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REVIEW

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Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine

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ABSTRACT

Introduction: Proton Pump inhibitors (PPIs) are commonly used for a variety of acid related disorders. Despite the overall effectiveness and safety profile of PPIs, some patients do not respond adequately or develop treatment related adverse events. This variable response among patients is in part due to genotype variability of *CYP2C19*, the gene encoding the CYP450 (CYP2C19) isoenzyme responsible for PPIs metabolism.

Areas covered: This article provides an overview of the pharmacokinetics and mechanism of action of the currently available PPIs, including the magnitude of CYPC19 contribution to their metabolism. Additionally, the role of *CYP2C19* genetic variability in the therapeutic effectiveness or outcomes of PPI therapy is highlighted in details, to provide supporting evidence for the potential value of *CYP2C19* genotype-guided approaches to PPI drug therapy.

Expert opinion: There is a large body of evidence describing the impact of *CYP2C19* variability on PPIs and its potential role in individualizing PPI therapy, yet, *CYP2C19* pharmacogenetics has not been widely implemented into clinical practice. More data are needed but *CYP2C19* genotype-guided dosing of PPIs is likely to become increasingly common and is expected to improve clinical outcomes, and minimize side effects related to PPIs.

1. Introduction

Proton pump inhibitors (PPIs) are widely used to treat a variety of acid-related disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, and Helicobacter pylori (H. pylori) infections, among other indications for PPI use [,1]. The effectiveness and safety of PPIs have led to their wide spread use, yet a subset of patients may not gain the full therapeutic benefit of these drugs, or may develop treatment-related adverse events.

It is well documented that the degree of acid suppression is closely related to variation in pharmacokinetic parameters (PK) of PPIs, specifically, the area under the serum (or plasma) concentration vs. time curve (AUC) [2,3].The underlying mechanism of this variability is multifactorial and includes genetic and nongenetic factors that can alter the disposition of PPIs. Examples of these nongenetic factors include timing of PPI administration in relation to meals [4,5], co-administration with other anti-secretory agents including histamine receptor blockers, both of which may affect absorption and activation of PPIs. PPIs are predominantly cleared by CYP2C19 and to a lesser extent by CYP3A4, and therefore, factors affecting CYP2C19 activity including age [6], medications, among others may also influence PPI metabolism, with the resultant changes in AUC altering their activity. Variation in *CYP2C19*, the gene encoding for CYP2C19, is the most important and well-studied pharmacogenetic factor affecting response to PPIs. Although many nongenetic factors can influence PPIs, variability due to *CYP2C19* genotype is significant and accounts for large percent of the PK variability of PPIs. Gawronska-Szklarz et al., for

example, demonstrated that 57% of variability in pantoprazole population clearance in adults was attributed to *CYP2C19* genotype [7].

Precision medicine is an approach that offers great potential to prescribe the right medicine, at the right dose to the right patient at the right time. Pharmacogenetics is at the heart of precision medicine, and promises to identify and use genotype information to guide treatment decisions and personalize treatment plans. Importantly, pharmacogenetics is one of the tools that can be readily deployed to advance the concept of precision medicine. To date, pharmacogenetic information exists in US FDA labeling for over 190 drugs [8], alongside a growing body of evidence to support the contribution of genetic variability in the range of drug responses observed across the population. Internationally recognized efforts have been developed to facilitate use of pharmacogenetic information in clinical practice. For example, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established in the US to effectively facilitate the interpretation and use of genetic information, should it be available for a patient, and guide prescribing decisions [9]. As of February 2017, CPIC has published 21 sets of guidelines for 35 drugs, spanning a wide range of medical areas, including cardiovascular, cancer, pain, immunosuppressants, antidepressants, anti-infective agents and others. Similar efforts to advance the field are also led by the Royal Dutch Pharmacogenetics Working Group (DPWG) [10,11], and the Ubiquitous Pharmacogenomics Consortium to integrate pharmacogenetics into clinic care across multiple countries in Europe [12].

Article Highlights

- PPIs are commonly used for acid related disorders, yet variable responses exist
- PPIs are metabolized to a varying degree by CYP2C19
- The difference in response or adverse events is related to the variability in *CYP2C19*, the gene encoding CYP2C19
- Large body of evidence document the effect of genotype variability on PK/PD and therapeutic outcomes of PPIs
- Large epidemiological studies document a relationship between dose and PPI-related adverse events, which suggest the plausible relation between *CYP2C19*, PPI drug concentrations and adverse events
- Genotype-guided dosing holds a promise of improving therapeutic outcomes and minimizing adverse events
- Clinical Implementation of *CYP2C19* in PPI therapy have started and data documenting its usefulness are likely in the near future

This box summarizes key points contained in the article.

Herein, we will review the pharmacogenetic data on PPIs, focusing on the impact of *CYP2C19* genotype on clinical outcomes and adverse events of PPIs as it relates to the degree of contribution of CYP2C19 in PPI metabolism. We focus on *CYP2C19* genotypic effects on PPIs in adults, with secondary attention to pediatrics, owing to the paucity of data in this population. We will also discuss the potential for clinical use of *CYP2C19* genotype data to guide PPI treatment decisions and affect individualized PPI drug therapy. Such personalized treatment approaches may have clinical value to improve response rates and reduce PPI-related adverse events.

2. PPI mechanisms

Six PPIs are currently approved in the US including omeprazole, the prototype in this class, lansoprazole, dexlansoprazole, pantoprazole, rabeprazole, and esomeprazole (stereoisomer of omeprazole). PPIs exert their pharmacological action through irreversibly inhibiting H^+/K^+-ATPase proton pumps in the gastric parietal cells, and thus inhibiting gastric acid secretion [13,14].

PPIs are weak bases that can be maximally protonated only in the extreme acidic medium of the parietal cells, and hence are considered pro-drugs [15].Once activated by protonation, they bind to one or more of the cysteine residues of the H^+/K^+-ATPase proton pumps, rendering the pumps nonfunctional [4,16]. The function of the pump can be regained through synthesis of new pumps (half-life of new pump biosynthesis is ~54 h) [4], which explains the persistent inhibition of acid secretion despite the short PK half-life of PPIs (~90 min). The optimal activity of PPIs is achieved when they are administered on an empty stomach, preferably 30–60 min before meals. Taking PPIs on an empty stomach not only improves their absorption, but also ensures that their peak plasma levels match the presence of a large pool of pumps that get activated by presence of food [5,17]. Patients are therefore advised to take their PPIs in a fasting state to ensure maximum absorption and activation of PPIs. Additionally, the concomitant administration of an acid-reducing agent, such as histamine receptor blockers, can elevate the pH of gastric acid content, which may reduce the activation of PPIs and negatively influence their response. Given these factors that may introduce variability in PPI absorption and or activation, cross over study designs were frequently used in PPI studies, in which individuals serve as their own controls, to eliminate biases/confounders other than the research question related to the particular PPI under evaluation.

2.1. PPI metabolism: similarities and differences

PPIs are enzymatically cleared in the liver primarily by the cytochrome P450 2C19 (CYP2C19) enzyme, and to a lesser extent by CYP3A4 (Table 1) [4,18–20]. PPI metabolism has been studied in adults, and thus the PK parameters summarized in Table 1 apply to adults. There are some differences in the extent to which PPIs are metabolized by CYP2C19, leading to variability in their PK and pharmacodynamic (PD) parameters, ultimately impacting their efficacy. It is documented that CYP2C19 is responsible for > 80% of the metabolism of omeprazole, lansoprazole and pantoprazole metabolism [21]. Dexlansoprazole, the R enantiomer of lansoprazole, is metabolized by hydroxylation via CYP2C19 and oxidation into sulfone metabolite via CYP3A4 [22], suggesting a similar metabolic pathway to lansoprazole.

