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# Benefit of Pharmacogenomic Testing in a Patient with Refractory Gastroesophageal Reflux Disease: A Case Report

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## Abstract

**Background:** Pharmacogenomics is the branch of genetics that evaluates potential drug-gene interactions. Genetic variation may affect patient exposure, efficacy, and tolerability of medications. FDA PGx labeling exists for >100 medications across most specialties and evidence-based, actionable guidelines are published by the Clinical Pharmacogenomics Implementation Consortium (CPIC), including guidelines for several Proton Pump Inhibitors (PPIs) in the treatment of Gastroesophageal Reflux (GERD). Here we describe a case of refractory (GERD) successfully treated using a next-generation PPI therapy guided by PGx.

**Case Report:** A 55-year-old female with a 12-year history of GERD had unresolved symptoms. The patient had seen various specialists, experienced endoscopies with biopsies, and had no symptom improvement despite trialing various PPIs and supplementation with additional medications. After PGx testing, the patient was found to be *CYP2C19* *1/*17 genotype, rapid metabolizer phenotype and was initiated on rabeprazole, a PGx-appropriate PPI based on her *CYP2C19* metabolism status. This resulted in long-standing (>1 year) resolution of GERD symptoms and lifestyle modifications.

**Conclusion:** Variations in drug metabolism can affect patient outcomes. This has been well reported for many indications. This case reports a patient with GERD refractory to standard treatment who experienced symptom resolution with PGx-directed treatment. Prospective studies to further evaluate the utility of PGx as standard of care for treatment are needed.

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## Introduction

Pharmacogenomics (PGx) is the branch of genetics that evaluates potential drug-gene interactions. Genetic variation may affect a patient's medication exposure, efficacy, and tolerability [1]. Patients with genetic variation(s) may experience altered medication metabolism, or may lack receptors required for medication response. The most common genetic variants are alterations in Cytochrome P450 (CYP) enzyme activity, which are responsible for metabolizing approximately 90% of medications [2].

FDA PGx labeling exists for >100 medications [3]. These are detailed in the FDA PGx Association Table highlighting drug-gene interactions that have therapeutic management recommendations, potential impact on safety or response, or potential impact on pharmacokinetic properties [3]. The Clinical Pharmacogenetics Implementation Consortium (CPIC) is an international group that synthesizes known PGx implications and emerging evidence [4]. CPIC publishes actionable, evidence-based guidelines to address these drug-gene interactions. Guidelines include several gastrointestinal medications such as Proton Pump Inhibitors (PPIs), antiemetics, and biologics. PGx testing adoption rates remain extremely low in the clinical setting.

*CYP2C19* is a major pathway for first-generation PPI clearance, with lesser contributions in subsequent generations (Figure 1). CPIC provides guidelines for use of several PPIs based on *CYP2C19* metabolism [5]. Common agents such as omeprazole, lansoprazole, and, less so, esomeprazole are metabolized by *CYP2C19*.

Approximately 40% of esomeprazole and 87% of r-omeprazole are cleared by *CYP2C19* [6]. Similarly, lansoprazole shows significant clearance by *CYP2C19* across both the R (Dexlansoprazole)

and S enantiomers [7]. Pantoprazole also has substantial *CYP2C19* metabolism and subsequent effects on drug exposure [8]. This can create clinically significant treatment implications for patients with altered *CYP2C19* metabolism.

The later generation PPI, rabeprazole, undergoes primarily nonenzymatic clearance, circumventing implications of altered *CYP2C19* metabolism. Despite this, no recommendation regarding rabeprazole as an alternative agent appears in CPIC guidelines. This case lends supporting evidence to use of rabeprazole in patients with increased *CYP2C19* metabolism and lack of symptom improvement with other PPIs.

## Case Presentation

A 55-year-old female with a twelve-year Gastroesophageal Reflux Disease (GERD) history presented for routine follow-up at her primary care office. Pertinent medical history included dysphagia, hyperlipidemia, and environmental allergies. Pertinent procedural history included multiple endoscopies with biopsies, and cholecystectomy.

The patient experienced ongoing, significant GERD symptoms despite trials of esomeprazole, omeprazole, and pantoprazole, with addition of famotidine or ranitidine for breakthrough symptoms (Table 1). Given symptom severity, she had extensive workup as described in her procedural history. Multiple endoscopies and biopsies showed chronic inactive gastritis without signs of eosinophilic esophagitis or *Helicobacter pylori* infection (Table 2).

The patient completed thorough trials of nonpharmacologic interventions. At the time of her visit, she was utilizing a mechanical bed for head elevation, altering her diet to avoid symptom-triggering foods and beverages, and avoiding late night meals. Despite multiple medication trials and nonpharmacologic interventions, the patient experienced significant GERD symptoms almost daily, with a significant decrease in quality of life.

The patient was identified for participation in an ongoing prospective, randomized, controlled PGx research study at The Christ Hospital, approved by The Christ Hospital's Institutional Review Board. She completed pre-appointment education on PGx and chose to proceed with PGx study enrollment. A clinic-embedded ambulatory care pharmacist then utilized an advanced Clinical Decision Support Tool (CDST) [9,10] that is fully integrated into the EMR to review the patient's medications. It was determined PGx testing may provide additional clinically relevant information, and testing was initiated.

