

Supplement to:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2C19* and Proton Pump Inhibitor Dosing

John J. Lima¹, Cameron D. Thomas², Julia Barbarino³, Zeruesenay Desta⁴, Sara L. Van Driest⁵, Nihal El Rouby^{2,6}, Julie A. Johnson², Larisa H. Cavallari², Valentina Shakhnovich^{7,8,9}, David L. Thacker^{10,11}, Stuart A. Scott^{12,13}, Matthias Schwab^{14,15,16}, Chakradhara Rao S Uppugunduri^{17,18}, Christine M. Formea¹⁹, James P. Franciosi^{20,21}, Katrin Sangkuhl³, Andrea Gaedigk⁷, Teri E. Klein³, Roseann S. Gammal^{22,23}, Takahisa Furuta²⁴

¹ Center for Pharmacogenomics and Translational Research, Nemours Children's Health, Jacksonville, FL, USA

² Department of Pharmacotherapy and Translational Research, and Center for Pharmacogenomics and Precision Medicine, College of Pharmacy, University of Florida, Gainesville, FL, USA

³ Department of Biomedical Data Science, Stanford University, Stanford, CA, USA

⁴ Department of Medicine, Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA

⁵ Departments of Pediatrics and Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA

⁶ Division of Pharmacy Practice & Administrative Sciences, University of Cincinnati James Winkle College of Pharmacy, Cincinnati, OH, USA

⁷ Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children's Mercy Kansas City and University of Missouri Kansas City School of Medicine, Kansas City, MO, USA

⁸ Division of Gastroenterology, Hepatology, and Nutrition, Children's Mercy Kansas City, Kansas City, MO, USA

⁹ Center for Children's Healthy Lifestyles & Nutrition, Kansas City, MO, USA

¹⁰ Department of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, IN, USA

¹¹ Translational Software, Bellevue, WA, USA

¹² Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

¹³ Sema4, Stamford, CT, USA

¹⁴ Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

¹⁵ Department of Clinical Pharmacology, University Hospital, Tuebingen, Germany

¹⁶ Department of Pharmacy and Biochemistry, University of Tuebingen, Tuebingen, Germany

¹⁷ CANSEARCH Research Laboratory, Department of Paediatrics, Gynaecology and Obstetrics, Faculty of Medicine, University of Geneva, Geneva, Switzerland

¹⁸ Oncology-Hematology Unit, Department of Paediatrics, Gynaecology and Obstetrics, Geneva University Hospital, Geneva, Switzerland

¹⁹ Department of Pharmacy Services and Intermountain Precision Genomics, Intermountain Healthcare, Salt Lake City, UT, USA

²⁰ Division of Gastroenterology, Hepatology and Nutrition, Nemours Children's Hospital, Orlando, FL

²¹ Department of Pediatrics, University of Central Florida College of Medicine, Orlando, FL, USA

²² Department of Pharmacy Practice, MCPHS University School of Pharmacy, Boston, MA, USA

²³ Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, USA

²⁴ Center for Clinical Research, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

TABLE OF CONTENTS

GUIDELINE UPDATES	4
LITERATURE REVIEW	4
GENETIC TEST INTERPRETATION	4
AVAILABLE GENETIC TEST OPTIONS	5
LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE	6
STRENGTH OF RECOMMENDATIONS	8
RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT	9
PEDIATRIC CONSIDERATIONS	12
TABLE S1. EVIDENCE LINKING <i>CYP2C19</i> TO OMEPRAZOLE PHENOTYPE	14
TABLE S2. EVIDENCE LINKING <i>CYP2C19</i> TO LANSOPRAZOLE PHENOTYPE	22
TABLE S3. EVIDENCE LINKING <i>CYP2C19</i> TO PANTOPRAZOLE PHENOTYPE	27
TABLE S4. EVIDENCE LINKING <i>CYP2C19</i> TO DEXLANSOPRAZOLE PHENOTYPE	30
TABLE S5. EVIDENCE LINKING <i>CYP2C19</i> TO ESOMEPRAZOLE PHENOTYPE	31
TABLE S6. EVIDENCE LINKING <i>CYP2C19</i> TO RABEPRAZOLE PHENOTYPE	33
TABLE S7. EVIDENCE LINKING <i>CYP2C19</i> TO PROTON PUMP INHIBITOR PHENOTYPE (MIXED COHORT)	38
TABLE S8. DOSING RECOMMENDATIONS FOR ESOMEPRAZOLE AND RABEPRAZOLE BASED ON <i>CYP2C19</i> PHENOTYPE	41
REFERENCES	42

GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C19* and proton pump inhibitor (PPI) dosing is published in full on the CPIC website (1). Relevant information will be reviewed periodically and updated guidelines published online.

LITERATURE REVIEW

The PubMed® database (1966 to April 2018) was searched for the following keywords: (CYP2C19 OR cytochrome P450 2C19) AND (proton pump inhibitor OR PPI OR *omeprazole OR *lansoprazole OR pantoprazole OR rabeprazole). The search was limited to studies conducted in humans and written in the English language, and review articles were excluded. Using these search terms, 831 publications were identified. Study inclusion criteria included publications that incorporated analyses for the association between *CYP2C19* genotype and PPI pharmacokinetic parameters or PPI-related clinical outcomes. Following the application of these criteria, 244 publications were reviewed and included in the evidence tables (**Tables S1-S7**).

GENETIC TEST INTERPRETATION

The haplotype, or star (*) allele name, is determined by a specific single nucleotide polymorphism (SNP) or a combination of SNPs that are interrogated in the genotyping analysis. Numerous deletion and duplication events affecting the *CYP2C* gene locus have been described (see Botton et al for a comprehensive summary (2) and the PharmVar Structural Variation document at <https://www.pharmvar.org/gene/CYP2C19>). Many of the gene deletion and duplication events involve more than one of the *CYP2C* genes and can even encompass a large number of genes within this chromosomal region. To date, PharmVar has defined deletion events

encompassing the entire *CYP2C19* gene under the *CYP2C19**36 designation and those with partial *CYP2C19* gene deletion events (that include at least exon 1) as *CYP2C19**37 (2). *CYP2C* copy number variants appear to be rare and are typically not part of pharmacogenetic testing.

The genotypes that constitute the haplotype, or star (*) alleles for *CYP2C19*, and the rs# for each of the specific genomic nucleotide alterations that define the alleles, are described in the ***CYP2C19* Allele Definition Table** online (1, 3). The genotype results are generally reported as a diplotype, which includes one maternal and one paternal star allele (e.g., *1/*2). The *CYP2C19* function associated with each of the common star alleles is summarized in the ***CYP2C19* Allele Functionality Table** online (1, 3).

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. The Genetic Testing Registry provides a central location for voluntary submission of genetic test information by providers and is available at <http://www.ncbi.nlm.nih.gov/gtr>. Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (4). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables adhere to these allele nomenclature standards. Moreover, these tables (***CYP2C19* Allele Definition Table**, ***CYP2C19* Allele Functionality Table**, and ***CYP2C19* Allele Frequency Table**) may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles (1, 3). Furthermore, the Association for Molecular Pathology has published a recommendation for the key attributes of alleles

recommended for clinical testing and a minimum set of variants that should be included in clinical genotyping assays for *CYP2C19* (5).

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Tables S1-S7** is graded on a scale of high, moderate, and weak (6) based upon the level of evidence:

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality or consistency of the individual studies, generalizability to routine practice, or the indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

To determine these levels of evidence for major finding statements, individual studies are first evaluated using a structured framework:

1. Quality elements for individual studies are evaluated as yes, no, partially, unclear, or not relevant:
 - Confounders and use of concomitant medications with possible drug interactions are reported and potential impact on the major finding are analyzed and reported.
 - Phenotype assignments (when comparing phenotype groups) are based on CPIC phenotype assignment or similar.
 - Reported data are based on steady-state kinetics where appropriate.

- Sample size adequate to assess difference between genotype/phenotype groups, especially for negative findings.
 - Adequate phenotyping or genotyping methods:
 - States all genetic variants screened
 - Alleles tested are adequate to determine “wild-type” genotype
 - Adequate phenotyping or genotyping method used
 - Appropriate attainment of samples
 - Defines how * alleles are defined, if applicable
 - Clearly states which genotypes were found in the study
 - Race and/or ancestry is discussed and appropriately considered.
 - Outcome definition clearly defined and measured.
 - Appropriate statistics performed.
2. The individual study is rated with respect to how well it supports the major finding statement:
- First, it is determined whether the study supports the major finding statement or does not support it.
 - Second, a qualifier is added to the statement (if needed) based on the quality elements listed above:
 - **Some study quality flaws:** Enough of the items in step 1 are rated “partially,” “unclear,” or “no” to introduce some uncertainty about the validity of the conclusions.