Esomepazole is the S-isomer of omeprazole; however, it is metabolized to a lesser extent by CYP2C19 than omeprazole [23]. *In vitro* and *in vivo* data suggest that CYP2C19 is responsible for approximately 70% and 90% of clearance of esomeprazole and omeprazole, respectively [23,24]. Both compounds exhibit nonlinear PK, with increased area under the serum (or plasma) concentration vs. time curve (AUC) after repeated administration, which is presumed to be the result of CYP2C19 inhibition, leading to decreased clearance [25]. While the decreased clearance is

Table 1. Pharmacokinetic properties of proton pump inhibitors (References 5, 19–21).

PPI	Omeprazole (OME)	Esomeprazole (ESO)	Lansoprazole (LNZ)	Dexlansoprazole (DEX)	Pantoprazole (PNZ)	Rabeprazole (RPZ)
Bioavailability (%)	30–40%	64–90%	80–85%	NA	77%	52%
Time to plasma peak levels (Tmax)	0.5–3.5h	1.5h	1.7h	1–2h	2–3h	2–5h
Volume of distribution (L/Kg)	0.13–0.35	0.22–0.26	0.4	0.54	0.15	0.34
Clearance (mL/min)	400–620	150–266	400–650	190–193	90–225	160–330
Protein Binding %	95%	95%	97%	96%	96%	95–98%
Half-life (T1/2)	0.5–1h	1.3–1.6h	1.6h	1–2h	1–1.9h	1–2h
Hepatic metabolism	CYP2C19 (major), CYP3A4 (minor)	CYP2C19 (major), CYP3A4 (minor)	CYP2C19 (major), CYP3A4 (minor)	CYP2C19 (major), CYP3A4 (minor)	CYP2C19 (major), CYP3A4 (minor)	Nonenzymatic clearance, minor metabolism through CYP2C19
Fraction of CYP2C19 metabolism	>80%	~70%	>80%	>80%	>80%	Minimal
Inhibition of CYP2C19	Yes	Yes	No	No	No	No
Pharmacokinetics	Nonlinear	Nonlinear	Linear	Linear	Linear	Linear

evident with both drugs, the increase in AUC with repeated administration is greater with esomeprazole compared with omeprazole [25]. For example, on repeated administration of the same 20 mg dose, the AUC achieved with esomeprazole was 67% higher than with omeprazole [26]. Rabeprazole is nonenzymatically converted into a thioether with CYP2C19 and CYP3A4 contributing less to its hepatic metabolism [27], and therefore, CYP2C19 genetic variation or drug interactions may influence rabeprazole less than the other PPIs.

The acid suppression effect of PPIs relies on the plasma concentration of the parent compound, and the AUC of the PPIs is correlated with the degree of acid inhibition [2,3]. It is therefore logical that variations in the metabolic activity of CYP2C19, for which genetic variability is a major contributor, would ultimately affect the therapeutic activity of PPIs.

2.2. PPI metabolism in pediatrics

CYP2C19 shows reduced activity between birth and 6 months, followed by attainment of adult activity in early infancy [6]. Activity is then increased throughout childhood and finally reverts to levels similar to that in adults by puberty [6]. Earlier studies in pediatrics suggested little effect of CYP2C19 variation on PPIs, however, recent data have supported the role of CYP2C19 genotype in PPI therapy similar to that in adulthood [28,29]. Whether the effect of genotype on CYP2C19 is the same as in adults depends on the developmental stage of CYP2C19. Ward, et al. characterized the PK parameters of pantoprazole after single and multiple doses in children [30]. Children with an age range between 6 and 16 years old were randomized to either 20 or 40 mg of pantoprazole, and AUC was calculated following single and multiple doses. The investigators concluded that pantoprazole PK parameters in children of age 6–16 years of age are similar to these in adults. It may be assumed that the effect of genotype on PPIs in older children, whose CYP2C19 maturation is the closest to adults, can be extrapolated from adult data. The assumption that the relationship between CYP2C19 genotype and PK/PD in older children may be somewhat similar to that in adults has to take into account the developmental stage and ontogeny of CYP2C19. This is important if we were to extrapolate suggested genotype-guided dosing from adults to pediatric population.

3. CYP2C19 polymorphisms and phenotypes

According to assignment of allele function (CYP2C19 allele definition table) and citations for allele function that are posted on PharmGKB [31] (accessed on February, 2018), the phenotypic status of the CYP2C19 metabolizing activity is classified into ultra-rapid, rapid, normal, intermediate or poor metabolizer, depending on the genotypic combination (or diplotye) of an individual. Table 2 lists the several CYP2C19 haplotypes/diplotypes based on genotype determinations and the related metabolizer phenotypes. The most common polymorphism in CYP2C19 that leads to a 'no function', is CYP2C19*2 (rs4244285, c.G681A, p.P227P), which generates a cryptic splice site leading to an aberrantly spliced mRNA and a nonfunctional protein [32]. Approximately 25–35% of individuals of European and African ancestry and ~ 60% of Asians carry at least one copy of no function allele [33]. CYP2C19 *3, *4, *5, *6, *7, and *8 are other less frequent no function alleles, with *3 and *8 being the most common among this group [34]. Poor metabolizers (PM), carrying two copies of CYP2C19 no function alleles make up about 2–5% of European and African individuals and 15% of Asians [35]. Intermediate metabolizers (IM) are those who are heterozygous, with only one copy of a no function allele comprise 25–35% of Europeans and Africans and 45–50% of Asians [35]. Thus a large proportion of individuals have an impaired ability to metabolize PPIs via CYP2C19. On the other hand, the identified increased function polymorphism in CYP2C19 (*17: rs12248560) contributes to enhanced clearance of drugs metabolized by CYP2C19. This is also a common polymorphism in CYP2C19 with approximately 30% of individuals of European and African ancestry [34,36] and ~ 2–4% of Asians carrying at least one copy of CYP2C19*17 [37]. Individuals with two copies of the normal function allele are classified as CYP2C19 normal metabolizer status (NM) while individuals with one normal function allele and one increased function allele (*17) are rapid metabolizers (RM). Individuals with two copies of *17 are classified as ultra-metabolizers (UM). The increased activity of *17 allele does not offset the no-function allele (*2) in individuals with (*2/*17) diplotype, who are therefore assigned an IM phenotype status, which is a provisional classification.

It is important to note that the nomenclature used to describe CYP2C19 metabolizer status has varied somewhat over time. For example, many studies used different nomenclature for the metabolizer phenotype than the one described according to the most recent CPIC allele classification. To provide greater clarity for the body of literature, and for purposes of consistency within this review, we have unified the nomenclature based on the actual genotyping from the study, aligning our phenotype definitions with those described in Table 2. Thus, the phenotype we use to describe metabolizer status in the studies summarized in Tables 3 and 4 may be different than that used by the original author, and reflects the most recent CPIC classifications for CYP2C19 metabolizer phenotype (NM, IM, PM, RM, and UM).

Table 2. Frequency of CYP2C19 genotype/diplotype-defined metabolizer phenotypes.

