Jordyn Yokoyama[2], Paige O'Brien Daly[3], Radhika Misra[4], Tsz Chun Chung[5], Sydney Eismeier[6], Julisa Galan[5], Allysse Thomas[7]

[1]Nuvance Health/Vassar Brothers Medical Center, Poughkeepsie, NY, USA
[2]School of Osteopathic Medicine, A.T. Still University, Visalia, CA, USA
[3]Edward Via College of Osteopathic Medicine, Blacksburg, VA, USA
[4]Des Moines University School of Osteopathic Medicine, West Des Moines, IA, USA
[5]School of Osteopathic Medicine, A.T. Still University, Santa Maria, CA, USA
[6]School of Osteopathic Medicine, A.T. Still University, Tucson, Arizona, USA
[7]School of Osteopathic Medicine, A.T. Still University, Seattle, WA, USA
Email: *mhsn014@gmail.com

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Abstract

Background and Aims: The influence of genetic variations on drug efficacy has garnered interest in the treatment of gastrointestinal (GI) disorders, particularly gastroesophageal reflux disease (GERD). Proton pump inhibitors (PPIs), the cornerstone of GERD management, are metabolized by the cytochrome P450 enzyme CYP2C19, whose activity is variable due to genetic polymorphisms. Pharmacogenomic testing offers a novel approach to personalize PPI therapy, maximizing efficacy and minimizing adverse effects. This study aims to evaluate the role of CYP2C19 polymorphisms in PPI metabolism and explore the clinical implications of pharmacogenomic-guided therapy for GERD. **Methods:** A comprehensive literature review was conducted, examining clinical trials, observational studies, and meta-analyses related to CYP2C19 polymorphisms and their impact on PPI efficacy in GERD management. Sources included PubMed-indexed articles from 2000 to 2023, focusing on genetic variability, pharmacogenomic testing, and its integration into clinical practice. Data on metabolizer phenotypes, dosing strategies, and patient outcomes were synthesized to identify trends and inform recommendations. **Results:** CYP2C19 polymorphisms significantly influence PPI metabolism and therapeutic outcomes. Poor metabolizers (PMs) exhibit prolonged PPI exposure, enhanced acid suppression, and improved symptom control, whereas ultra-rapid metabolizers (UMs) experience suboptimal effects due to faster drug clearance. Gen-

otype-guided dosing improves therapeutic outcomes by tailoring PPI regimens to individual metabolic profiles. Despite evidence supporting pharmacogenomic testing, barriers to implementation include cost, limited clinician education, and lack of standardized protocols. **Conclusions:** Pharmacogenomic testing holds promise for optimizing GERD treatment by personalizing PPI therapy based on CYP2C19 genotype. Addressing barriers to clinical implementation and expanding research to include second-generation PPIs and pediatric populations will enhance the applicability of this approach. Integrating pharmacogenomics into routine practice may reduce adverse effects and improve patient outcomes.

Keywords

Gastroesophageal Reflux Disease (GERD), Proton Pump Inhibitors (PPIs), CYP2C19 Polymorphisms, Genetic Variations, Pharmacogenomics, Drug Metabolism, Personalized Medicine, Therapeutic Outcomes, Pharmacogenomic Testing, Metabolizer Classification

1. Introduction

Gastroesophageal reflux disease (GERD) represents a significant global health challenge, affecting millions of individuals worldwide and significantly impacting quality of life. This disorder affects approximately 10% - 20% of adults in Western countries and is more common in individuals over 50 [1]. The condition is more common in individuals over the age of 50, but it can affect people of all ages, including children. Factors contributing to GERD include obesity, smoking, certain medications, and dietary habits [2]. GERD not only impacts individuals, but burdens the healthcare system with costs; each patient averages a cost of $12,232 annually, $4277 of which is spent on drugs [3]. GERD occurs when the lower esophageal sphincter (LES) fails to close, allowing the stomach contents to leak back into the esophagus. As a chronic condition in which stomach acid or bile irritates the lining of the esophagus, it results in symptoms such as heartburn, acid regurgitation, and, in more severe cases, esophagitis. This condition can significantly impact quality of life, causing sleep disturbances, chronic pain, and dysphagia [2]. If left untreated, GERD can result in complications such as Barrett's esophagus, esophageal strictures, and an increased risk of esophageal adenocarcinoma [1].