- **Major study quality flaws:** Enough of the items in step 1 are rated “partially,” “unclear,” or “no” to introduce serious uncertainty about the validity of the conclusions.
- **No qualification on statement:** If few items in step 1 are rated as “partially,” “unclear,” or “no.”
- There are six possible ratings for individual studies:
 - Supports the statement
 - Supports the statement but with some quality flaws
 - Supports the statement but with major quality flaws
 - Does not support the statement
 - Does not support the statement but with some quality flaws
 - Does not support the statement but with major quality flaws

STRENGTH OF RECOMMENDATIONS

CPIC’s therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include *in vivo* pharmacokinetic and pharmacodynamic data, *in vitro* enzyme activity of tissues expressing wild-type/reference or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for recommendations adopted from the rating scale for evidence-based guidelines on the use of antiretroviral agents (7):

- **Strong** recommendation for the statement: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Moderate** recommendation for the statement: There is a close or uncertain balance as to whether the evidence is high quality and the desirable effects clearly outweigh the undesirable effects.
- **Optional** recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
- **No recommendation:** There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (8-13). See <https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/> for resources to support the adoption of CPIC guidelines within an EHR (1, 14). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common

starting point for incorporating *CYP2C19* genotype results in an EHR to guide proton pump inhibitor dosing.

Effective incorporation of pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (15). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main manuscript; *CYP2C19* Diplotype to Phenotype Table** (1, 3)). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient’s summary section; these phenotypes are best stored in the EHR at the “person level” rather than at the date-centric “encounter level”. Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **PPI Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts; <https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/>) (16, 17).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include complete diplotype to phenotype translation tables, diagram(s) that illustrate how *CYP2C19* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see <https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/>) (1, 18).

Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (see <https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19> (1)).

There are some unique implementation challenges associated with *CYP2C19*/PPIs given the indication-specific recommendations (increased dose for *H. pylori* infection and erosive esophagitis) for *CYP2C19* RMs and NMs and time-dependent recommendations (short-term vs long-term use >12 weeks) for *CYP2C19* IMs, *CYP2C19* likely IMs, *CYP2C19* PMs, and *CYP2C19* likely PMs. CDS post-test alert language is provided for all *CYP2C19* phenotypes; however, the possibility of alert fatigue must be considered given the frequency with which PPIs are prescribed. Considering that for most initial PPI prescriptions the recommendation will be to initiate standard dosing, pre-test alerts are not recommended to fire for all PPI orders. Given these challenges, implementation will ultimately be institution-specific and may require creative solutions. Alternative CDS solutions include incorporating an option to order *CYP2C19* genotype into disease-specific order sets (e.g., for *H. pylori* infection and/or erosive esophagitis); custom-built order sets that include PPIs for specific indications (e.g., *H. pylori* infection and/or erosive esophagitis) that account for known *CYP2C19* results; limit pre-test and/or post-test alerts to providers within a specific specialty area (e.g., gastrointestinal specialists); and include pre-test and/or post-test alerts when all the required elements for a specific indication are present (e.g., alert will fire only when all medications for the treatment of *H. pylori* are added to the

patient's active medication list or *H. pylori* infection and/or erosive esophagitis are in the patient's problem list). See the pre- and post-test alert tables for examples of CDS alerts (1).

PEDIATRIC CONSIDERATIONS

PPIs are some of the most commonly prescribed drugs for pediatric populations, and prescription rates continue to rise (19-21). PPIs are available over-the-counter (without prescriptions) in some countries. In children younger than 18 years of age, PPIs currently have U.S. Food and Drug Administration (FDA)-approved indications for the short-term treatment of symptomatic gastroesophageal reflux disease (GERD), healing of erosive esophagitis, treatment of peptic ulcer disease, and for eradication of *H. pylori* as part of a multi-drug regimen (22-24). Despite current lack of FDA approval for the indication of eosinophilic esophagitis, PPI therapy is now considered standard of care for this condition in North America and Europe (25). Off-label use of long-term PPI therapy in children is common, and there are increasing concerns that PPIs are over-utilized in pediatric populations (26, 27). Esomeprazole has been FDA-approved for infants as young as one month of age only for confirmed erosive esophagitis, yet many PPIs are frequently prescribed incorrectly for symptoms suspected to be secondary to GERD without proven benefit. PPI therapy has been studied in children with respiratory symptoms, sleep disorders, and excessive crying, with minimal benefit demonstrated (28-30).

There are emerging concerns that PPI therapy use (and/or misuse) is associated with numerous side effects including, but not limited to, gastrointestinal and respiratory infections, malabsorption of vitamins and minerals, bone fracture, and possible association to chronic diseases such as celiac disease and chronic kidney disease (31-36). PPI therapy did not show

benefit in children with asthma in terms of lung function but did demonstrate increased rates of respiratory infections (37), highlighting this specific side effect.

CYP2C19 enzyme function is reported to be very low during early fetal life, consistent with very low apparent clearance of PPIs in preterm neonates and term infants less than 2-3 months of age, but clearance is consistent with adult values after that age (38-40). There is emerging evidence for the influence of CYP2C19 function on PPI pharmacokinetics and response in children (41-46). CYP2C19 RM or UM phenotypes have been associated with decreased therapeutic efficacy compared to PM and NM phenotypes when treating children with GERD and eosinophilic esophagitis (47-50). The CYP2C19 PM phenotype has been associated with higher rates of pediatric respiratory and gastrointestinal infections than NM, RM, or UM phenotypes (51). There is one report of increased infection events in infants and young children treated with PPIs who are CYP2C19 NMs versus UMs (52). A recent pilot study of *CYP2C19* genotype-guided dosing of PPI medications in children has been promising, and additional studies are ongoing (53, 54). These data support optimization of PPIs therapy in infants and children over one year of age based on *CYP2C19* genotype data, with weaker evidence to support genotype-guided dosing in pre-term infants or infants less than 2-3 months of age (55).

TABLE S1. EVIDENCE LINKING *CYP2C19* TO OMEPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of omeprazole as compared to IMs.	Ieiri, <i>et al.</i> 1996 (56) Herrlin, <i>et al.</i> 1998 (57) Furuta, <i>et al.</i> 1999 (58) Furuta, <i>et al.</i> 1999 (59) Sakai, <i>et al.</i> 2001 (60) Shirai, <i>et al.</i> 2001 (61) He, <i>et al.</i> 2003 (62) Yin, <i>et al.</i> 2004 (63) Rosemary, <i>et al.</i> 2005 (64) Ohnishi, <i>et al.</i> 2005 (65) Qiao, <i>et al.</i> 2006 (66) Shimizu, <i>et al.</i> 2006 (67) Uno, <i>et al.</i> 2007 (68) Wang, <i>et al.</i> 2007 (69) Hu, <i>et al.</i> 2007 (70) Wang, <i>et al.</i> 2010 (71) Shiohira, <i>et al.</i> 2011 (72) Shiohira, <i>et al.</i> 2012 (73) Yamada, <i>et al.</i> 2013 (74) Payan, <i>et al.</i> 2014 (75) Park, <i>et al.</i> 2017 (76)	High
Clinical	CYP2C19 PMs (as determined by phenotyping) are associated with decreased metabolism of omeprazole as compared to IMs.	Chang, <i>et al.</i> 1995 (77)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of omeprazole as compared to NMs.	Rost and Roots 1996 (78) Ieiri, <i>et al.</i> 1996 (56)	High

		<p> Furuta, <i>et al.</i> 1999 (58) Furuta, <i>et al.</i> 1999 (59) Zhou, <i>et al.</i> 1999 (79) Sakai, <i>et al.</i> 2001 (60) Shirai, <i>et al.</i> 2001 (61) Kita, <i>et al.</i> 2002 (80) He, <i>et al.</i> 2003 (62) Yin, <i>et al.</i> 2004 (63) Rosemary, <i>et al.</i> 2005 (64) Ohnishi, <i>et al.</i> 2005 (65) Ieiri, <i>et al.</i> 2005 (81) Qiao, <i>et al.</i> 2006 (66) Shimizu, <i>et al.</i> 2006 (67) Uno, <i>et al.</i> 2007 (68) Wang, <i>et al.</i> 2007 (69) Niioka, <i>et al.</i> 2007 (82) Hu, <i>et al.</i> 2007 (70) Uno, <i>et al.</i> 2008 (83) Chen, <i>et al.</i> 2009 (84) Chaudhry, <i>et al.</i> 2009 (85) Wang, <i>et al.</i> 2010 (71) Shiohira, <i>et al.</i> 2011 (72) Shiohira, <i>et al.</i> 2012 (73) Yamada, <i>et al.</i> 2013 (74) Payan, <i>et al.</i> 2014 (75) Park, <i>et al.</i> 2017 (76) </p>	
Clinical	CYP2C19 PMs (as determined by phenotyping) are associated with decreased metabolism of omeprazole as compared to NMs.	<p> Rost, <i>et al.</i> 1992 (86) Yasuda, <i>et al.</i> 1995 (87) Tybring, <i>et al.</i> 1997 (88) Bottiger, <i>et al.</i> 1997 (89) Andersson, <i>et al.</i> 1998 (90) Mihara, <i>et al.</i> 1999 (91) Tassaneeyakul, <i>et al.</i> 2000 (92) </p>	High