CYP2C19 genotypes/diplotypes	Predicted CYP2C19 phenotype	whites	African Americans	Asians
*17/*17	CYP2C19 ultrarapid metabolizer (UM)	5%	4%	~1%
*1/*17	CYP2C19 rapid metabolizer (RM)	27%	24%	2-16%
*1/*1	CYP2C19 normal metabolizer (NM)	42%	39%	23–45%
*1/*2, *1/*3	CYP2C19 intermediate metabolizer (IM)	27%	32%	46-47%
*2/*2, *2/*3, *3/*3, other No function alleles	CYP2C19 poor metabolizer (PM)	3%	4%	12–15%

The CYP2C19 phenotype is based on allele function from PharmGKB

Table 3. Effect of CYP2C19 variability on PK/PD parameters of proton pump inhibitors.

Ref	Population/study design; agent(s)	Effect of genotypes on PK or PD (intragastric pH)	Comments
Tanaka et al[44]	14 healthy Japanese: NM/IM (N = 7), PM (N = 7); PNZ	AUC ratio of (NM/IM):PM = 6:1	PNZ disposition is influenced by CYP2C19 genotype
Shirai et al[40]	15 healthy: NM = 6,IM = 5, PM = 4; OME 20 mg or RPZ 20 mg for 8 days	OME AUC ratio of NM:IM:PM = 1: 2.3: 6.8 OME intragastric pH in NM:IM:PM = 4.1:4.7:5.9 RPZ AUC ratio of NM:IM:PM = 1: 3.0: 5.3 RPZ intragastric pH in NM:IM:PM = 4.8:5.0:6.0 (NS)	CYP2C19 affects PK and PD of OME. No significant effects on PD of RPZ
Furuta et al[41]	18 healthy Japanese: NM = 7,IM = 7, PM = 4; LNZ 30 mg or placebo Five NM received LNZ 30 mg four times daily	AUC ratio of NM:IM:PM = 1: 2.4: 5.4 Intragastric PH in NM:IM:PM = 4.5: 4.9:5.5 pH in NM after frequent administration of LNZ was 7.4	CYP2C19 significantly affects PK and PD of LNZ. NM may be at risk of lower plasma concentrations of LNZ with once-daily administration of 30 mg
Furuta et al[42]	15 healthy Japanese: NM = 5,IM = 4, PM = 6; OME 20 mg	AUC ratio of NM:IM:PM = 1:3.3: 12.2 Intragastric pH in NM:IM:PM = 2.1: 3.3:4.5	CYP2C19 significantly affects PK and PD of OME
Qiao et al[45]	18 healthy Chinese: NM = 6,IM = 6,PM = 6; randomized crossover; OME 20 mg, LNZ 30 mg or RPZ 20 mg	AUC ratio of NM:IM:PM OME = 1:2.8:7.5 LNZ = 1:1.7:4.0 RPZ = 1:1.6:3.7	CYP2C19 significantly influences PK of the three PPIs, however with a lesser extent in RPZ
Leiri et al[47]	15 healthy Japanese: NM = 5,IM = 5, PM = 5; randomized crossover to once-daily dose; LNZ 30 mg or RPZ 10 mg	AUC ratio of NM:IM: PM LNZ = 1:1.7:3.9 RPZ = 1:1.7:3.8	CYP2C19 influenced PK of both LNZ and RPZ
Hu YM et al[46]	20 healthy Chinese: NM = 7, IM = 6, PM = 7; single daily dose of RPZ 20 mg	AUC ratio of NM:IM:PM = 1.0:1.1: 1.7 No difference in median intragastric pH or percent of time pH > 4 between three phenotypes	CYP2C19 influenced PK of RPZ with no significant effect on PD
Adachi et al[48]	20 healthy Japanese: NM = 7,IM = 9, PM = 4; randomized crossover to RPZ 20 mg or LNZ 30 mg	Nighttime pH in NM:IM:PM LNZ = 1.8: 2.2: 5.9 RPZ = 3.1: 4.3: 4.0	Acid inhibition is significantly influenced by CYP2C19 genotype in LNZ but not RPZ
Sahara et al[51]	40 healthy Japanese: NM = 15,IM = 15, PM = 10; randomized crossover to twice-daily; OME 20 mg, ESO 20 mg, LNZ 30 mg, RPZ 10 mg	Median pH in NM:IM:PM OME = 5.0: 5.7: 6.6 LNZ = 4.7: 5.4: 6.4 ESO = 5.4: 5.6: 6.2 RPZ = 4.8: 5.0: 6.4	Acid inhibition is significantly influenced by CYP2C19 with lesser magnitude in ESO and RPZ
Sugimoto et al[49]	183 healthy Japanese; prospective cohort; once-daily doses; OME 20 mg, LNZ 30 mg, RPZ 10 mg; OME: NM = 16, IM = 19, PM = 15 LNZ: NM = 35, IM = 21, PM = 12 RPZ: NM = 23, IM = 23,PM = 19	Median pH in NM:IM:PM OME = 3.8: 4.8: 5.2 LNZ = 4.5: 4.8: 5.2 RPZ = 4.8: 5.0:5.9	Median pH is significantly influenced by CYP2C19. In NM phenotype, pH was significantly highest in RPZ compared to other PPIs
Gawronska-Szklarz et al[7]**	32 healthy Polish: NM = 6, RM = 6,UM = 6, IM(*1/*2) = 6,IM(*2/*17) = 6,PM = 2; single dose; PNZ 40 mg	AUC ratio in NM:IM:PM = 1: 1.5: 5.0 AUC ratio in NM:RM:UM = 1: 0.7: 0.6	UM phenotype had significantly lower PNZ levels compared to NM 57% of interindividual variability in PNZ clearance was explained by CYP2C19
Hunfeld et al[53]**	19 healthy Dutch: NM = 7, RM = 2,IM(*2/ *17) = 2,IM(*1/*2) = 7, PM = 1; randomized crossover; ESO 40 mg or PNZ 20 mg	Significantly higher % of time with pH> 4 for IM (38%) compared to NM (22%) in PNZ only	CYP2C19 affects PD of PNZ and not ESO
Hunfeld et al[58]**	26 healthy Dutch; randomized crossover to LNZ 15 mg, OME 10 mg (study A), or OME 20 mg, PNZ 40 mg (study B); Study A (NM = 5,RM = 1,IM = 5) Study B (NM = 6,RM = 6,IM = 3)	Study A: Only IM (*1/*2) demonstrated significant acid suppression after one dose of OME Study B: NM and RM demonstrated significant acid suppression after repeated administration of OME or PNZ	Individuals with NM and RM phenotypes may need strong acid suppression

Omeprazole: OME, esomeprazole: ESO, pantoprazole: PNZ, lansoprazole: LNZ, rabeprazole: RPZ, dexlansoprazole: DEX, NS: nonsignificant, **denotes that *17 allele was assessed in that study

4. CYP2C19 and PPI pharmacogenetics

As noted earlier, the currently available PPIs are metabolized primarily by CYP2C19 and to a lesser extent by CYP3A4 [18,38]. Several papers highlighting the effect of CYP2C19 polymorphisms on PPI PK, and the role of CYP2C19 pharmacogenetics in the clinical setting were published in the beginning of this millennium. It is important to note that the degree to which CYP2C19 genotype impacts the PK and PD of PPIs depends on contribution of CYP2C19 to the metabolism of the individual PPI (Table 1). Specifically, CYP2C19 variation may have less impact on the metabolism of rabeprazole, for which the clearance is less dependent on CYP2C19 as it undergoes a nonenzymatic clearance [39].