At this institution, PGx testing is performed using a buccal swab, with results available after approximately two weeks. Testing utilized was an expanded, commercially available panel (Invitae), with 25 genes tested. For the *CYP2C19* gene, alleles *2, *3, *4, *5, *6, *7, *8, *9, *10, *12, *17, and *35 were detectable. Laboratory results, directly sent into the EMR as discrete data, were available for analysis using the EMR-integrated advanced CDST. Importantly, the CDST warns of potential cumulative impact of multidrug and gene interactions as multi-factor interactions, or phenoconversion. This is common and can lead to significant changes in drug exposure [11,12]. PGx variants and medications were reviewed using the CDST by the clinic-embedded ambulatory care pharmacist.

Results revealed a *CYP2C19* *1/*17 rapid metabolizer phenotype, relevant to her current medication regimen as outlined below. The results also indicated other PGx variants, however, these would only be pertinent for future treatments as they didn't have significant interactions with current medications.

Considering her *CYP2C19* rapid metabolizer phenotype status, CPIC guidelines advised she was at elevated risk for PPI failure. Increased metabolism likely reduced drug exposure, thus reducing drug efficacy. CPIC guidelines state patients with this metabolism phenotype should be considered for higher PPI dosing and are at increased risk of therapeutic failure. Although no specific alternate agents are listed in CPIC guidance, knowledge of PPI metabolism gave rise to discussion of alternative agents as well as dose adjustments.

Given the patient's report of no symptom improvement with prior or current PPI (Pantoprazole) treatment including dose adjustments, the pharmacist, patient, and Primary Care Provider (PCP) collectively opted to trial an alternate agent rather than an increased dose of her current PPI. Remaining PPI options included both rabeprazole and esomeprazole. The patient had previously trialed and failed esomeprazole. Rabeprazole 20 mg daily was initiated the same day results were reviewed. Rabeprazole is generic, and patient insurance coverage was adequate.

After initiation of rabeprazole, the patient reported resolution of GERD symptoms. She was able to discontinue other pharmacologic and nonpharmacologic interventions, and reported improvement in quality of life. Given her lengthy history of high disease burden, her

**Table 1:** Patient medication list.

| Medication | Dates of Use | Comments |
|---|---|---|
| Omeprazole 10 mg daily | May 2010 to March 2016 | Initial trial by patient as over the counter medication |
| Esomeprazole 40 mg daily | April 2017 to May 2017 | Initiated by GI after an EGD, higher dose not continued by PCP |
| Esomeprazole 20 mg daily | March 2016 to April 2017<br>May 2017 to May 2018<br>September 2018 to December 2020 | Initiated by GI after an EGD, briefly stopped after acute liver injury |
| Pantoprazole 40 mg daily | December 2020 to PGx testing | Initiated by GI after an EGD |
| Ranitidine 150 mg PRN | September 2018 to September 2021 | Used PRN as add on |
| Famotidine 20 mg PRN | November 2020 to PGx testing | Used PRN as add on |

EGD: Esophagogastroduodenoscopy; GI: Gastroenterology; PRN: as needed

**Table 2:** Patient procedure results.

| Endoscopy Result History | |
|---|---|
| March 2016 | LA Grade B esophagitis, 2 cm sliding hiatal hernia with Schatzki's ring status post 60 Fr Maloney dilation, and gastritis |
| December 2020 | LA Grade A esophagitis, 3 cm hiatal hernia, Schatzki's ring status post 20 mm balloon dilation |