Clinical	CYP2C19 PMs are associated with decreased metabolism of omeprazole as compared to RMs.	Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 PMs are associated with decreased metabolism of omeprazole as compared to UMs.	Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of omeprazole as compared to NMs.	Chang, <i>et al.</i> 1995 (93) Marinac, <i>et al.</i> 1996 (94) Herrlin, <i>et al.</i> 1998 (57) Furuta, <i>et al.</i> 1999 (59) Furuta, <i>et al.</i> 1999 (58) Shu, <i>et al.</i> 2000 (95) Sakai, <i>et al.</i> 2001 (60) Kim, <i>et al.</i> 2002 (96) He, <i>et al.</i> 2003 (62) Kearns, <i>et al.</i> 2003 (97) Yin, <i>et al.</i> 2004 (63) Rosemary, <i>et al.</i> 2005 (64) Shimizu, <i>et al.</i> 2006 (67) Uno, <i>et al.</i> 2007 (68) Wang, <i>et al.</i> 2007 (69) Niioka, <i>et al.</i> 2007 (82) Hunfeld, <i>et al.</i> 2008 (98) Yamada, <i>et al.</i> 2013 (74) Roman, <i>et al.</i> 2014 (99) Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 IMs (as determined by phenotyping) are associated with decreased metabolism of omeprazole as compared to NMs.	Chang, <i>et al.</i> 1995 (77)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of omeprazole as compared to RMs.	Roman, <i>et al.</i> 2014 (99) Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of omeprazole as compared to UMs.	Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 NMs are associated with decreased metabolism of omeprazole as compared to RMs.	Sim, <i>et al.</i> 2006 (100) Hunfeld, <i>et al.</i> 2008 (98) Roman, <i>et al.</i> 2014 (99)	Weak

		Payan, <i>et al.</i> 2014 (75)	
Clinical	CYP2C19 NMs are associated with decreased metabolism of omeprazole as compared to UMs.	Sim, <i>et al.</i> 2006 (100) Baldwin, <i>et al.</i> 2008 (101) Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 RMs are associated with decreased metabolism of omeprazole as compared to UMs.	Payan, <i>et al.</i> 2014 (75)	Moderate
Clinical	CYP2C19 PMs are associated with decreased metabolism of omeprazole as compared to IMs+NMs.	Chang, <i>et al.</i> 1995 (93) Ishizawa, <i>et al.</i> 2005 (102) Kuhlmann, <i>et al.</i> 2014 (103) Nazir, <i>et al.</i> 2015 (104) Nazir, <i>et al.</i> 2016 (105)	Moderate
Clinical	CYP2C19 PMs have decreased metabolism of omeprazole as compared to NMs+RMs+UMs.	Zhao, <i>et al.</i> 2018 (46)	Moderate
Clinical	CYP2C19 PMs+IMs are not associated with altered metabolism of omeprazole as compared to NMs.	Denisenko, <i>et al.</i> 2017 (106)	Weak
Clinical	CYP2C19 PMs+IMs are not associated with altered metabolism of omeprazole as compared to UMs.	Denisenko, <i>et al.</i> 2017 (106)	Weak
Clinical	CYP2C19 IMs have decreased metabolism of omeprazole as compared to NMs+RMs+UMs.	Zhao, <i>et al.</i> 2018 (46)	Moderate
Clinical	CYP2C19 NMs are associated with decreased metabolism of omeprazole as compared to RMs+UMs.	Denisenko, <i>et al.</i> 2017 (106)	Weak
Clinical	<i>CYP2C19</i> is associated with omeprazole metabolism when comparing PMs vs IMs vs NMs.	Roh, <i>et al.</i> 1996 (107) Sagar, <i>et al.</i> 1998 (108) Furuta, <i>et al.</i> 1999 (58) Furuta, <i>et al.</i> 1999 (59) Roh, <i>et al.</i> 2004 (109) Isaza, <i>et al.</i> 2007 (110)	Moderate
Clinical	<i>CYP2C19</i> is related to omeprazole metabolism when comparing PMs vs IMs vs NMs vs RMs.	Koukoula, <i>et al.</i> 2017 (111)	Weak
Clinical	<i>CYP2C19</i> is associated with omeprazole metabolism when comparing PMs vs IMs vs NMs vs RMs+UMs.	Xavier, <i>et al.</i> 2016 (112)	Weak

Clinical	<i>CYP2C19</i> is not associated with omeprazole metabolism when comparing PMs vs IMs vs NMs vs RMs vs UMs.	Kearns, <i>et al.</i> 2010 (113)	Weak
Clinical	<i>CYP2C19</i> is not associated with omeprazole metabolism when comparing IMs vs NMs vs RMs.	Chwiesko, <i>et al.</i> 2016 (114)	Weak
Clinical	<i>CYP2C19</i> is not associated with omeprazole metabolism when comparing IMs vs NMs vs RMs+UMs.	Chwiesko, <i>et al.</i> 2016 (114)	Weak
In vitro	<i>CYP2C19</i> *9, *10, *16, *19 and *26 are associated with decreased metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Hanioka, <i>et al.</i> 2008 (115) Lee, <i>et al.</i> 2009 (116) Wang, <i>et al.</i> 2011 (117) Langae, <i>et al.</i> 2014 (118)	Weak
In vitro	<i>CYP2C19</i> *1B, *11, *13, *15 and *18 are not associated with altered metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Hanioka, <i>et al.</i> 2008 (115) Wang, <i>et al.</i> 2011 (117)	Weak
In vitro	<i>CYP2C19</i> *3, *5, *6, and *24 are associated with absent metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Wang, <i>et al.</i> 2011 (117) Dai, <i>et al.</i> 2015 (119) Lau, <i>et al.</i> 2017 (120)	Weak
In vitro	<i>CYP2C19</i> *8 is associated with decreased metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Wang, <i>et al.</i> 2011 (117)	Weak
In vitro	<i>CYP2C19</i> *14 and *32 (H99R) are not associated with altered metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Wang, <i>et al.</i> 2011 (117) Dai, <i>et al.</i> 2015 (119)	Weak
In vitro	<i>CYP2C19</i> *23, *29 (K28I), *30, *31 (H78Y) and *33 (D188N) are associated with decreased metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Dai, <i>et al.</i> 2015 (119) Lau, <i>et al.</i> 2017 (120)	Weak
In vitro	<i>CYP2C19</i> *2B (E92D), *2C (A161P), *2E (M271I), *2F (D341N), *2G (D360V), *2H (H396D), *2J (K421Q), *3B (D360N) and *3C (M136K) are associated with decreased metabolism of omeprazole as compared to <i>CYP2C19</i> *1.	Wang, <i>et al.</i> 2011 (117) Dai, <i>et al.</i> 2015 (119)	Weak
Efficacy			
Remission or Healing			
Clinical	<i>CYP2C19</i> IMs are associated with increased remission of reflux when treated with omeprazole as compared to NMs.	Zendehdel, <i>et al.</i> 2010 (121)	Weak
Clinical	<i>CYP2C19</i> IMs are associated with increased healing rate of ulcers when treated with omeprazole as compared to NMs.	Ando, <i>et al.</i> 2005 (122) Ando, <i>et al.</i> 2008 (123)	Weak