4.1. Influence of CYP2C19 genetic variation on PK and PD of PPIs

4.1.1. No function variants and impact on PPIs

The relationships between CYP2C19 genotype, PK and intragastric acid pH are summarized comprehensively in Table 3 The evidence of the link between genotype and PPI emerged with the publication of several PK studies, mostly in healthy individuals. Many of these studies were conducted in individuals of Asian ancestry, well before the identification of the CYP2C19*17 haplotype that is more prevalent in individuals of European ancestry. Therefore, the majority of early studies documenting the relation between CYP2C19 and PK/PD did not assess for CYP2C19*17 that was identified in 2006 [36].

Table 4. Effect of CYP2C19 variability on therapeutic outcomes with PPI therapy (GERD and H. Pylori eradication).

Ref	Population/study design; agent(s)	Effect of genotypes on outcomes	Comments
Saitoh et al[59]	99 Japanese patients with GERD: NM = 26, IM = 55, PM = 18; randomized to RPZ 10 mg, OME 20 mg, LNZ 15 mg	GERD recurrence rates in RM:IM: PM = (38.5%, 10.9%, 5.6%) regardless of the drug Recurrence rates in OME: LNZ: RPZ = 25%: 31%: 4%	CYP2C19 significantly affects GERD recurrence rates of PPIs GERD outcomes are less affected by genotype in RPZ
Furuta et al[60]	124 Japanese patients with GERD: NM = 54, IM = 56, PM = 14; LNZ 30 mg Dose reduced to 15 mg if reflux occurred less than once/week	Hazard ratio (HR) of GERD recurrence in IM compared to NM = 0.4, p = 0.021 HR of GERD recurrence in PM compared to NM = 0.2, p = 0.011	NM phenotype is at risk of GERD recurrence
Ariizumi et al[73]	103 Japanese patients: NM = 36, IM = 50, PM = 17; RPZ 10 mg	Healing rates for NM:IM:PM = 86%: 92%:82% (NS)	No difference in healing rates among CYP2C19 genotypes
Schwab et al[71]	205 Europeans with GERD diagnosis were defined as cases (non-healed GERD) and controls (healed GERD): NM = 148,IM = 51, PM = 6; ESO 40 mg	No significant difference in the distribution of healed and non-healed GERD among genotypes NM = 75%:70% IM = 22%:28% PM = 3%:3%	No effect of CYP2C19 on GERD healing
Saito et al[62]	78 Japanese patients with H. pylori: NM = 22, IM = 43, PM = 13; ESO 40 mg based H. pylori regimen	Eradication rates for NM,IM and PM = (52.2%, 72.1%, 84.6%), p(PM vs NM) = 0.048	CYP2C19 genotype had a significant effect on H. pylori eradication
Kurzawski et al[74]**	125 Polish patients with H. pylori were defined as successful eradication (N = 78:NM = 23,RM = 27,UM = 5,IM = 22, PM = 1) and eradication failure (N = 47: NM = 21,RM = 18,UM = 3,IM = 5,PM = 0)	Distribution of *17 allele carriers between successful and failure eradication = 50%:45% (NS) Distribution of *2 allele carriers between successful and failure eradication = 30%:11%	*2 allele but not *17 allele had significant effect on H. pylori eradication rates in case of PNZ
Ichikawa H et al[64]	Meta-analysis of 19 published studies up to 2014 including 'GERD and CYP2C19', 'esophagitis and CYP2C19', and 'non-erosive reflux disease and CYP2C19': NM = 604, IM = 526 PM = 225; different agents	Efficacy rates in PM:IM: NM = 61.3%:56.7%:52.2%, p = 0.047 CYP2C19 NM had a higher risk of PPI refractoriness in NM compared with PM (Odds ratio (OR): 1.7, 95% CI: 1.0–2.7)	CYP2C19 influenced healing rates of reflux esophagitits and not nonerosive reflux disease NM phenotype are at a higher risk of PPI refractoriness
Tang et al[63]	Meta-analysis of 16 studies up to 2013: NM = 1173, IM = 1603 PM = 621, different agents	OR of H. pylori eradication in IM compared to NM = (0.7; 95% CI 0.6–0.9) OR of eradication in PM compared to IM (OR 0.7; 95%CI 0.5–0.9)	NM are at higher risk of eradication failure compared to IM and PM Significant eradication differences across genotypes in OME and LNZ but not ESO and RPZ

Omeprazole: OME; esomeprazole: ESO; pantoprazole: PNZ; lansoprazole: LNZ; rabeprazole: RPZ; dexlansoprazole: DEX; NS: nonsignificant; **denotes that *17 allele was assessed in that study

These studies (Table 3) demonstrated differences in acid inhibiting properties of PPIs between CYP2C19 genotypes that were well correlated with differences in PK parameters, namely, AUC and Cmax. Specifically, individuals who carry no function alleles were shown to have higher AUC of PPIs compared to individuals with normal function CYP2C19 alleles, due to reduced clearance by CYP2C19. These studies also demonstrate the link between CYP2C19 genotype, PPI disposition and effect. Specifically, many studies have shown that no function alleles are associated with significantly higher PPI exposure (AUC and plasma levels) leading to a more pronounced acid suppression effect, as measured by intragastric pH. (Table 3). In contrast, the NM metabolizer phenotype was shown to have lower plasma levels of PPI, which correlated with reduced acid suppression [40,41].

The PK studies demonstrated that the AUC of omeprazole and lansoprazole in PM was 4–12-folds higher than in individuals with NM phenotypes [41,42]. Similarly, the AUC following the administration of equal doses of pantoprazole in PM was sixfold higher than NM and IM [43,44]. Although reports have documented the impact of CYP2C19 genotype on PK for both rabeprazole [40,45–49] and esomeprazole [50,51], these associations with PK parameters such as AUC were of smaller magnitude than the effects reported for other PPIs, suggesting

less influence of CYP2C19 genotype on these newer generations PPIs. This is not surprising given that rabepeprazole and esomeprazole are less dependent on CYP2C19 for their metabolism (Table 1). There have been fewer studies on the relation between CYP2C19 genotype and PK/PD of dexlansoprazole compared to other PPIs. One report of five healthy individuals (four NM; one PM) has shown that dexlansoprazole clearance was 12% of its clearance in individuals with NM phenotype [22]. Despite the limited data on the impact of CYP2C19, the FDA labeling of dexlansoprazole, accessed through PharmGKb [31]-included pharmacogenetic information that documented 12-fold and twofold increases in dexlansoprazole AUC in Japanese individuals with PM and IM phenotype compared to NM, suggesting that dexlansoprazole is also influenced by CYP2C19 genotype.

Regarding PPI effect on acid suppression, the median intragastric pH is higher in PM compared to IM, NM, RM and UM when standard PPI doses were given, suggesting that these doses may not be sufficient for acid inhibition in patients with the NM phenotype, or that patients with the PM phenotype are exposed to high PPI drug concentrations [41,42]. Some reports have shown that variations in acid suppression are less significant when PPIs with less CYP2C19 dependent metabolism such as rabeprazole [27,47–49] or esomeprazole [50,52,53], are administered. CYP2C19

genotype dependent variation in median gastric PH was less for esomeprazole and rabeprazole compared to omeprazole and lansoprazole [51].