Gastroesophageal reflux disease is a clinical diagnosis based on history and physical exam. Typically, when GERD is suspected, treatment begins with an 8-week trial of empiric proton pump inhibitors (PPIs) once daily before a meal [4]. PPIs have long been the cornerstone of GERD treatment, offering effective acid suppression and symptomatic relief. They work by irreversibly inhibiting the hydrogen-potassium ATPase enzyme in stomach parietal cells. This action reduces gastric acid production, aiding in symptom relief and healing of esophagitis [5]. PPIs are generally considered more effective than histamine-2 receptor antago-

nists (H2RAs) in providing long-term acid suppression and are often prescribed for both short- and long-term management of GERD. However, the efficacy of proton pump inhibitor therapy varies among patients due to factors such as genetic differences in drug metabolism and adherence to therapy, which has prompted researchers to explore more personalized treatment methodologies.

Pharmacogenomic testing provides a sophisticated tool for unraveling these complex relationships, offering insights into why some patients respond more effectively to PPI therapy than others. This innovative approach focuses particularly on the CYP2C19 gene polymorphisms, which play a crucial role in determining how patients metabolize and respond to PPI therapy. By understanding the genetic variations that affect drug metabolism, healthcare providers can develop more targeted and personalized treatment strategies that maximize therapeutic outcomes while minimizing potential adverse effects. This review comprehensively explores the role of pharmacogenomic testing in optimizing proton pump inhibitor therapy for gastroesophageal reflux disease, with a particular emphasis on CYP2C19 polymorphisms and their significant impact on treatment outcomes.

2. Methods

A systematic review of the literature was conducted to evaluate the impact of CYP2C19 polymorphisms on PPI efficacy in GERD management. PubMed, MEDLINE, and Cochrane databases were searched using terms such as "CYP2C19 polymorphisms," "pharmacogenomics," "GERD," and "PPIs" to identify clinical trials, observational studies, and meta-analyses published between 2000 and 2023. Studies were selected based on their relevance to CYP2C19 allele distribution, metabolizer phenotypes, and clinical outcomes, with an additional focus on genotype-guided dosing strategies. Data extraction included information on acid suppression, symptom control, and adverse effects across metabolizer categories: poor, intermediate, normal, and ultra-rapid. Studies involving pediatric populations, second-generation PPIs, and related GI conditions were also reviewed for broader context. The findings were synthesized to identify patterns, assess clinical implications, and provide recommendations for integrating pharmacogenomic testing into routine practice.

3. The Role of CYP2C19 in PPI Metabolism

Proton pump inhibitors (PPIs) are primarily metabolized by the cytochrome P450 enzyme system in the liver, with cytochrome P450 family 2 subfamily C member 19 (CYP2C19) playing a dominant role. Variations in the CYP2C19 gene, known as CYP2C19 polymorphisms, significantly affect drug metabolism [6]. Research has shown that patients with different CYP2C19 genotypes respond variably to PPIs, influencing healing rates [7] [8]. This raises important questions about the role of pharmacogenetics in influencing how individuals metabolize medications, including PPIs.

Pharmacogenomic testing extends beyond GERD treatments; it is increasingly

integrated into clinical practice across various medical fields, guiding treatments such as antidepressants in psychiatry and warfarin dosing in cardiology [9] [10]. Despite its promise, pharmacogenomics faces challenges including selecting appropriate testing platforms and effectively communicating results within clinical workflows, often leading to underutilization. Healthcare providers and patients need more education to correctly understand and use pharmacogenetic information, and a more standardized protocol and approach, in order to overcome these challenges.

Current understanding of CYP2C19 polymorphisms includes both loss-of-function and gain-of-function alleles. Common loss-of-function alleles include CYP2C19*2 (681 G > A), causing a splicing defect, and CYP2C19*3 (636 G > A), causing a premature stop codon [11] [12]. These defects are more commonly seen in East Asians and Oceanian populations, resulting in poorer drug metabolism and enhanced therapeutic outcomes [13]. The gain-of-function allele CYP2C19*17 (-806 C > T) is associated with increased transcriptional activity, leading to enhanced drug metabolism and, therefore, suboptimal therapeutic effects from PPIs [11] [12]. This allele is more prevalent in Mediterranean-South Europeans and Middle Eastern populations [13] [14]. These polymorphisms significantly impact drug efficacy and safety, highlighting the crucial role of healthcare professionals and researchers in developing personalized medication regimens. **Table 1** summarizes the distribution of these CYP2C19 alleles and their frequencies across different populations, providing a visual reference that clarifies the genetic variability described above.