Clinical	CYP2C19 NMs have a decreased healing rate of ulcers when treated with omeprazole.	Hizawa, <i>et al.</i> 2006 (124)	Weak
Clinical	CYP2C19 IMs have a decreased healing rate of ulcers when treated with omeprazole compared to CYP2C19 NMs.	Okamura, <i>et al.</i> 2013 (125)	Weak
Clinical	CYP2C19 RMs have a decreased healing rate of reflux when treated with omeprazole compared to CYP2C19 NMs.	Fukaya, <i>et al.</i> 2016 (126)	Weak
Clinical	CYP2C19 PMs are not associated with healing rate of ulcers when treated with omeprazole as compared to IMs+NMs.	Ji, <i>et al.</i> 2006 (127)	Weak
Clinical	<i>CYP2C19</i> is not associated with healing rate of reflux when treated with omeprazole when comparing PMs vs IMs vs NMs.	Ohkusa, <i>et al.</i> 2005 (128)	Weak
<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with omeprazole as compared to IMs.	Furuta, <i>et al.</i> 1998 (129) Lin, <i>et al.</i> 2017 (130)	Weak
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with omeprazole as compared to NMs.	Furuta, <i>et al.</i> 1998 (129) Chaudhry, <i>et al.</i> 2009 (85) Lin, <i>et al.</i> 2017 (130)	Moderate
Clinical	CYP2C19 IMs are associated with an increased <i>H. pylori</i> eradication rate when treated with omeprazole as compared to NMs	Furuta, <i>et al.</i> 1998 (129) Sapone, <i>et al.</i> 2003 (131) Miehlke, <i>et al.</i> 2006 (132) Sezgin, <i>et al.</i> 2014 (133) Lin, <i>et al.</i> 2017 (130)	Weak
Clinical	CYP2C19 PMs are associated with increased <i>H. pylori</i> eradication rate when treated with omeprazole as compared to IMs+NMs.	Tanigawara, <i>et al.</i> 1999 (134) Miwa, <i>et al.</i> 2001 (135) Yang, <i>et al.</i> 2011 (136)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with omeprazole as compared to NMs.	Sheu, <i>et al.</i> 2005 (137) Hong, <i>et al.</i> 2016 (138)	Moderate
Clinical	<i>CYP2C19</i> is associated with <i>H. pylori</i> eradication rate when treated with omeprazole when comparing PMs vs IMs vs NMs.	Furuta, <i>et al.</i> 1998 (129) Dojo, <i>et al.</i> 2001 (139) Inaba, <i>et al.</i> 2002 (140) Higuchi, <i>et al.</i> 2006 (141) Zhang, <i>et al.</i> 2010 (142) Nabinger, <i>et al.</i> 2016 (143)	Weak
Acid secretion indices			

Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with omeprazole as compared to IMs.	Furuta, <i>et al.</i> 1999 (58) Shirai, <i>et al.</i> 2001 (61) Shimatani, <i>et al.</i> 2003 (144) Hu, <i>et al.</i> 2007 (70) Wang, <i>et al.</i> 2010 (71) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146) Park, <i>et al.</i> 2017 (76)	Moderate
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with omeprazole as compared to NMs.	Furuta, <i>et al.</i> 1999 (58) Shirai, <i>et al.</i> 2001 (61) Shimatani, <i>et al.</i> 2003 (144) Sugimoto, <i>et al.</i> 2006 (147) Hu, <i>et al.</i> 2007 (70) Wang, <i>et al.</i> 2010 (71) Furuta, <i>et al.</i> 2010 (148) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146) Park, <i>et al.</i> 2017 (76)	Moderate
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with omeprazole as compared to NMs.	Furuta, <i>et al.</i> 1999 (58) Adachi, <i>et al.</i> 2000 (149) Sagar, <i>et al.</i> 2000 (150) Sagar, <i>et al.</i> 2000 (151) Sagar, <i>et al.</i> 2000 (150) Shirai, <i>et al.</i> 2001 (61) Sugimoto, <i>et al.</i> 2006 (147) Hu, <i>et al.</i> 2007 (70) Hunfeld, <i>et al.</i> 2008 (98) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146)	Moderate
Clinical	CYP2C19 NMs are not associated with altered acid secretion indices when treated with omeprazole as compared to RMs	Hunfeld, <i>et al.</i> 2008 (98) Chwiesko, <i>et al.</i> 2016 (114)	Weak
Clinical	CYP2C19 PMs have better acid secretion indices when treated with omeprazole as compared to IMs+NMs.	Yang, <i>et al.</i> 2011 (136)	Weak

Clinical	CYP2C19 NMs are not associated with altered acid secretion indices when treated with omeprazole as compared to RMs+UMs.	Chwiesko, <i>et al.</i> 2016 (114)	Weak
Clinical	<i>CYP2C19</i> is associated with acid secretion indices when treated with omeprazole when comparing PMs vs IMs vs NMs.	Furuta, <i>et al.</i> 1999 (58) Roh, <i>et al.</i> 2004 (109)	Weak
Toxicity			
Clinical	CYP2C19 PMs are not associated with risk for adverse events when treated with omeprazole as compared to IMs.	Ohkusa, <i>et al.</i> 2005 (128)	Weak
Clinical	CYP2C19 PMs are not associated with risk for adverse events when treated with omeprazole as compared to NMs.	Ohkusa, <i>et al.</i> 2005 (128)	Weak
Clinical	CYP2C19 PMs do not have an altered risk for acute interstitial nephritis when treated with omeprazole as compared to NMs.	Helsby, <i>et al.</i> 2010 (152)	Weak
Clinical	CYP2C19 UMs have an increased risk for agranulocytosis when treated with omeprazole.	Dury, <i>et al.</i> 2012 (153)	Weak
Clinical	<i>CYP2C19</i> is not associated with risk for visual disorders when treated with omeprazole when comparing PMs vs IMs vs NMs.	Lutz, <i>et al.</i> 2002 (154)	Weak

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S2. EVIDENCE LINKING *CYP2C19* TO LANSOPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of lansoprazole as compared to IMs.	Sakai, <i>et al.</i> 2001 (60) Ieiri, <i>et al.</i> 2001(155) Furuta, <i>et al.</i> 2001 (156) Shirai, <i>et al.</i> 2002 (157) Furuta, <i>et al.</i> 2002 (158) Schwab, <i>et al.</i> 2004 (159) Miura, <i>et al.</i> 2004 (160) Uno, <i>et al.</i> 2005 (161) Saito, <i>et al.</i> 2005 (162) Uno, <i>et al.</i> 2005 (163) Qiao, <i>et al.</i> 2006 (66) Xu, <i>et al.</i> 2010 (164) Zhang, <i>et al.</i> 2011 (165) Gumus, <i>et al.</i> 2012 (166) Li, <i>et al.</i> 2014 (167)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of lansoprazole as compared to NMs.	Ko, <i>et al.</i> 1999 (168) Sakai, <i>et al.</i> 2001 (60) Ieiri, <i>et al.</i> 2001 (155) Furuta, <i>et al.</i> 2001 (156) Shirai, <i>et al.</i> 2002 (157) Kim, <i>et al.</i> 2002 (169) Furuta, <i>et al.</i> 2002 (158) Hu, <i>et al.</i> 2004 (170) Schwab, <i>et al.</i> 2004 (159) Miura, <i>et al.</i> 2004 (160) Uno, <i>et al.</i> 2005 (161) Saito, <i>et al.</i> 2005 (162)	High

		Uno, <i>et al.</i> 2005 (163) Qiao, <i>et al.</i> 2006 (66) Niioka, <i>et al.</i> 2008 (171) Miura, <i>et al.</i> 2010 (172) Xu, <i>et al.</i> 2010 (164) Zhang, <i>et al.</i> 2011 (165) Gumus, <i>et al.</i> 2012 (166) Li, <i>et al.</i> 2014 (167)	
Clinical	CYP2C19 PMs (as determined by phenotyping) are associated with decreased metabolism of lansoprazole as compared to NMs.	Sohn, <i>et al.</i> 1997 (173) Andersson, <i>et al.</i> 1998 (90)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of lansoprazole as compared to NMs.	Ieiri, <i>et al.</i> 2001 (155) Sakai, <i>et al.</i> 2001 (60) Furuta, <i>et al.</i> 2001 (156) Schwab, <i>et al.</i> 2004 (159) Howden, <i>et al.</i> 2006 (174) Miura, <i>et al.</i> 2006 (175) Hunfeld, <i>et al.</i> 2008 (98) Zhang, <i>et al.</i> 2008 (40) Miura, <i>et al.</i> 2010 (172) Xu, <i>et al.</i> 2010 (164) Zhang, <i>et al.</i> 2011 (165) Gumus, <i>et al.</i> 2012 (166) Zalloum, <i>et al.</i> 2012 (176) Li, <i>et al.</i> 2014 (167) Zhang, <i>et al.</i> 2014 (177)	Moderate
Clinical	CYP2C19 NMs are not associated with altered metabolism of lansoprazole as compared to RMs.	Gumus, <i>et al.</i> 2012 (166)	Weak
Clinical	CYP2C19 NMs are associated with decreased metabolism of lansoprazole as compared to UMs,	Gumus, <i>et al.</i> 2012 (166)	Weak
Clinical	CYP2C19 PMs are associated with decreased metabolism of lansoprazole as compared to IMs+NMs.	Katsuki, <i>et al.</i> 1997 (178) Ko, <i>et al.</i> 1999 (168) Miura, <i>et al.</i> 2010 (179) Zhang, <i>et al.</i> 2012 (180)	High