Whether the effect of genotype can be overcome by increasing doses of PPI in NM has been a focus of many research papers. Therefore, the use of higher once-daily doses or multiple daily doses of PPIs to overcome the effect of CYP2C19 genotype, has been investigated as an alternative option in individuals in whom standard doses may be insufficient to produce adequate acid suppression due to a fully functional or increased CYP2C19 activity [41,50,54]. A study by Furuta et al. reported that individuals with the NM phenotype achieved an intragastric pH of 7.4 when lansoprazole 30 mg was given four times daily, suggesting that high doses of lanzoprazole may overcome the effect of genotype in individuals with NM status[41] (Table 3). Data using rabeprazole showed that divided daily doses (10mg four times daily) achieved sustained acid inhibition (higher percentage of time with pH>4) compared to once-daily doses of rabeprazole 40mg in individuals with NM phenotype.[54.] Given the short half-life of PPIs, their frequent dosing (more than once-daily dosing) is expected to inhibit more pumps, and thus improve acid inhibition. While the multiple dosing of PPIs was shown to improve acid suppression and has been proposed to improve response rates in patients with refractoriness to PPIs [55], compliance with multiple dosing regimen may pose real challenges and adversely affect compliance [56]. Additionally, although the half-life of the drug is short, the effect of PPIs on reduced acid suppression is sustained once the pumps are inhibited, as a result of irreversible binding of the proton pumps until the synthesis of new pumps. This may actually argue against multiple dosing beyond the twice-daily administration of PPIs. Taken together, the data in Table 3 clearly demonstrate that no function alleles lead to higher exposure to PPIs and greater acid suppression following administration of equal doses of PPIs that are predominantly metabolized by CYP2C19. These data highlight that standard once-daily dosing of PPIs in IM and PM phenotypes may be sufficient for adequate acid inhibition, in contrast to those with the NM, RM, or UM phenotypes who may need higher or more frequent doses of PPIs, or treatment with a drug with less dependence on CYP2C19 metabolism.

4.1.2. Increased function *17 allele and impact on PPIs

CYP2C19*17, a haplotype variant that leads to enhanced transcription of CYP2C19 was discovered by sequencing the 5′-flanking region of CYP2C19 in 107 Swedish and 126 Ethiopian participants [36]. Most of the PK/PD studies were conducted in Asian populations, therefore, far less data exist on the effect CYP2C19*17 on PPIs.

While there are fewer data on the influence of CYP2C19*17 on PPI drug exposure compared to no function alleles, the existing data support that CYP2C19*17 is associated with lower PPI levels as a result of enhanced clearance, which could lead to increased risk for therapeutic failure with PPIs. That the *17 haplotype is associated with enhanced CYP2C19 activity and reduced PPI exposure is supported by several studies. For example, individuals with *17 allele had lower plasma concentrations of pantoprazole compared to NM [7,57,58]. Hunfeld et al. investigated the effect of CYP2C19 variants: *2–*6 and *17 on PK parameters of different doses of PPIs

(omeprazole 10 mg and 20 mg, lansoprazole 15 mg and pantoprazole 40 mg, Table 3) and percentage of time with intragastric pH > 4 post PPI administration [58]. While individuals with IM phenotype demonstrated significant acid suppression after a single-dose treatment with lansoprazole 15 mg or omeprazole 10 mg, those with NM and RM phenotypes showed significant acid reduction (pH>4) only after repeated PPI treatment with omeprazole 20 mg or pantoprazole 40 mg. These data suggest a potential risk for under dosing in individuals with NM, RM and UM phenotypes, and highlight the need for a stronger acid suppression regimen for individuals with these genotypes.

Overall, the data support that CYP2C19 no function alleles lead to a higher active PPI concentration in the plasma, whereas the *17 allele leads to significantly lower concentration, with a potential for under treatment. However, more studies are needed to further delineate the effect of CYP2C19*17 on PPIs. Particularly needed are studies that are large enough to provide insight into the phenotype that should be attributed to those who carry the *2/*17 diplotype. Additionally, more data are needed in children, for whom the prevalence of PPI use is increasing without enough data to describe the effect of CYP2C19 genotype on PPIs.

4.2. CYP2C19 polymorphisms and therapeutic outcomes

4.2.1. GERD symptoms

That the genotype of CYP2C19 may affect the therapeutic outcomes of PPIs was demonstrated with a string of publications documenting lower intragastric pH[48,49,50] (Table 3) with diminished control of GERD symptoms[59,60,61,] and lower eradication rates of H. pylori in patients with a NM phenotype status[62,63] (Table 4). As further evidence for the impact of genotype on therapeutic outcomes, Furuta et al.[60.] showed that 89% of NM who had lansoprazole dose stepped down from 30 mg to 15 mg had GERD recurrence versus 79% of IM and 50% of PM phenotypes who also had a step down of their dose to 15 mg [60]. The hazards ratio (HR) of GERD recurrence comparing PM and IM were calculated. PM had 80% reduction (HR: 0.2, 95% CI: 0.10–0.70, P = 0.011) and IM had 60% reduction (HR: 0.4, 95% CI: 0.20–0.90, P = 0.021) in GERD recurrence compared to NM [60]. These data support the value of CYP2C19 genotyping to determine the optimal PPI doses in GERD maintenance therapy, especially in patients who are at risk of PPI underdosing if they have normal function or increased CYP2C19 activity.

Convincing evidence for the effect of CYP2C19 on the clinical outcomes of GERD treatment comes from a recent meta-analysis by Ichikawa et al. highlighting the risk of therapeutic failure associated with the NM phenotype [64]. In this analysis, the effect of genotype status was evaluated using combined analysis of 19 published studies, which included patients with GERD. The efficacy rates of PPIs in patients with reflux esophagitis and nonerosive reflux disease (NERD) were significantly different among genotypes (NM: 52.2%; IM: 56.7%; PM: 61.3%; P = 0.047). Further, patients with NM CYP2C19 experienced higher risk of GERD recurrence compared with PM (OR: 10.3, 95% CI: 2.7–38.5; P = 0.001). Additionally, the odds ratio of refractoriness to PPI comparing NM to PM was calculated. Patients with the NM phenotype

had 66% higher risk of being refractory to standard doses of PPIs compared to PM (OR: 1.66, 95% CI: 1.02–2.66, P = 0.04). In this meta-analysis, CYP2C19 genotype was not significant in studies that included patients with NERD alone. It is important to note that NERD is a sub-entity of GERD with several distinct anatomical and histological features that distinguish patients with NERD [65,66]. NERD is characterized by the absence of mucosal tear on endoscopy. Additionally, NERD includes at least 4 subcategories of whom, only patients in which acid exposure is implicated in symptoms, are responsive to PPIs [67]. While the nonsignificant association in patients with NERD may not be surprising given its distinct pathophysiology, it is important to note that this meta-analysis included a small number of studies in patients with NERD (n = 5).

4.2.2. Helicobacter bacteria eradication

Treatment for eradication of H. pylori includes PPIs along with antimicrobial agents [68,69]. The role of PPIs is to increase the intragastric pH, allowing the bacteria to reach the growth phase and become more sensitive to antibiotics [69]. Additionally, the increased pH increases the stability of antibiotics, allowing for increased antimicrobial activity [68]. It is clear from the literature that CYP2C19 genotype impacted the outcomes of H. pylori eradication. Specifically, CYP2C19 no function alleles were associated with higher eradication rates due to decreased clearance of PPIs and higher plasma levels. A recent study by Saito et al. included 80 Japanese patients who were on esomeprazole-based H. pylori treatment at a daily dose of 40 mg (Table 4) [62]. The study found a statistically significant difference in eradication rates based on genotype. As expected, lowest eradication rates were observed in NM compared to IM and PM, respectively (52.2%, 72.1%, and 84.6%). Another study observed that 30–40% of patients with NM phenotype failed their PPI regimens. When these patients had their doses escalated, H. pylori eradication rate increased to about 80% [70], supporting the need for escalated doses in CYP2C19 NM phenotypes. Contrary to the results by Saito et al. [62], that found significant effect of CYP2C19 genotype on H.pylori eradication in esomeprazole Schwab et al. [71] did not document an effect for CYP2C19 genotype on GERD healing in a relatively large cohort of European patients (N = 205) who used esomeprazole. It is important to note that the study by Schwab et al. was conducted before the discovery of *17, and therefore *17 allele, which is present in 30% of patients with European ancestry was not assessed. This may have led to the nonsignificant effect of CYP2C19 genotype on GERD outcomes. While *17 allele was not assessed in the study by Saito et al, this would have had a much smaller impact on the results since this is relatively an uncommon variant in Asians.