Table 1. Ethnic variations in CYP2C19 polymorphisms.

Population	Common Variants	Clinical Significance	References
East Asian	Higher prevalence of CYP2C19*2, *3 (loss-of-function)	More likely to be poor metabolizers	Fricke *et al.*, 2016
Mediterranean-South European	Higher prevalence of CYP2C19*17 (gain-of-function)	More likely to be ultra-rapid metabolizers	Petrović *et al.*, 2020
Middle Eastern	Increased frequency of CYP2C19*17	Enhanced drug metabolism	Fricke *et al.*, 2016
Western populations	Variable distribution	Mixed metabolizer status	Zabalza *et al.*, 2012

4. Pharmacogenomic Testing and Metabolizer Classification

Pharmacogenomic testing involves analyzing patient saliva samples or genomic databases to determine CYP2C19 genotypes [15]. Each individual has two CYP2C19 haplotypes, forming a diplotype that determines their metabolizer status [9]. The most common alleles are CYP2C19*1 (fully functional), *2 and *3 (inactive), and *17 (increased functionality). Patients are classified as normal (1*/1* or 1/17), intermediate metabolizers (IMs) (1*2* or 2*/17*), poor metabolizers (PMs) (2*/2*), or ultrarapid metabolizers (UMs) (17*/17*) [16]. Studies indicate that 25% - 30% of individuals are PMs, 40% - 45% are IMs, and 10% - 15% are UMs, with these polymorphisms more prevalent in Asian populations [9]. Due

to PMs (CYP2C19*2/2) inability to metabolize PPIs at a fast rate, PMs exhibit higher plasma PPI concentrations and improved symptom resolution, while UMs (CYP2C1917/*17) experience reduced efficacy due to faster clearance, necessitating dose escalation [16] [17]. These findings support genotype-guided dosing to enhance GERD outcomes by improving symptom control and minimizing adverse effects. Table 2 provides a detailed summary of CYP2C19 diplotypes, their associated metabolizer phenotypes, and the clinical implications for PPI therapy.

Table 2. CYP2C19 metabolizer classifications and clinical implications.

Metabolizer Status	Genotype	Prevalence	Clinical Implications	References
Poor Metabolizer (PM)	CYP2C19*2/*2	25% - 30% overall; 20% in Asians, 5% in Caucasians/Africans	Higher plasma PPI concentrations; Better symptom resolution; May require lower doses	Brouwer *et al.*, 2024; Hippman *et al.*, 2019
Intermediate Metabolizer (IM)	CYP2C19*1/*2 or *2/*17	40% - 45%	Moderate drug metabolism; May need dose adjustment	Brouwer *et al.*, 2024; Ionova *et al.*, 2020
Normal Metabolizer (NM)	CYP2C19*1/*1 or *1/*17	Variable	Standard drug metabolism; Standard dosing typically effective	Lima *et al.*, 2020
Ultra-rapid Metabolizer (UM)	CYP2C19*17/*17	10% - 15%	Faster drug clearance; Reduced efficacy; May need higher doses or alternative therapy	Brouwer *et al.*, 2024; Lima *et al.*, 2020

