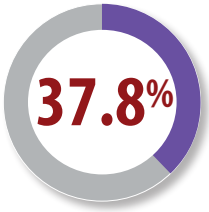
U.S. Department of Veterans Affairs
Veterans Health Administration
PBM Academic Detailing Services

Applying Pharmacogenomic (PGx) Testing to Proton Pump Inhibitor (PPI) Therapy

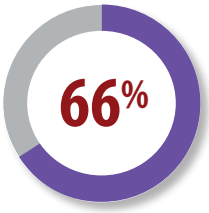
Applying PGx testing to PPI Therapy

PPIs bind to proton pumps in the stomach, irreversibly **inhibiting gastric acid secretion** and have various indications with **specific durations of therapy**.[1,2] Prolonged PPI therapy is associated with several adverse effects.[1,3] Patients without a definitive indication should be evaluated for a trial of **PPI de-prescribing**.[1]



PPI therapy prevalence in the United States in adults ≥65 years.[4]

Patients on PPI therapy for GERD **without symptom relief**.[5]



Patients on PPI therapy **without a documented indication** for use.[5,6]

GERD: gastroesophageal reflux disease

Table 1. American Gastroenterological Association (AGA) PPI therapy indications and durations of use.[1]

Definitively indicated for >8 weeks	Conditionally indicated for long-term use	Not indicated for long-term use	Definitely indicated for ≤8 weeks

• Barrett's esophagus
• Clinically significant erosive esophagitis
• Esophageal strictures from GERD
• Zollinger-Ellison syndrome
• Eosinophilic esophagitis
• Protection in those taking ASA/NSAIDs at high risk for GI bleed
• Prevention of progression of idiopathic pulmonary fibrosis
	• PPI-responsive condition below with recurrence on PPI cessation
	  • Endoscopy-negative reflux
	  • Functional dyspepsia
	  • Upper airway symptoms ascribed to laryngopharyngeal reflux
	• Refractory steatorrhea in chronic pancreatic insufficiency with enzyme replacement
	• Secondary prevention of gastric and duodenal peptic ulcers with no concomitant antiplatelet drugs
		• Symptoms of non-erosive reflux disease with no sustained response to high-dose PPI therapy
		• Functional dyspepsia with no sustained response to PPI therapy
		• Steroid therapy in the absence of ASA/NSAID
		• Prevention of recurrent upper GI bleeding from causes other than PUD, including gastric and duodenal erosions
		• Erosive esophagitis
			• *H. Pylori* eradication
			• Stress ulcer prophylaxis for ICU patients with risk factors
			• Uninvestigated GERD/dyspepsia
			• NSAID-related gastric and duodenal peptic ulcers

Refer to the AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review[1] for diseases **conditionally indicated and not indicated for acute/short-term use** of PPI therapy. ASA = aspirin; GI = gastrointestinal; *H. Pylori* = *Helicobacter pylori*; ICU = intensive care unit; NSAID = non-steroidal anti-inflammatory drug; PUD = peptic ulcer disease.

Table 2. Currently available PPIs.[2,7]

Generation	Medication	Formulary Status	Major Metabolic Pathway
First	Lansoprazole[†]	Non-formulary	~80% cleared by the **cytochrome P450 2C19 *(CYP2C19)* enzyme**
	Omeprazole[†]	Formulary	
	Pantoprazole	Formulary	
Second	Esomeprazole[†]	Non-formulary[‡]	Less dependent on *CYP2C19* for metabolism
	Dexlansoprazole	Non-formulary	Limited evidence but expected to have a similar metabolism pathway to lansoprazole
	Rabeprazole	Non-formulary	Primarily cleared by non-enzymatic pathways

[†]Available over the counter (OTC). [‡]The oral formulation is non-formulary and the intravenous formulation is formulary.

PGx test results confirm *CYP2C19* function and provide more information to optimize PPI efficacy or assess for discontinuation.

- Pre-emptive testing for PPI therapy is not currently recommended. However, incidental drug-gene interactions may be identified when testing for another indication.
- If available, PGx test results may be considered as an additional piece of information in conjunction with other patient-specific clinical factors impacting PPI-related pharmacotherapy decisions.

  - For patients **with** indications for PPI therapy and confirmed adherence, PGx test results may help optimize the dose or PPI regimen to ensure clinical benefit.
  - For patients **without** an indication for chronic therapy, PGx test results may further support discontinuation. For example, if a patient is found to be an ultrarapid or rapid *CYP2C19* metabolizer, clinicians may discuss risks and benefits of de-escalation or discontinuation given the likelihood of low PPI plasma concentrations and therefore decreased likelihood of efficacy with standard dosing.