One of the most informative analyses regarding the effect of genotype on H. pylori eradication comes from a 2013 meta-analysis that included data from 16 randomized controlled trials, in which patients were randomized to one of the H. pylori eradication regimens (N = 3680) [63]. The odds ratio of H. pylori eradication comparing NM to IM, and IM to PM were calculated. Regardless of the PPI used, the rate of eradication in NM was lower compared to IM (OR 0.72; 95% CI 0.59–0.88). Similarly, the rate of eradication in IM was lower compared to PM (OR 0.69; 95%CI 0.51–0.92). A sub-

analysis of CYP2C19 influence on H. pylori eradication by individual PPI found significantly lower rate of eradication for NM compared to IM or PM for omeprazole and lansoprazole; this effect was not significant when esomerazole or rabeprazole were analyzed. Results of this meta-analysis were in line with another meta-analysis by Zhao et al. [72], also documenting that patients with NM have lower odds of H. pylori eradication compared to IM and PM. The nonsignificant results for CYP2C19 effect on therapeutic outcomes of rabeprazole and esomeprazole in this meta-analysis and few other studies [71,73] can be explained by the lower contribution of CYP2C19 in esomeprazole and rabeprazole metabolism compared to other PPIs. Specifically, rabeprazole is predominantly metabolized via nonenzymatic clearance. Another unique PK characteristic that distinguishes esomeprazole [26,53], is that it inhibits its own metabolism with repeated administration leading to higher PPI plasma levels with diminished genotype effect on acid suppression.

Most data on the association with therapeutic outcomes such as H. pylori eradication and CYP2C19 come from studies that did not evaluate CYP2C19*17, due to its low frequency in Asians, and therefore the impact of RM and UM phenotypes on therapeutic outcomes is not well documented. Gawrońska-Szklarz et al. analyzed the H. pylori eradication rates in Caucasians, and found no difference in CYP2C19*17 carrier status between patients who were treated successfully and those who failed therapy [74]. This study however might have been underpowered to detect association with *17 and H. pylori eradication due to limited sample size (Table 4). Other recent data however provide early evidence on the risk for therapeutic failure in RM and UM. For example, Franciosi et al. analyzed 74 children with GERD who were classified as cases (*17 carriers without no function alleles) or controls (all other patients) and underwent pH probe testing [75]. In this study, *17 carriers without no function alleles experienced a significantly longer time with pH < 4 compared to controls (76.5 vs 33.5 min, p = 0.03), and higher percentage of time with pH < 4 (5.7% vs 2.7%, p = 0.04). The poor response rates observed in *17 carriers with no function alleles, suggest lower PPI plasma levels compared to controls, who could have responded to higher PPI doses, thus eliminating the need for pH probe testing. Another study documented the link between response to PPIs and CYP2C19*17 in patients with eosinophilic esophagitis, whereby the CYP2C19 RM phenotype was shown to be an independent predictor of reduced efficacy of PPIs in patients with eosinophilic esophagitis who mostly responded to PPI dose escalations [76]. These data together suggest that CYP2C19 *17 carriers taking conventional doses of PPIs are at a risk of inadequate acid suppression and thus treatment failure due to increased CYP2C19 activity, leading to low drug concentrations of PPIs. More data are needed in populations where the *17 allele is common, in order to understand its potential role on therapeutic outcomes with PPI therapy. But the early evidence suggests that UM and RM are at risk for therapeutic failure, which is consistent with the PK literature on these phenotypes.

Collectively, the data support better outcomes in management of GERD and higher success rate of H. pylori eradication in IM and PM phenotypes compared to NM, RM, and UM phenotypes (Table 4) [59,60,62–64], which is consistent with

the higher intragastric pH achieved in patients with reduced CYP2C19 activity and higher PPI concentrations [77–79]. While many studies suggest this to be true regardless of the PPI used, some reports have suggested that the therapeutic outcomes are less influenced by genotype in PPIs with less dependence on CYP2C19 metabolism, namely rabeprazole and esomeprazole [71,73,80]. Nonetheless, other studies suggest CYP2C19 is important for all PPIs. We conclude that based on the current literature, CYP2C19 should be considered for all PPIs, recognizing that rabeprazole, based on its metabolic path, should be the least influenced by CYP2C19 variation.

4.2.3. CYP2C19 and adverse outcomes of PPIs

Multiple observational studies have linked the prolonged use of PPI to a multitude of adverse events including infections, electrolyte imbalances such as hypomagnesemia, kidney disease, osteoporosis, bone fractures, and dementia[81–89] (Table 5).

The associations between PPIs and increased frequency of infections including respiratory and gastro-enteric infections such as Clostridium difficile (C. difficile), are a major concern. One plausible explanation of these adverse events, especially infections, is that prolonged, PPI-induced acid suppression may result in alterations in the gut flora, as well as microbiome changes, leading to increased load of bacterial pathogens, and hence increasing the risk of infections [90,91]. A large meta-analysis (Table 5) including 43 studies found an association with incident and recurrent C. difficile and PPI use [81]. This prompted the FDA to issue a safety alert warning of C. difficile association with PPI use [92]. In addition to the associations with C. difficile infections, several links with enteric infections have been documented [93,94]. Respiratory infections such as community acquired pneumonia have been also linked to PPI use. A recent met-analysis of 26 studies reported 49% increase in the risk of community acquired pneumonia, which was at its highest during the first 30 days of PPI initiation [82]. Data also have shown associations between PPIs and increased upper respiratory tract infections and asthma exacerbation in pediatric population [83,95].

Another concerning adverse event is the association of PPI use with kidney disease. A recent analysis of patients from the Atherosclerosis Risk in Communities study (N = 10,439) who were followed for 13.9 years found that the prevalence of CKD is 50% higher in patients who used PPI compared to nonusers [84]. This association remained significant after performing a propensity-adjusted analysis. Additionally, there was a dose response association with increased doses of PPI and CKD. The association was replicated in another independent cohort from Geisinger Health system [84]. In addition to the association with CKD, PPI use has been associated with acute kidney injury (AKI). The rates of AKI and acute interstitial nephritis were 2.5 and 3 times higher in individuals who use PPI compared to nonusers, in a population-based analysis [85]. Additionally, PPI use has been linked to osteoporosis and fractures. A recent meta-analysis of 18 observational studies found 58%, 26%, and 33% greater risk of spine fracture, hip fracture, and fracture at any site, respectively, among PPI users compared to nonusers [86].

Hypomagnesemia has been associated with PPI use, which led to the FDA warning statement about hypomagnesemia. The use of PPI was associated with 40% higher risk of hypomagnesemia in PPI users compared to nonusers in a meta-analysis of ~110,000 patients [87]. PPIs use has been also linked to dementia risk. A recent 2016 analysis of observational data from Allgemeine Ortskrankenkassen (AOK), the largest German health mandatory insurer demonstrated a 44% increased risk of incident dementia in PPI users compared to nonusers, which was significant in a model adjusted for potential confounding factors [88].