5. Impact on PPI Therapy and Dosing Recommendations

The wide variability in CYP2C19 function necessitates flexible PPI dosing strategies to accommodate metabolic differences. A genotype-based dosing algorithm represents a significant advancement in personalized medicine, leveraging genetic information to guide adjustments in PPI therapy. For example, poor metabolizers often require lower doses to prevent excessive drug exposure, whereas ultra-rapid metabolizers may need higher doses or alternative medications to achieve therapeutic efficacy. Current guidelines recommend standard dosing followed by a 50% reduction for poor and intermediate metabolizers to minimize long-term risks [17]. In contrast, normal metabolizers may benefit from a 50–100% dose increase, while ultra-rapid metabolizers often require a 100% increase in dosing or frequency to overcome enhanced drug clearance [18]. For ultra-rapid metabolizers, traditional PPI dosing may still be insufficient, necessitating alternative therapeutic options, such as switching to different PPIs or considering non-PPI therapies, to ensure effective acid suppression and symptom control. Integrating pharmacogenomic testing into routine clinical practice holds the promise of improving both the efficacy and safety of GERD treatment. However, these recommendations primarily apply to first-generation PPIs in adults, as evidence for second-generation PPIs and pediatric populations remains limited [17]. Continued research into these areas will be critical for refining dosing recommendations and broadening the applicability of pharmacogenomic-guided therapy. Table 3 outlines the recommended PPI dosing adjustments for each CYP2C19 metabolizer

phenotype, providing a guide to support the clinical application of genotype-based dosing strategies.

Table 3. PPI dosing recommendations based on CYP2C19 genotype.

Metabolizer Status	Recommended Dose Adjustment	Additional Considerations	References
Poor Metabolizer	50% reduction from standard dose	Monitor for adverse effects	Lima *et al.*, 2020
Intermediate Metabolizer	50% reduction from standard dose	Regular monitoring of symptom control	Dean & Kane, 2021
Normal Metabolizer	Standard dose to 50% - 100% increase	Adjust based on symptom response	Lima *et al.*, 2020
Ultra-rapid Metabolizer	100% dose increase or increased frequency	Consider alternative therapy if inadequate response	Dean & Kane, 2021

6. Genetic Factors Influencing PPI Efficacy and GERD Management

Pharmacogenetic research has shed light on the variability in PPI metabolism and its impact on GERD treatment outcomes. CYP2C19, a key enzyme in PPI pharmacokinetics, has been extensively studied for its genetic polymorphisms and their role in altering drug efficacy. Often referred to as S-mephenytoin 48-hydroxylase, the CYP2C19 enzyme is characterized by a phenotype known as S-mephenytoin 48-hydroxylator, which is highly correlated with omeprazole metabolism [19]. Mutations in exons 4 and 5 of CYP2C19 result in significant differences in omeprazole pharmacokinetics between homozygous and heterozygous individuals. For instance, individuals heterozygous for both mutations or homozygous for the exon 5 mutation exhibit a marked deficiency in omeprazole's 5-hydroxylation pathway. While external factors, such as environmental or physiological influences, may skew the expected phenotypic and genotypic correlations [20], these findings firmly establish CYP2C19 as a crucial determinant of omeprazole efficacy in GERD treatment.

In addition to CYP2C19, other genetic factors play a significant role in influencing PPI efficacy and GERD pathogenesis, underscoring the need for personalized treatment strategies. Genes involved in gastric acid secretion and mucosal defense, such as ATP4A, which encodes the H^+/K^+-ATPase pump, may alter PPI affinity or pump density, impacting acid suppression. Similarly, polymorphisms in mucin genes like MUC1, MUC2, and MUC5AC are associated with GERD susceptibility and esophageal mucosal healing, providing further evidence of genetic variability in GERD outcomes. Inflammatory pathways add another layer of complexity, with cytokine gene polymorphisms, such as IL-1β, TNF-α, and IL-6, being linked to disease severity and response to therapy. Variations in immune regulation genes further highlight the intricate interplay between genetic predisposition and environmental triggers in GERD.

7. Clinical Implications and Therapeutic Drug Monitoring

Proton pump inhibitors are most effective when taken before meals and reach a

steady state after 3 to 5 days of consistent dosing [21] [22]. Adhering to a regular dosing schedule rather than using PPIs on an "as needed" basis serves to optimize GERD symptom management [23]. Long-term PPI use raises concerns about potential adverse effects including nutritional deficiencies (e.g., vitamin B12, magnesium, calcium, iron), which can lead to bone mineral density loss and increased fracture risk [24]-[26]. Other adverse side effects of PPI use are increased risk for *Clostridium difficile*, triggering an acute profuse diarrheal disease. Optimizing PPI dosing through pharmacogenomic insights can help mitigate these risks by ensuring appropriate use and minimizing unnecessary prolonged exposure. By refining dosing strategies based on genetic profiles, healthcare providers can improve patient outcomes and reduce the likelihood of adverse effects associated with long-term proton pump inhibitor therapy.