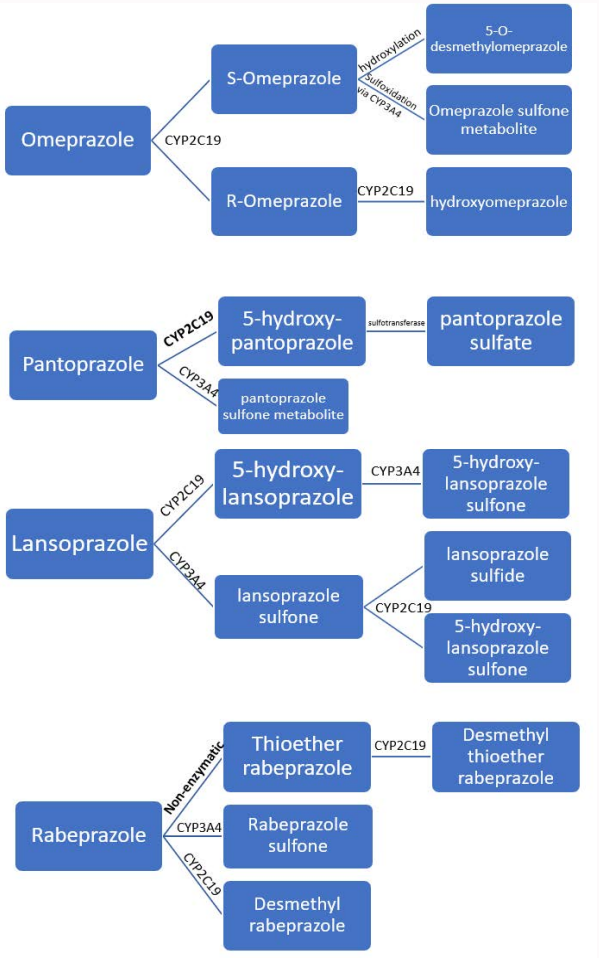


**Figure 1:** Proton pump inhibitor metabolism.
Adapted from: Scott SA, et al. Antiplatelet Drug Interactions with Proton Pump Inhibitors. Expert Opinion on Drug Metabolism & Toxicology. 2013.

PCP determined she wasn't a candidate for PPI cessation after 8 to 12 weeks, as is often considered for patients with GERD [7]. The patient has continued rabeprazole therapy, and has experienced a sustained alleviation of all reported GERD symptoms for >1 year.

## Discussion

Once a patient has received a GERD diagnosis, PPIs are the initial drug of choice [13]. If initial PPI therapy is unsuccessful, then a Histamine 2 Receptor Antagonist (H2RAs) may be added. The majority of PPIs have PGx testing recommendations included in FDA labeling and CPIC guidelines, yet the evidence and management is specific to each PPI. In each instance, the PGx labeling primarily relates to *CYP2C19* genotype/phenotype.

The *CYP2C19* enzyme has been well described in PGx literature, primarily in relation to the antiplatelet agent clopidogrel [14,15]. *CYP2C19* is a member of the cytochrome P450 family, which is responsible for Phase 1 detoxification and drug metabolism. Altered *CYP2C19* metabolism in the context of drug metabolism can alter patient exposure, efficacy, and potentially drug response. Poor metabolizer phenotypes will have higher levels of drug exposure, and potentially greater incidence of adverse effects. Conversely rapid or ultrarapid metabolizer phenotypes will have lower levels of drug exposure and potentially decreased regimen efficacy. Regarding clopidogrel, which is delivered as a prodrug that is metabolized to the active form by *CYP2C19*, poor metabolizer status is correlated with a higher risk of antiplatelet therapy failure, as defined by death, myocardial infarction, or urgent coronary revascularization [12,13].

As it relates to PPIs, the effects of *CYP2C19* variants are evidenced by divergent outcomes. Studies have shown increased effectiveness of PPIs in patients with reduced metabolizer statuses, likely related to the higher exposure that results with typical dosing [16]. Further supporting this assertion, patients with rapid metabolizer status have shown poorer clinical outcomes [17]. While adverse effects of PPIs are generally few, there is limited yet conflicting evidence on the impact of *CYP2C19* metabolizer status. Trials evaluating *CYP2C19* metabolizer status have found no increase in adverse events related to bone, however, evaluation of other toxicities, such as infection, have demonstrated mixed results, warranting further consideration [16,18,19].

In the current case described, PGx testing indicated a possible cause for failed GERD treatment after initial trials of multimodal nonpharmacologic therapy and pharmacologic therapy. Additionally, this case indicates there may be value in utilizing rabeprazole as an alternate in *CYP2C19* rapid metabolizer phenotypes. While the FDA labeling is primarily concerned with poor metabolizers, CPIC guidelines also indicate that there may be therapeutic impact for rapid/ultrarapid metabolizers [5]. This has been validated in several studies, showing the impact of various *CYP2C19* phenotypes on PPI exposure and direct clinical outcomes [20-22]. Further dose increases of other agents may have provided similar results as were achieved in our case with rabeprazole, however this wasn't implemented due extensive prior medication trials and dose adjustments.

The patient experienced no barriers in obtaining rabeprazole, although this is a consideration for non-generic medications. Though increases in prescription cost should be considered, so too should costs related to uncontrolled GERD including additional procedures, nonpharmacologic treatment and impact on performance and quality of life.

The patient observed significant clinical improvement, evidenced by her ability to discontinue other treatment modalities. Preemptive PGx testing for this patient would have avoided numerous visits with various gastrointestinal specialists, several endoscopies, financial burden and over a decade of poor quality of life. This case highlights the potential of PGx testing to improve outcomes, reduce financial toxicity and optimize health resource utilization.

## Conclusion

Appropriate use of PGx testing and pharmacist-guided intervention significantly improved outcomes for this patient. She was able to discontinue the nonpharmacologic therapies she had trialed, and experienced a complete resolution of long-standing symptoms. There were no issues obtaining medication due to insurance coverage, nor any adverse effects reported. The patient had sustained efficacy for >1 year at the time of this article submission. PGx testing is a vital component of therapy guidance for patients in whom first line, guideline-directed prescription therapies have been ineffective or intolerable. Current guidance is lacking for many drugs and metabolic mutations, as evidenced by the successful use of rabeprazole in this patient. Ideally, prospective, randomized, controlled studies should be carried out to further support the use of PGx panels and therapy alterations in routine practice, for current

and future medication management.

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