Most alarming is the recent analysis of mortality risk using data from the Veteran Affairs (VA) national database [89]. The study demonstrated increased incidence of mortality in patients on PPIs compared to histamine 2 receptor antagonists (H2RAs). Using a high-dimensional propensity score analysis, PPI users had a 16% greater risk of all-cause mortality compared to H2Rs users. Additionally, PPI use was associated with a 23% higher mortality risk compared to patients who were not on any acid suppressive therapy. Importantly, the increase in mortality risk was associated with longer exposure to PPIs as compared to shorter duration (≤30 days).

While many of these epidemiological studies did not evaluate the influence of PPI dose, most of studies that evaluated doses, have shown that the documented risks are increased with higher PPI doses [84,89,94,96]. While these large epidemiological

Table 5. Summary of meta-analyses of PPI-associated adverse effect (AE).

Adverse effect	N	Average follow-up	Adjusted OR or HR (95%CI)	Was the dose-AE relationship examined
Clostridium Difficile[81]	313,000	NA	1.74 (1.47–2.85)	NA
Infectious gastroenteritis[94]	38,019	3.9 years	1.4 (1.20–1.50)	Higher average daily dose was associated with higher risk of infectious hospitalization
Community acquired pneumonia[82]	6,351,656	NA	1.49 (1.16–1.92)	Highest risk at 1 month regardless of dose
Chronic kidney disease[84]	10,482	13.9 and 6 years in discovery and replication	1.50 (1.11–1.90)	Higher dose was associated with higher risk
Acute kidney disease[85]	290,592	120 days	2.52 (2.27–2.79)	NA
Bone fracture[86]	244,109	≥ 4 years	1.33 (1.15–1.54)	NA
Hypomagnesemia[87]	109,798	NA	1.43 (1.08–1.88)	NA
Dementia[88]	73, 679	7 years	1.44 (1.36–1.52)	NA
Mortality[89]	2,886, 879	5.7 years	1.23 (1.22–1.24)	Higher mortality risk with longer duration compared to low duration (≤30 days)

N: number of patients in the study; NA: not reported; Median average follow up is reported in days or years; OR: odds ratio of outcome of interest in PPI users compared to nonusers; HR: hazards ratio of the outcome of interest in PPI users compared to nonusers

studies do not provide insight into the risk relative of *CYP2C19* genotype, given that there does appear to be a link between dose and risk, it is plausible that these PPI-related adverse events are linked to higher exposure to PPIs in patients with CYP2C19 PM/IM phenotype versus NM or RM/UM phenotypes.

Most pharmacogenetic studies conducted to date demonstrated the effect of genotype on PPI effectiveness, with few studies that investigated the genotype influence on adverse events. Only recently, through the epidemiologic studies (Table 5) described previously, have potential serious risks of PPIs been identified. Thus, the data are currently limited on the link between *CYP2C19* genotype and PPI associated adverse outcomes. However, two small studies point to the possibility of such a link. Lima et al. evaluated the association between *CYP2C19* genotype and respiratory adverse events including upper respiratory tract infections and sore throats, using data from a clinical trial of pediatric patients who were treated with lansoprazole [97]. Results of this study showed that the average plasma concentrations in IM/PM (defined as having ≥ one *2, *3, *8, or *9 alleles; N = 45) were higher than NM (without no function alleles, N = 91) (207 ± 179 ng/mL vs 132 ± 141 ng/mL ($p = 0.04$)). This was also associated with higher frequency of upper respiratory infections in IM/PM than NM, which was also higher than placebo (69% vs 60% vs 48%, respectively p trend = 0.0039). These data suggest that the incidence of respiratory adverse events in PM may be related to higher drug concentrations, a preventable adverse event that can be mitigated by genotype-adjusted dosing in IM/PM genotype.

Another study by Lang et al. [98] investigated the association between *CYP2C19* genotype and asthma control (assessed by Asthma Control Questionnaire (ACQ)) in pediatric patients who were classified as IM/PM or NM and were treated with lansoprazole. At 6 months, IM/PM phenotype was associated with worsened asthma as compared to NM phenotype (+0.16 vs. −0.13; p = 0.02) and placebo (+0.16 vs. −0.23; $p < 0.01$) at 6 months. The authors proposed that the worsening asthma control in IM/PM at 6 months may be due to upper respiratory tract infections, which was previously documented to be higher [97] within the same cohort with IM/PM phenotype .

5. Available guidelines for clinical implementation of PPI pharmacogenetics (PGX)

FDA labeling: On the basis of *CYP2C19* genotype effect on PPIs, the FDA labeling of PPIs contains pharmacogenetic information to highlight the impact of genotype on PK parameters of the six PPIs, but do not provide specific dose change recommendations. This information may be easily accessed through the drug Labels section of PharmGKB [31] (http://www.pharmgkb.org).

The CPIC [9] and DPWG [10,11] publish guidelines, whose primary focus is to provide guidance on the use of genetic information to guide prescribing practices, should these genetic information become available. Currently, DPWG provide dose recommendations for four out of six PPIs: omeprazole, esomeperazole, pantoprazole, and lansoprazole. They recommend the highest dose changes for PPIs whose metabolisms are more dependent on CYPC19. In the case of UM/

RM phenotypes, they recommend a dose increase of 400%, 200%, and 100–200% for pantoprazole, lansoprazole, and omeprazole, respectively [11]. For esomeprazole whose metabolism is less dependent on CYPC19, they recommend a 50–100% increase in dose for individuals with UM/RM phenotype. They however do not provide recommendations for patients with IM/PM status. While there is not currently a CPIC guideline for PPIs, such a guideline is in process by the CPIC group (personal communication, Mary Relling, CPIC PI).

Other recommendations for genotype-guided dosing were provided by Lima et al. [99]. The authors recommended a dose increase of 50–100% for patients with RM and UM, respectively, regardless of PPI used. For IM and PM, they recommend a dose reduction by 60%. In their recommendations, they did not take into account differences in CYP2C19 involvement in PPIs metabolism, and therefore, recommendations were provided on an equal basis for all PPIs.

6. Potential clinical benefits of pharmacogenetics-guided approaches with PPIs

Implementation of pharmacogenetics in clinical practice has made progress over the years, and numerous institutions within the US, including our institutions, have embraced pharmacogenetic-guided approaches, leading to the implementation of several gene-drug pairs, for which evidence and genotype-guided recommendations exist [100–102]. Implementation approaches generally have ranged from genotyping a single gene of a given gene-drug pair, to a preemptive, multi SNP/gene-based testing panel [101–104]. The latter is viewed by many as the most efficient, and logical means to a sustainable clinical implementation, as it would allow genomic information to be generated once and deposited within the electronic health record (EHR) as discreet data to be used at clinicians' discretion at any point of a patient's life. The most common implementation at this point is *CYP2C19*-clopidogrel. This means that *CYP2C19* genotype information may be readily available for patients within institutions who implemented *CYP2C19* pharmacogenetics.

Currently, under the NIH supported, Implementing GeNomics in PracTicE (IGNITE), the Univeristy of Florida and Vanderbilt University are evaluating PPI efficacy and safety in the approximately 10,000 patients in the respective health systems who have received a *CYP2C19* genotype and been treated with a PPI. Using a computable phenotype approach, the research teams will use data within the EHR to evaluate whether there are relationships between *CYP2C19* genotype and PPI-related outcomes.