Table 3. Implications of variation in *CYP2C19* function on lansoprazole, omeprazole, and pantoprazole therapy.[2]

CYP2C19 Phenotype	PPI plasma concentrations	Efficacy and safety implications
Ultrarapid and rapid metabolizer	Decreased compared to normal metabolizers	**Increased risk of therapeutic failure**
Normal metabolizer	As expected	**Increased risk of therapeutic failure** compared with intermediate and poor metabolizers
Intermediate and poor metabolizers (includes likely intermediate and likely poor metabolizers)	Increased or likely increased compared to normal metabolizers	**Increased chance of therapeutic success** and potential toxicity

Efficacy rate

A meta-analysis of 19 studies evaluating PPI therapy in over 1,500 GERD patients showed an **efficacy rate** of 52% in *CYP2C19* rapid metabolizers and 61% in poor metabolizers (p = 0.047).[8]

Eradication failure

A meta-analysis of 57 studies in patients taking PPIs for *H. Pylori* found that ultrarapid, rapid, and normal *CYP2C19* metabolizers had a **82% higher likelihood of eradication failure** compared to poor and intermediate metabolizers (p <0.001).[9]

Safety

Prolonged PPI use has been associated with an **increased risk for enteric infection**.[10] The evidence linking *CYP2C19* genotype to risk of other adverse events, such as chronic kidney disease, osteoporosis, and dementia, is limited.[3]

Apply PGx test results to optimize indicated PPI pharmacotherapy or assess for discontinuation.

Applying PGx test results to optimize PPI efficacy and safety

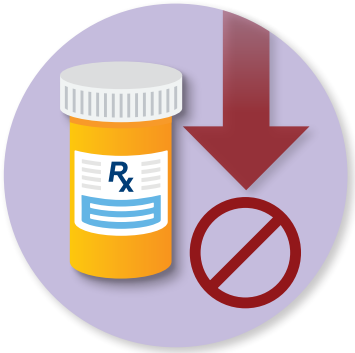
Table 4. Clinical Pharmacogenetics Implementation Consortium (CPIC) dosing recommendations for oral and intravenous omeprazole, lansoprazole, and pantoprazole based on *CYP2C19* phenotype.[2]

CYP2C19 Phenotype	Recommendation	Classification of Recommendation
Ultrarapid metabolizer	Increase starting dose by 100%; consider twice daily dosing.	Optional
Rapid or normal metabolizer	Initiate standard starting dose; consider twice daily dosing. *Consider **increasing** dose by 50-100% for **H. Pylori infections or erosive esophagitis***	Moderate
Intermediate or likely intermediate metabolizer	Initiate standard starting dose. *For therapy >12 weeks and efficacy achieved, consider 50% **reduction** in daily dose, and monitor for efficacy.*	Optional
Poor or likely poor metabolizer		Moderate

- CPIC dosing recommendations for **dexlansoprazole** are the same as those for the first-generation PPIs. *CYP2C19* genotype is expected to impact dexlansoprazole given its similar metabolic pathway to lansoprazole. However, due to limited data, the strength of the recommendations are all designated as **optional**.[2]

- **Esomeprazole** and **rabeprazole** are nonformulary medications but may be requested for consideration via the local nonformulary review process. See VA Formulary Advisor (https://www.va.gov/formularyadvisor/) for more information. While *CYP2C19* impacts esomeprazole and rabeprazole metabolism less than first-generation PPIs, the extent remains undefined. A meta-analysis of 57 studies evaluating PPI therapy for *H. Pylori*, found **no significant association between eradication failure and metabolizer phenotype** with either of these alternative PPIs.[9]
- Food & Drug Administration (FDA) designations for pharmacogenetic associations with PPIs are for the impact on pharmacokinetic properties and provide no dosing guidance in the adult population.[11]

Discontinuing PPI therapy[1,12]



- Both abrupt discontinuation and a tapering regimen may be considered.
- Patients discontinuing PPI therapy should be advised they may experience transient upper gastrointestinal symptoms due to rebound acid secretion. This does not necessarily indicate a need to restart therapy.
- Use of an as needed histamine type-2 receptor antagonists and/or neutralizing antacids may provide relief from rebound symptoms.
- Rebound symptoms persisting beyond two months may indicate need for continued PPI therapy and should be reassessed by a clinician.
- For more information about discontinuing PPI therapy, refer to the AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review (https://pubmed.ncbi.nlm.nih.gov/35183361/).

Clinical Pharmacist Practitioners (CPPs)

PGx CPPs are Advanced Practice Providers who are highly trained members of the healthcare team with additional education or experience in pharmacogenomics. Consult services are available within the electronic medical record for providers to request PGx CPP services (http://tinyurl.com/bdft5zd8). CPPs can evaluate PPI pharmacotherapy based on the PGx test results, adjust if needed, and contact patients for follow-up education.

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