		Zhang, <i>et al.</i> 2013 (181)	
Clinical	CYP2C19 PMs+IMs are associated with decreased metabolism of lansoprazole as compared to NMs.	Lima, <i>et al.</i> 2013 (51)	Weak
Clinical	<i>CYP2C19</i> is associated with lansoprazole metabolism when comparing PMs vs IMs vs NMs.	Yasui-Furukori, <i>et al.</i> 2004 (182) Niioka, <i>et al.</i> 2006 (183) Sakurai, <i>et al.</i> 2007 (184)	Moderate
Efficacy			
Remission or Healing			
Clinical	CYP2C19 PMs are associated with increased remission of reflux when treated with lansoprazole as compared to IMs.	Kawamura, <i>et al.</i> 2007 (185)	Moderate
Clinical	CYP2C19 PMs are associated with increased remission and healing rate of reflux when treated with lansoprazole as compared to NMs.	Furuta, <i>et al.</i> 2002 (158) Kawamura, <i>et al.</i> 2007 (185) Furuta, <i>et al.</i> 2009 (186)	High
Clinical	CYP2C19 PMs are not associated with altered healing rate of ulcers when treated with lansoprazole as compared to NMs.	Yoshizawa, <i>et al.</i> 2016 (187)	Weak
Clinical	CYP2C19 IMs are associated with increased remission and healing rate of reflux when treated with lansoprazole as compared to NMs.	Furuta, <i>et al.</i> 2002 (158) Kawamura, <i>et al.</i> 2003 (188) Furuta, <i>et al.</i> 2009 (186)	High
Clinical	CYP2C19 IMs are not associated with healing rate of ulcers when treated with lansoprazole as compared to NMs.	Yoshizawa, <i>et al.</i> 2016 (187)	Weak
Clinical	CYP2C19 IMs have a decreased healing rate of ulcers when treated with lansoprazole.	Okamura, <i>et al.</i> 2013 (125)	Weak
<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with lansoprazole as compared to IMs.	Okudaira, <i>et al.</i> 2005 (189)	Weak
Clinical	CYP2C19 PMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole as compared to NMs.	Isomoto, <i>et al.</i> 2003 (190) Okudaira, <i>et al.</i> 2005 (189) Furuta, <i>et al.</i> 2005 (191) Furuta, <i>et al.</i> 2007 (192) Suzuki, <i>et al.</i> 2007 (193) Settin, <i>et al.</i> 2014 (194)	Moderate

Clinical	CYP2C19 IMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole as compared to NMs.	Isomoto, <i>et al.</i> 2003 (190) Okudaira, <i>et al.</i> 2005 (189) Furuta, <i>et al.</i> 2005 (191) Furuta, <i>et al.</i> 2007 (192) Suzuki, <i>et al.</i> 2007 (193) Ozdil, <i>et al.</i> 2010 (195) Settin, <i>et al.</i> 2014 (194)	Moderate
Clinical	CYP2C19 PMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole as compared to IMs+NMs.	Schwab, <i>et al.</i> 2004 (159)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole as compared to NMs.	Kawabata, <i>et al.</i> 2003 (196) Liou, <i>et al.</i> 2016 (197) Liou, <i>et al.</i> 2016 (197) Liou, <i>et al.</i> 2016 (198)	High
Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with lansoprazole when comparing PMs vs IMs vs NMs.	Inaba, <i>et al.</i> 2002 (140) Hagiwara, <i>et al.</i> 2007 (199) Sugimoto, <i>et al.</i> 2007 (200) Srinarong, <i>et al.</i> 2014 (201)	Weak
Acid secretion indices			
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with lansoprazole as compared to IMs.	Adachi, <i>et al.</i> 2000 (149) Furuta, <i>et al.</i> 2001 (156) Furuta, <i>et al.</i> 2005 (202) Sugimoto, <i>et al.</i> 2007 (200) Furuta, <i>et al.</i> 2009 (203) Nishino, <i>et al.</i> 2011 (204) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146)	High
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with lansoprazole as compared to NMs.	Adachi, <i>et al.</i> 2000 (149) Ieiri, <i>et al.</i> 2001 (155) Furuta, <i>et al.</i> 2001 (156) Shirai, <i>et al.</i> 2002 (157) Furuta, <i>et al.</i> 2005 (202) Sugimoto, <i>et al.</i> 2007 (200) Furuta, <i>et al.</i> 2009 (203)	High

		Nishino, <i>et al.</i> 2011 (204) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146)	
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with lansoprazole as compared to NMs.	Furuta, <i>et al.</i> 2001 (156) Shirai, <i>et al.</i> 2002 (157) Furuta, <i>et al.</i> 2005 (202) Howden, <i>et al.</i> 2006 (174) Hunfeld, <i>et al.</i> 2008 (98) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146)	High
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with lansoprazole as compared to IMs+NMs.	Hata, <i>et al.</i> 2013 (205)	Moderate
Other			
Clinical	CYP2C19 PMs+IMs are associated with decreased asthma control when treated with lansoprazole as compared to NMs.	Lang, <i>et al.</i> 2015 (206)	Weak
Toxicity			
Clinical	CYP2C19 PMs+IMs have an increased risk for upper respiratory infection or sore throat when treated with lansoprazole as compared to NMs.	Lima, <i>et al.</i> 2013 (51)	Weak

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S3. EVIDENCE LINKING *CYP2C19* TO PANTOPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of pantoprazole as compared to IMs.	Desta, <i>et al.</i> 2009 (207) Furuta, <i>et al.</i> 2009 (203) Furuta, <i>et al.</i> 2010 (208) Thacker, <i>et al.</i> 2011 (209) Thacker, <i>et al.</i> 2013 (210)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of pantoprazole as compared to NMs.	Choi, <i>et al.</i> 2009 (211) Shao, <i>et al.</i> 2009 (212) Furuta, <i>et al.</i> 2009 (203) Furuta, <i>et al.</i> 2010 (208) Ward, <i>et al.</i> 2010 (213)	High
Clinical	CYP2C19 PMs (as determined by phenotyping) have decreased metabolism of pantoprazole as compared to NMs.	Andersson, <i>et al.</i> 1998 (90)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to NMs.	Kearns, <i>et al.</i> 2008 (44) Furuta, <i>et al.</i> 2009 (203) Furuta, <i>et al.</i> 2010 (208) Hunfeld, <i>et al.</i> 2010 (214) Gawronska-Szklarz, <i>et al.</i> 2012 (215) Roman, <i>et al.</i> 2014 (99)	High
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to RMs.	Roman, <i>et al.</i> 2014 (99)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to UMs.	Roman, <i>et al.</i> 2014 (99)	Moderate
Clinical	CYP2C19 NMs are not associated with altered metabolism of pantoprazole as compared to RMs.	Hunfeld, <i>et al.</i> 2008 (98) Roman, <i>et al.</i> 2014 (99)	Weak
Clinical	CYP2C19 NMs are associated with decreased metabolism of pantoprazole as compared to UMs.	Gawronska-Szklarz, <i>et al.</i> 2012 (215)	Weak

		Roman, <i>et al.</i> 2014 (99)	
Clinical	CYP2C19 PMs are associated with decreased metabolism of pantoprazole as compared to IMs+NMs.	Tanaka, <i>et al.</i> 1997 (216) Tanaka, <i>et al.</i> 2001 (217)	Moderate
Clinical	CYP2C19 PMs are associated with decreased metabolism of pantoprazole as compared to NMs+RMs.	Desta, <i>et al.</i> 2009 (207) Thacker, <i>et al.</i> 2011 (209) Thacker, <i>et al.</i> 2013 (210)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to NMs+RMs.	Desta, <i>et al.</i> 2009 (207) Thacker, <i>et al.</i> 2011 (209) Thacker, <i>et al.</i> 2013 (210) Shakhnovich, <i>et al.</i> 2018 (218) Shakhnovich, <i>et al.</i> 2018 (43)	Moderate
Clinical	CYP2C19 PMs+IMs+NMs are associated with decreased metabolism of pantoprazole as compared to RMs+UMs.	Karaca, <i>et al.</i> 2017 (219)	Moderate
Clinical	CYP2C19 PMs+IMs are associated with decreased metabolism of pantoprazole as compared to NMs+RMs.	Kearns, <i>et al.</i> 2010 (113)	Weak
Clinical	<i>CYP2C19</i> is associated with metabolism of pantoprazole when comparing IMs vs NMs vs RMs vs UMs.	Gawronska-Szklarz, <i>et al.</i> 2010 (220)	Weak
Efficacy			
Remission or Healing			
Clinical	CYP2C19 PMs+IMs are associated with increased healing rate of reflux when treated with pantoprazole as compared to NMs.	Sheu, <i>et al.</i> 2012 (221)	High
Clinical	<i>CYP2C19</i> is associated with remission of reflux when treated with pantoprazole when comparing PMs vs IMs vs NMs.	Chen, <i>et al.</i> 2010 (222)	Moderate
<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to IMs.	Oh, <i>et al.</i> 2009 (223)	Weak
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to NMs.	Oh, <i>et al.</i> 2009 (223)	Weak
Clinical	CYP2C19 NMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to RMs.	Kurzwski, <i>et al.</i> 2006 (224)	Weak
Clinical	CYP2C19 NMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to UMs.	Kurzwski, <i>et al.</i> 2006 (224)	Weak

Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to IMs+NMs.	Kang, <i>et al.</i> 2008 (225) Lee, <i>et al.</i> 2014 (226)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to NMs.	Kurzwski, <i>et al.</i> 2006 (224) Ormeci, <i>et al.</i> 2016 (227)	Moderate
Clinical	CYP2C19 PMs+IMs are not associated with altered <i>H. pylori</i> eradication rate when treated with pantoprazole as compared to NMs+RMs+UMs.	Gawronska-Szklarz, <i>et al.</i> 2010 (220)	Weak
Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with pantoprazole when comparing PMs vs IMs vs NMs.	Hsu, <i>et al.</i> 2015 (228)	Moderate
Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with pantoprazole when comparing PMs+IMs vs NMs vs RMs+UMs.	Karaca, <i>et al.</i> 2017 (219)	Weak
Acid secretion indices			
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with pantoprazole as compared to IMs.	Oh, <i>et al.</i> 2007 (229)	Weak
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with pantoprazole as compared to NMs.	Oh, <i>et al.</i> 2007 (229)	Weak
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with pantoprazole as compared to NMs.	Oh, <i>et al.</i> 2007 (229) Hunfeld, <i>et al.</i> 2010 (214)	Moderate
Clinical	CYP2C19 NMs are not associated with altered acid secretion indices when treated with pantoprazole as compared to RMs.	Hunfeld, <i>et al.</i> 2008 (98)	Weak
Other			
Clinical	CYP2C19 PMs are associated with a decreased number of required pantoprazole tablets in patients with reflux in remission as compared to IMs+NMs.	Sheu, <i>et al.</i> 2012 (221)	Moderate

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S4. EVIDENCE LINKING *CYP2C19* TO DEXLANSOPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of dexlansoprazole as compared to IMs.	Sun, <i>et al.</i> 2017 (230)	Moderate
Clinical	CYP2C19 PMs are associated with decreased metabolism of dexlansoprazole as compared to NMs.	Sun, <i>et al.</i> 2017 (230)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of dexlansoprazole as compared to NMs.	Sun, <i>et al.</i> 2017 (230)	Moderate
Clinical	CYP2C19 PMs have decreased metabolism of dexlansoprazole as compared to IMs+NMs.	Grabowski and Lee, <i>et al.</i> 2012 (231)	Weak
Efficacy			
Clinical	CYP2C19 PMs are not associated with altered acid secretion indices when treated with dexlansoprazole as compared to IMs.	Sun, <i>et al.</i> 2017 (230)	Moderate
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with dexlansoprazole as compared to NMs.	Sun, <i>et al.</i> 2017 (230)	Moderate
Clinical	CYP2C19 IMs are not associated with altered acid secretion indices when treated with dexlansoprazole as compared to NMs.	Sun, <i>et al.</i> 2017 (230)	Weak

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S5. EVIDENCE LINKING *CYP2C19* TO ESOMEPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of esomeprazole as compared to IMs.	Lou, <i>et al.</i> 2009 (232)	Weak
Clinical	CYP2C19 PMs are associated with decreased metabolism of esomeprazole as compare to NMs.	Lou, <i>et al.</i> 2009 (232) Liu, <i>et al.</i> 2009 (232)	Weak
Clinical	CYP2C19 IMs are associated with decreased metabolism of esomeprazole as compared to NMs.	Liu, <i>et al.</i> 2009 (232) Hunfeld, <i>et al.</i> 2009 (232) Hunfeld, <i>et al.</i> 2012 (233)	Weak
Clinical	<i>CYP2C19</i> is associated with metabolism of esomeprazole when comparing PMs vs IMs vs NMs.	Yi, <i>et al.</i> 2017 (234)	Moderate
Efficacy			
Remission or Healing			
Clinical	<i>CYP2C19</i> is associated with remission of reflux when treated with esomeprazole when comparing PMs vs IMs vs NMs.	Sheu, <i>et al.</i> 2008 (235)	Weak
Clinical	<i>CYP2C19</i> is not associated with healing rate of reflux when treated with esomeprazole when comparing PMs vs IMs vs NMs.	Schwab, <i>et al.</i> 2005 (236) Sheu, <i>et al.</i> 2008 (235)	Moderate
<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with esomeprazole as compared to IMs+NMs.	Kang, <i>et al.</i> 2008 (225) Lee, <i>et al.</i> 2014 (226) Su, <i>et al.</i> 2017 (237)	High
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with esomeprazole as compared to NMs.	Miehlke, <i>et al.</i> 2006 (132) Miehlke, <i>et al.</i> 2008 (238) Kuo, <i>et al.</i> 2009 (239) Kuo, <i>et al.</i> 2013 (240) Saito, <i>et al.</i> 2015 (241) Hong, <i>et al.</i> 2016 (138) Shimoyama, <i>et al.</i> 2017 (242)	Moderate

Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with esomeprazole when comparing PMs vs IMs vs NMs.	Sheu, <i>et al.</i> 2005 (137) Lee, <i>et al.</i> 2010 (243) Pan, <i>et al.</i> 2010 (244) Wu, <i>et al.</i> 2011 (245) Liou, <i>et al.</i> 2011 (246) Song, <i>et al.</i> 2016 (247) Song, <i>et al.</i> 2016 (248)	High
Acid secretion indices			
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with esomeprazole as compared to IMs.	Sahara, <i>et al.</i> 2013 (145) Sahara, <i>et al.</i> 2015 (249)	Moderate
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with esomeprazole as compared to NMs.	Sahara, <i>et al.</i> 2013 (145) Sahara, <i>et al.</i> 2015 (249)	Moderate
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with esomeprazole as compared to NMs.	Hunfeld, <i>et al.</i> 2010 (214) Hunfeld, <i>et al.</i> 2012 (233) Kagami, <i>et al.</i> 2016 (250) Yi, <i>et al.</i> 2017 (234)	Moderate
Clinical	CYP2C19 PMs are not associated with altered acid secretion indices when treated with esomeprazole as compared to IMs+NMs.	Li, <i>et al.</i> 2007 (251)	Weak
Clinical	<i>CYP2C19</i> is not associated with acid secretion indices when treated with esomeprazole when comparing PMs vs IMs vs NMs.	Kagami, <i>et al.</i> 2016 (250) Yi, <i>et al.</i> 2017 (234)	Weak
Toxicity			
Clinical	CYP2C19 UMs have an increased risk for agranulocytosis when treated with esomeprazole.	Dury, <i>et al.</i> 2012 (153)	Weak
Clinical	<i>CYP2C19</i> is not associated with risk for adverse events when treated with esomeprazole when comparing PMs vs IMs vs NMs.	Miehlke, <i>et al.</i> 2008 (238)	Moderate

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S6. EVIDENCE LINKING *CYP2C19* TO RABEPRAZOLE PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs are associated with decreased metabolism of rabeprazole as compared to IMs.	Horai, <i>et al.</i> 2001 (252) Ieiri, <i>et al.</i> 2001 (155) Sugimoto, <i>et al.</i> 2004 (253) Hu, <i>et al.</i> 2005 (254) Hu, <i>et al.</i> 2006 (255) Qiao, <i>et al.</i> 2006 (66) Uno, <i>et al.</i> 2006 (256) Miura, <i>et al.</i> 2006 (257) Shimizu, <i>et al.</i> 2006 (258) Yamano, <i>et al.</i> 2008 (259) Hayato, <i>et al.</i> 2012 (260)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of rabeprazole as compared to NMs.	Horai, <i>et al.</i> 2001 (252) Ieiri, <i>et al.</i> 2001 (155) Shirai, <i>et al.</i> 2001 (61) Lin, <i>et al.</i> 2003 (261) Sugimoto, <i>et al.</i> 2004 (253) Hu, <i>et al.</i> 2005 (254) Qiao, <i>et al.</i> 2006 (66) Uno, <i>et al.</i> 2006 (256) Miura, <i>et al.</i> 2006 (257) Shimizu, <i>et al.</i> 2006 (258) Niioka, <i>et al.</i> 2006 (262) Hu, <i>et al.</i> 2006 (255) Yamano, <i>et al.</i> 2008 (259) Sheng, <i>et al.</i> 2010 (263) Hayato, <i>et al.</i> 2012 (260)	High