Other ongoing efforts include those led by Nemours Children's Health System and UF to test the implementation of *CYP2C19*-genotype-guided PPI therapy by comparing a genotype-guided versus conventional standard of care approach. The Implementation of PPI Medication PGX Testing (PGX) at Nemours Children's Health System (Clinical Trial Identifier: NCT02794844) is designed to evaluate *CYP2C19* genotype-guided treatment of PPIs in children. The study recruited children 2–17 years old diagnosed with GERD or other acid-related conditions for which PPIs are prescribed. Patients are genotyped for *CYP2C19* using point

of care Spartan™ RX *CYP2C19* system (Spartan Bioscience), and the metabolic phenotype is inferred based on the genotype. PPI is then prescribed based on CYP2C19 metabolic status. Primary outcomes of the study will include percent of adverse events, as well as improved or worsened clinical symptoms that are recorded pre and post genotype-guided treatment.

At the University of Florida, we are also conducting a pilot implementation (Clinical Trial Identifier: NCT0293082).

Data from these studies and others will advance the evidence base for a genotype-guided approach to PPI treatment, and if the studies document a benefit, may lead to more widespread clinical implementation of use of *CYP2C19* genotype to guide dosing and treatment decisions for PPIs.

7. Conclusion

The data in aggregate support the potential benefit for implementing *CYP2C19* genotype to guide PPI use and dosing in clinical practice. Genotype-guided dosing of PPIs is likely to optimize GERD control and H. pylori eradication, as well as reduce risk for PPI-related adverse events. The evidence supporting *CYP2C19*-guided PPI therapy and documentation of benefit for this approach seems likely to emerge in the near future.

8. Expert opinions

The literature summarized herein provide clear evidence for a relationship between *CYP2C19* genotype-inferred phenotype, PPI PKs, and PPI efficacy, as defined by intragastric pH and related measures, GERD control and H. pylori eradication. Specifically, at traditional doses there is compelling evidence that PM have the highest drug concentrations and greatest response rates, with IM, NM, RM and UM having progressively lower drug concentrations and poorer response rates with standard doses. This is particularly true for omeprazole, lansoprazole and pantoprazole, which are highly dependent on CYP2C19 for their metabolism, with a large body of evidence documenting the effect of *CYP2C19* genotype on PK/PD and therapeutic outcomes of these drugs. While less data exist on the influence*CYP2C19* genotype on dexlansoprazole, similar effects of the genotype on deslansoprazole drug levels and/or therapeutic outcomes are likely to be observed given its similar metabolic pathway to its racemate (lansoprazole).

When it was recognized in the early 2000s that response rates were lower in NM, then doses were increased in all patients, to ensure adequate treatment for these patients with NM phenotype. While current standard PPI dosing may be effective for patients with normal CYP2C19 metabolizing activity (NM), it may actually be higher than effective therapeutic doses in patients with reduced or nonfunctional CYP2C19 phenotypes (IM or PM), leading to excessive drug concentrations, yet may be subtherapeutic for patients with rapid or ultra-metabolizing CYP2C19 phenotypes (RM/UM).

Historically there have been few concerns about dose escalation of PPIs, with the attitude that they were extremely safe drugs. However, recent epidemiological studies have suggested this may not be the case, with a number of serious adverse outcomes linked to PPI use. Importantly some of these studies document a link between the risk under study and prolonged duration or dose [84,89,94], suggesting that increased drug concentrations may increase the risk of PPI associated adverse events. If this is the case, there may also be a link between *CYP2C19* PM genotype and PPI associated risks as a result of increased drug concentrations. This was illustrated in the small genetic study within pediatrics, documenting the association between PM, higher PPI drug concentrations, increased risk of infection and worsened asthma control.

While the literature base for the increased allele (*17) is considerably smaller than that for the no function alleles, it is highly plausible that the approximately one-third of those of European and African ancestry who carry *CYP2C19**17 (RM or UM) are at risk of therapeutic failure due to inadequate drug concentrations of PPIs. This raises a question if the standard dosing of currently used PPIs is sufficient in the approximately 30% of patients who are carriers of *CYP2C19**17. Further, about one-third of those of European and African ancestry and greater than 50% of Asians carry a no function allele that means they are likely to respond to lower doses of PPIs. If there is a link between drug exposure and risk, then higher than necessary doses in these individuals might also be increasing their risk for adverse outcomes to traditional PPI doses. On the basis of the literature evaluated and presented earlier, we propose that pharmacogenetic testing for *CYP2C19* may be of great clinical value. The consistency of the data in the literature, including data from meta-analyses, support this view.

The use of intragastric pH studies is not clinically indicated to monitor pH suppression. However, they are only indicated to evaluate refractoriness to PPIs in patients with GERD. Currently, the guidelines for diagnosis and management of GERD support empiric PPI dose escalation in patients with refractory GERD prior to pH studies such as pH or pH-impedance testing [1]. Additionally, the guidelines do not recognize the involvement of pharmacogenetic factors in PPI metabolism. Similarly, the current North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) treatment guidelines support PPI dose increase for children with refractory GERD prior to esophageal pH testing [105]. Adopting a genotype-guided program for dosing of PPIs would allow clinicians to find individualized doses for patients and strike the balance between failed PPI therapy due to inadequate doses or adverse events as a result of empirical overprescribing approaches [106].

While an AUC ratio between PM/NM may range between 6.0 and 10 for PPIs that are extensively metabolized by CYP2C19 (omeprazole, pantoprazole and lansoprazole), this ratio is much lower (AUC PM/NM range 1.5 and 3.0) for PPIs with less CYP2C19 metabolism, such as esomeprazole and rabeprazole, respectively [45,46,50,107]. Additionally, while the *CYP2C19*- inferred metabolic phenotype was consistently associated with acid suppression and therapeutic outcomes for PPIs with extensive CYP2C19 metabolism, it is not always the case with esomeprazole and rabeprazole. While some studies have documented genotype dependent differences in acid suppression and outcomes, others showed no relation

between genotype and degree of acid suppression or outcomes for rabeprazole and esomeprazole [40,48,53,71,73,108]. This may be attributed in part to their lesser dependence on CYP2C19 metabolism, the higher potency of these PPIs [53,109,110], compared to other PPIs, lack of *17 testing [71], or combination of these factors, leading to diminished differences between the different CYP2C19 metabolizer phenotypes. Although the CYP2C19 genotype dependent increase of AUC in patients with PM phenotype may be less for PPIs that are minimally metabolized by CYP2C19, such as rabeprazole, the elevation in drug concentrations may still pose a risk of adverse events given its high potency. This may argue for the value of genotype-guided dose alterations, even in PPIs with low CYP2C19 involvement such as rabeprazole. The differences in CYP2C19 contribution in PPI metabolism has raised the question if genotype-guided dosing should be performed equally for all PPIs, or perhaps at a magnitude that is proportional to the fractional metabolic pathway of CYP2C19. While it seems logical that dose alterations should be smaller or perhaps not necessary in PPIs with minimal CYP2C19 involvement, such data to support PPI-specific, genotype-guided dosing are limited. Currently, the DPWG provide recommendations on dose escalation for patients with UM phenotype to varying degrees for omeprazole, pantoprazole, lansoprazole and esomeprazole. They do not provide recommendations for dose decrease in IM/PM phenotypes for any of the PPIs. Other recommendations for genotype-guided dose increase or decrease for all PPIs similarly come from the 2014 review by Lima et al. [99]. Future PK/PD studies that take into consideration not only the genotype-dependent PK parameters, but also the potency of the available PPIs are warranted to support PPI-specific dose alteration based on genotype. Further data from studies using a CYP2C19 genotype-guided approaches to PPI therapy are likely to refine the recommendations and provide insights into PPI-specific, genotype-guided dosing.

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Declaration of interest

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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