8. Novel Insights into the Role of Pharmacogenomics in GERD Management

Recent studies have revealed more complex interactions between pharmacogenomics and GERD, extending beyond drug metabolism to disease susceptibility and symptom presentation. Emerging evidence suggests that genetic variants may influence susceptibility to GERD symptoms, independent of drug metabolism. Variations in genes controlling esophageal motility, such as those affecting lower esophageal sphincter (LES) pressure, may influence reflux severity and symptom presentation. Genetic variations related to mucosal sensitivity or repair mechanisms may also impact symptom persistence and intensity. This broadens our understanding of GERD, highlighting a more intricate relationship between genetic predisposition and environmental factors.

Furthermore, recent research explores the correlation between specific genetic variants and extra-esophageal GERD symptoms, such as chronic cough or asthma. Genetic variants may influence PPI metabolism, affecting the amount of refluxate reaching the upper airways and the severity of these symptoms. However, further studies are needed to clarify these mechanisms and establish definitive causal relationships. This knowledge is essential for developing personalized treatments that address both esophageal and extra-esophageal symptoms. The integration of pharmacogenomics into personalized GERD management holds great potential. By incorporating both genetic profiles and symptom presentations, clinicians can optimize treatment strategies, minimizing adverse effects while maximizing efficacy.

9. Challenges and Research Gaps

Despite promising findings in pharmacogenomics and GERD management, several challenges and research gaps persist. These include the cost-effectiveness of genetic testing, clinician education, ethical concerns surrounding genetic information, and the need for larger-scale studies to confirm genetic associations with GERD symptoms. The lack of diversity in genetic databases significantly affects

the generalizability of findings, as CYP2C19 polymorphisms vary across ethnicities, with poor metabolizer (PM) status being more common in Asians (20%) compared to Caucasians and Africans (5%) [27] [28]. This underrepresentation of non-Caucasian populations in studies limits the applicability of pharmacogenomic-guided therapy to diverse patient populations. Furthermore, age is another critical factor influencing pharmacogenomic outcomes; elderly individuals with normal metabolizer (NM) or intermediate metabolizer (IM) phenotypes exhibit increased drug exposure compared to younger adults [3], underscoring the importance of considering age-related differences in drug metabolism. These limitations highlight the need for more inclusive studies encompassing diverse ethnicities, pediatric populations, and elderly patients.

Additionally, exploration of genetic factors beyond CYP2C19, investigation of gene-environment interactions in GERD pathogenesis, and longitudinal studies to assess long-term effects of genotype-guided therapy are necessary. Confounding factors such as smoking habits, sedentary lifestyle, and diet, which affect GERD symptom severity and PPI efficacy, also remain inadequately addressed. Furthermore, current studies primarily focus on first-generation PPIs, which may not apply to second-generation PPIs. More research is needed to investigate the efficacy and safety of pharmacogenomic-guided PPI therapy, particularly over extended periods, and to determine how long pharmacogenomic-guided dosing maintains its therapeutic benefits. No studies have explored potential long-term adverse effects of pharmacogenomic-guided dosing, which would better guide clinical practitioners in estimating treatment duration for individual patients. Ultimately, conducting studies that compare the effects of gastric acid suppression between pharmacogenomic-guided therapy and traditional dosing methods across diverse patient groups will enhance the applicability of pharmacogenomic-guided GERD management. Addressing these gaps will ensure the inclusivity and efficacy of treatment strategies, potentially revolutionizing approaches for this common condition.

10. Future Research Directions

To advance personalized gastroesophageal reflux disease management, future research should focus on several key areas. Longitudinal studies and randomized controlled trials are needed to assess the long-term effects of pharmacogenomic-guided PPI therapy on patients with newly recommended dosages. These studies should evaluate not only symptom control but also potential adverse effects and quality of life measures. Mendelian randomization studies could help establish causal relationships between genetic variants and GERD susceptibility or treatment response. Genome-wide association studies should be conducted to identify novel genetic markers related to GERD and PPI metabolism, including genes affecting P-glycoprotein, the H^+/K^+ ATPase pump, and H2 receptors. Such findings could influence the choice of administration route and precautions for drug interactions, leading to more effective treatment plans.