Clinical	CYP2C19 PMs (as determined by phenotyping) are associated with decreased metabolism of rabeprazole as compared to NMs.	Yasuda, <i>et al.</i> 1995 (87)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of rabeprazole as compared to NMs.	Horai, <i>et al.</i> 2001 (252) Ieiri, <i>et al.</i> 2001 (155) Sugimoto, <i>et al.</i> 2004 (253) Hu, <i>et al.</i> 2005 (254) Hu, <i>et al.</i> 2006 (255) Yamano, <i>et al.</i> 2008 (259) Sheng, <i>et al.</i> 2010 (263) Hunfeld, <i>et al.</i> 2012 (233) Hayato, <i>et al.</i> 2012 (260) Roman, <i>et al.</i> 2014 (99)	Weak
Clinical	CYP2C19 IMs are associated with decreased metabolism of rabeprazole as compared to RMs.	Roman, <i>et al.</i> 2014 (99)	Weak
Clinical	CYP2C19 NMs are not associated with altered metabolism of rabeprazole as compared to RMs.	Roman, <i>et al.</i> 2014 (99)	Weak
Clinical	CYP2C19 PMs are associated with decreased metabolism of rabeprazole as compared to IMs+NMs.	Yang, <i>et al.</i> 2009 (264)	Moderate
Clinical	CYP2C19 is associated with rabeprazole metabolism when comparing PMs vs IMs vs NMs.	Toda, <i>et al.</i> 2018 (265)	Weak
Efficacy			
Remission or Healing			
Clinical	CYP2C19 PMs are not associated with healing rate of ulcers when treated with rabeprazole as compared to IMs+NMs.	Ji, <i>et al.</i> 2006 (127)	Moderate
Clinical	CYP2C19 is not associated with remission of reflux when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Kinoshita, <i>et al.</i> 2011 (266)	Moderate
Clinical	CYP2C19 is not associated with healing rate of ulcers when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Ando, <i>et al.</i> 2005 (122) Ando, <i>et al.</i> 2008 (123) Nakamura, <i>et al.</i> 2016 (267)	Weak
Clinical	CYP2C19 does not alter healing rate of erosive lesions when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Yamano, <i>et al.</i> 2008 (259)	Weak
Clinical	CYP2C19 is not associated with healing rate of reflux when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Ariizumi, <i>et al.</i> 2006 (268) Kinoshita, <i>et al.</i> 2018 (269)	Moderate

<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with rabeprazole as compared to IMs.	Furuta, <i>et al.</i> 2001 (270) Lay, <i>et al.</i> 2010 (271) Lin, <i>et al.</i> 2017 (130)	Weak
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with rabeprazole as compared to NMs.	Furuta, <i>et al.</i> 2001 (270) Hokari, <i>et al.</i> 2001 (272) Lay, <i>et al.</i> 2010 (271) Lin, <i>et al.</i> 2017 (130)	Weak
Clinical	CYP2C19 IMs are associated with an increased <i>H. pylori</i> eradication rate when treated with rabeprazole as compared to NMs.	Furuta, <i>et al.</i> 2001 (270) Inaba, <i>et al.</i> 2002 (140) Hsu, <i>et al.</i> 2008 (273) Lay, <i>et al.</i> 2010 (271) Lin, <i>et al.</i> 2017 (130)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with rabeprazole as compared to NMs.	Ormeci, <i>et al.</i> 2016 (227) Sugimoto, <i>et al.</i> 2017 (274) Shimoyama, <i>et al.</i> 2017 (242)	Weak
Clinical	CYP2C19 PMs are not related to altered <i>H. pylori</i> eradication rate when treated with rabeprazole as compared to IMs+NMs.	Kawabata, <i>et al.</i> 2003 (196)	Weak
Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Dojo, <i>et al.</i> 2001 (139) Isomoto, <i>et al.</i> 2003 (275) Lee, <i>et al.</i> 2003 (276) Kuwayama, <i>et al.</i> 2007 (277) Yang, <i>et al.</i> 2009 (264) Lee, <i>et al.</i> 2010 (243) Zhang, <i>et al.</i> 2010 (142) Pan, <i>et al.</i> 2010 (244) Sugimoto, <i>et al.</i> 2014 (278) Sugimoto, <i>et al.</i> 2015 (279) Yang, <i>et al.</i> 2015 (280)	High
Acid secretion indices			
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with rabeprazole as compared to IMs.	Horai, <i>et al.</i> 2001 (252) Shirai, <i>et al.</i> 2001 (61) Sugimoto, <i>et al.</i> 2004 (253)	Weak

		Sugimoto, <i>et al.</i> 2005 (281) Yamano, <i>et al.</i> 2008 (259) Sugimoto, <i>et al.</i> 2010 (282) Nishino, <i>et al.</i> 2010 (283) Sugimoto, <i>et al.</i> 2012 (284) Hayato, <i>et al.</i> 2012 (260) Sugimoto, <i>et al.</i> 2014 (146)	
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with rabeprazole as compared to NMs.	Horai, <i>et al.</i> 2001 (252) Ieiri, <i>et al.</i> 2001 (155) Shirai, <i>et al.</i> 2001 (61) Lin, <i>et al.</i> 2003 (261) Shimatani, <i>et al.</i> 2004 (285) Sugimoto, <i>et al.</i> 2004 (253) Sugimoto, <i>et al.</i> 2005 (281) Yamano, <i>et al.</i> 2008 (259) Sugimoto, <i>et al.</i> 2010 (282) Nishino, <i>et al.</i> 2010 (283) Hayato, <i>et al.</i> 2012 (260) Sugimoto, <i>et al.</i> 2012 (284) Sahara, <i>et al.</i> 2013 (145) Sugimoto, <i>et al.</i> 2014 (146) Kagami, <i>et al.</i> 2015 (286)	High
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with rabeprazole as compared to NMs.	Horai, <i>et al.</i> 2001 (252) Shirai, <i>et al.</i> 2001 (61) Sugimoto, <i>et al.</i> 2005 (281) Hayato, <i>et al.</i> 2012 (260) Hunfeld, <i>et al.</i> 2012 (233) Sugimoto, <i>et al.</i> 2012 (284) Sugimoto, <i>et al.</i> 2014 (146) Kagami, <i>et al.</i> 2015 (286)	Weak
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with rabeprazole as compared to IMs+NMs.	Hata, <i>et al.</i> 2013 (205) Toda, <i>et al.</i> 2018 (265) Kinoshita, <i>et al.</i> 2018 (269)	Weak

Clinical	<i>CYP2C19</i> is associated with acid secretion indices when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Adachi, <i>et al.</i> 2000 (149) Hu, <i>et al.</i> 2005 (254) Hu, <i>et al.</i> 2006 (255) Li, <i>et al.</i> 2007 (251) Nishino, <i>et al.</i> 2010 (283) Sugimoto, <i>et al.</i> 2010 (282) Furuta, <i>et al.</i> 2010 (148) Sheng, <i>et al.</i> 2010 (263) Sugimoto, <i>et al.</i> 2010 (282)	Weak
Toxicity			
Clinical	CYP2C19 PMs are associated with increased risk for celecoxib-induced small bowel injury when treated with rabeprazole as compared to IMs+NMs.	Nuki, <i>et al.</i> 2017 (287)	Weak
Clinical	CYP2C19 PMs are not associated with risk for adverse events when treated with rabeprazole as compared to NMs.	Hokari, <i>et al.</i> 2001 (272)	Weak

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S7. EVIDENCE LINKING *CYP2C19* TO PROTON PUMP INHIBITOR PHENOTYPE (MIXED COHORT)