Furthermore, investigating how genetics interact with lifestyle factors like diet, weight management, alcohol, and tobacco use could provide valuable insights. High-fat diets, for instance, may impair PPI efficacy, especially in individuals with rapid-metabolizer phenotypes, while weight management has been shown to reduce symptoms and acid burden [29]. While PPIs are the cornerstone of GERD therapy, future studies could also examine alternative treatments such as H2 receptor antagonists (H2RAs), Potassium Competitive Acid Blockers, and GABA agonists. Pharmacogenomics could optimize these therapies, despite their drawbacks—for instance, tolerance to H2RAs over time [30]. Just as pharmacogenomics has enhanced PPI therapy, it holds the potential to improve the efficacy and personalization of other GERD treatments.

Research should also explore the cost-effectiveness of pharmacogenomic-guided PPI therapy. This includes investigating potential financial cost reductions by preventing ineffective PPI treatments and lowering the risk of PPI-associated complications, such as *C. difficile* infections and vitamin deficiencies. However, the potential increased burden of testing costs and unknown long-term side effects must also be considered. Studies should evaluate whether pharmacogenomic-guided PPI therapy reduces overall healthcare burden for patients, providers, and payers in the long run. Additionally, research on the role of pharmacogenomics in alternative GERD therapies, such as H2RAs and potassium-competitive acid blockers, is needed to investigate potential genetic influences on drug tolerance and response variability, as well as the cost-effectiveness of various treatment options.

Incorporating pharmacogenomic testing into electronic health record systems could allow for smooth clinical decision-making processes and real-time access to information for both healthcare providers and patients. Leveraging real-world data to track GERD patients over time and assess PPI effectiveness could provide more accurate, practical insights into pharmacogenomic-guided therapy. This collection of real-time data would enable further studies on improving the clinical implications of optimizing PPI therapy with pharmacogenomic testing. Future applications of pharmacogenomic testing could extend to other gastrointestinal disorders, such as inflammatory bowel disease and *H. pylori* infections, potentially leading to more effective and tailored therapies across various GI pathologies. As personalized medicine advances, incorporating pharmacogenomic insights into clinical decision-making processes could promote a more precise approach to treatment, minimizing adverse effects and optimizing drug efficacy across a range of gastrointestinal disorders.

11. Conclusion

Pharmacogenomics represents a transformative approach to GERD management, offering unprecedented opportunities for personalized treatment strategies by integrating genetic insights with clinical expertise. The study of CYP2C19 polymorphisms has revealed significant variability in PPI metabolism, ranging from poor

metabolizers to ultra-rapid metabolizers. These genetic variations profoundly impact drug efficacy, symptom resolution, and potential adverse effects, highlighting the critical importance of tailoring PPI therapy to individual genetic profiles. By understanding how specific genetic variants influence drug metabolism, healthcare providers can optimize dosing strategies, improve treatment outcomes, and minimize long-term risks associated with PPI therapy. While challenges remain in widespread implementation, including cost-effectiveness, standardization of testing protocols, and clinical education, the potential of pharmacogenomic testing to revolutionize GERD treatment is both promising and profound. As research continues to unravel the complex integration between genetic predisposition, drug metabolism, and disease progression, personalized medicine approaches will likely play an important role in GERD management, marking a significant advancement in precision medicine and patient-centered care.

Conflicts of Interest Statement

The authors of this manuscript declare that they have no conflicts of interest that are directly or indirectly related to the work submitted for publication. Specifically:

1) Financial Interests: None of the authors have received any financial compensation, funding, grants, or other monetary support that could be perceived as influencing the research, analysis, or conclusions presented in this work.

2) Professional Relationships: The authors have no employment, consultancy, board membership, or other professional relationships with organizations that could be perceived as influencing the work presented here.

3) Intellectual Property: The authors declare no patents, copyrights, or other intellectual property rights that could be affected by or affect the publication of this work.

4) Personal Relationships: The authors have no personal relationships with individuals or organizations that could inappropriately influence or bias the work presented here.

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