Type of experimental model	Major findings	References	Level of evidence ^a
Metabolism			
Clinical	CYP2C19 PMs have decreased metabolism of lansoprazole and pantoprazole as compared to NMs.	Metz, <i>et al.</i> 2006 (288)	Weak
Clinical	CYP2C19 IMs have decreased metabolism of lansoprazole and pantoprazole as compared to NMs.	Metz, <i>et al.</i> 2006 (288)	Weak
Efficacy			
Remission or Healing			
Clinical	CYP2C19 PMs+IMs are associated with increased esophageal eosinophilia remission rate when treated with esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole as compared to NMs+RMs+UMs.	Molina-Infante, <i>et al.</i> 2015 (49)	Moderate
Clinical	CYP2C19 PMs+IMs are associated with increased healing rate of erosive esophagitis when treated with lansoprazole, omeprazole and rabeprazole as compared to NMs.	Kawara, <i>et al.</i> 2017 (289)	Weak
Clinical	CYP2C19 PMs+IMs are associated with decreased healing rate of nonerosive reflux disease when treated with lansoprazole, omeprazole and rabeprazole as compared to NMs.	Kawara, <i>et al.</i> 2017 (289)	Weak
<i>H. pylori</i> eradication			
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with lansoprazole and omeprazole as compared to IMs.	Furuta, <i>et al.</i> 2001 (290)	Weak
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with lansoprazole, omeprazole and rabeprazole as compared to IMs.	Take, <i>et al.</i> 2003 (291)	Weak
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with lansoprazole and omeprazole as compared to NMs.	Furuta, <i>et al.</i> 2001 (290) Furuta, <i>et al.</i> 2004 (292)	Moderate

Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with lansoprazole and rabeprazole as compared to NMs.	Miki, <i>et al.</i> 2003 (293)	Weak
Clinical	CYP2C19 PMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole, omeprazole and rabeprazole as compared to NMs.	Take, <i>et al.</i> 2003 (291) Sugimoto, <i>et al.</i> 2006 (294)	Moderate
Clinical	CYP2C19 IMs are associated with an increased <i>H. pylori</i> eradication rate when treated with lansoprazole and omeprazole as compared to NMs.	Furuta, <i>et al.</i> 2001 (290) Furuta, <i>et al.</i> 2004 (292)	Moderate
Clinical	CYP2C19 IMs are associated with an increased <i>H. pylori</i> eradication rate when treated with omeprazole and pantoprazole as compared to NMs.	Gawronska-Szklarz, <i>et al.</i> 2005 (295)	Weak
Clinical	CYP2C19 IMs are not associated with altered <i>H. pylori</i> eradication rate when treated with lansoprazole and rabeprazole as compared to NMs.	Miki, <i>et al.</i> 2003 (293)	Weak
Clinical	CYP2C19 IMs are associated with increased <i>H. pylori</i> eradication rate when treated with lansoprazole, omeprazole and rabeprazole as compared to NMs.	Sugimoto, <i>et al.</i> 2006 (294)	Weak
Clinical	CYP2C19 PMs are associated with an increased <i>H. pylori</i> eradication rate when treated with esomeprazole and pantoprazole as compared to IMs+NMs.	Kang, <i>et al.</i> 2008 (225)	Weak
Clinical	CYP2C19 PMs are not associated with altered <i>H. pylori</i> eradication rate when treated with esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole as compared to IMs+NMs.	Lee, <i>et al.</i> 2014 (226)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with pantoprazole and rabeprazole as compared to NMs	Ormeci, <i>et al.</i> 2016 (227)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with esomeprazole and omeprazole as compared to NMs.	Hong, <i>et al.</i> 2016 (138)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased <i>H. pylori</i> eradication rate when treated with esomeprazole and rabeprazole as compared to NMs.	Kuo, <i>et al.</i> 2010 (296) Shimoyama, <i>et al.</i> 2017 (242)	Weak

Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with omeprazole and rabeprazole when comparing PMs vs IMs vs NMs.	Miyoshi, <i>et al.</i> 2001 (297)	Weak
Clinical	<i>CYP2C19</i> is not associated with <i>H. pylori</i> eradication rate when treated with esomeprazole or rabeprazole when comparing PMs vs IMs vs NMs.	Pan, <i>et al.</i> 2010 (244)	Weak
Acid secretion indices			
Clinical	<i>CYP2C19</i> PMs+IMs are associated with better acid secretion indices when treated with esomeprazole, lansoprazole and omeprazole as compared to NMs.	Egan, <i>et al.</i> 2003 (298)	Weak
Clinical	<i>CYP2C19</i> IMs+NMs are associated with better acid secretion indices when treated with esomeprazole, lansoprazole, omeprazole and pantoprazole as compared to RMs+UMs.	Franciosi, <i>et al.</i> 2018 (47)	Weak
Clinical	<i>CYP2C19</i> is not associated with acid secretion indices when treated with esomeprazole, lansoprazole and rabeprazole when comparing PMs vs IMs vs NMs.	Shiotani, <i>et al.</i> 2018 (299)	Weak
Other			
Clinical	<i>CYP2C19</i> PMs+IMs are associated with decreased resistance to treatment with esomeprazole, lansoprazole, omeprazole and pantoprazole in patients with reflux as compared to RMs+UMs.	Franciosi, <i>et al.</i> 2018 (48)	Weak
Clinical	<i>CYP2C19</i> PMs+IMs are associated with decreased resistance to treatment with esomeprazole, lansoprazole, omeprazole and pantoprazole in patients with reflux as compared to NMs.	Franciosi, <i>et al.</i> 2018 (48)	Weak
Clinical	<i>CYP2C19</i> is not associated with resistance to treatment with PPIs in patients with ulcers when comparing PMs vs IMs vs NMs.	Wada, <i>et al.</i> 2002 (300)	Weak

^aRating scheme described in the **Supplemental Material**

IM, intermediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; RM, rapid metabolizer; UM, ultrarapid metabolizer

TABLE S8. DOSING RECOMMENDATIONS FOR ESOMEPRAZOLE AND RABEPRAZOLE BASED ON CYP2C19 PHENOTYPE

CYP2C19 Phenotype^a	Implications for Phenotypic Measures	Therapeutic Recommendation	Classification of Recommendation^b
CYP2C19 ultrarapid metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 rapid metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 normal metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 likely intermediate metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 intermediate metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 likely poor metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 poor metabolizer	Inconsistent findings regarding the effect of <i>CYP2C19</i> genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation

^aThe online ***CYP2C19* Frequency Table** provides phenotype frequencies for major race/ethnic groups, and the online ***CYP2C19* Diplotype-Phenotype Table** provides a complete list of possible diplotypes and phenotype assignments.

^bRating scheme described in the **Supplemental Material**

REFERENCES

- (1) CPIC. CPIC® Guideline for Proton Pump Inhibitors and CYP2C19. <<https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/>> (2020).
- (2) Botton, M.R. *et al.* Structural variation at the CYP2C locus: Characterization of deletion and duplication alleles. *Hum Mutat* **40**, e37-e51 (2019).
- (3) PharmGKB. *Gene-specific Information Tables for CYP2C19*. <<https://www.pharmgkb.org/page/cyp2c19RefMaterials>>. Accessed Jan 20 2020.
- (4) Kalman, L.V. *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin Pharmacol Ther* **99**, 172-85 (2016).
- (5) Pratt, V.M. *et al.* Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. *J Mol Diagn* **20**, 269-76 (2018).
- (6) Valdes R, P.D., Linder MW. Laboratory Analysis and Application of Pharmacogenetics to Clinical Practice. In: *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* (Washington, DC, 2010).
- (7) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. <<https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>> (2018). Accessed June 18 2018.
- (8) Shuldiner, A.R. *et al.* The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. *Clin Pharmacol Ther* **94**, 207-10 (2013).
- (9) Wilke, R.A. *et al.* The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther* **89**, 379-86 (2011).
- (10) Peterson, J.F. *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genet Med* **15**, 833-41 (2013).
- (11) Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genet Med* **15**, 761-71 (2013).
- (12) Kullo, I.J., Jarvik, G.P., Manolio, T.A., Williams, M.S. & Roden, D.M. Leveraging the electronic health record to implement genomic medicine. *Genet Med* **15**, 270-1 (2013).
- (13) Hicks, J.K., Dunnenberger, H.M., Gumpfer, K.F., Haidar, C.E. & Hoffman, J.M. Integrating pharmacogenomics into electronic health records with clinical decision support. *Am J Health Syst Pharm* **73**, 1967-76 (2016).
- (14) Hoffman, J.M. *et al.* Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc* **23**, 796-801 (2016).
- (15) Hicks, J.K. *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clin Pharmacol Ther* **92**, 563-6 (2012).
- (16) Bell, G.C. *et al.* Development and use of active clinical decision support for preemptive pharmacogenomics. *J Am Med Inform Assoc* **21**, e93-9 (2014).
- (17) Pulley, J.M. *et al.* Operational implementation of prospective genotyping for personalized medicine: the design of the Vanderbilt PREDICT project. *Clin Pharmacol Ther* **92**, 87-95 (2012).

- (18) Caudle, K.E. *et al.* Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *Genet Med* **19**, 215-23 (2017).
- (19) Illueca, M., Alemayehu, B., Shoetan, N. & Yang, H. Proton pump inhibitor prescribing patterns in newborns and infants. *J Pediatr Pharmacol Ther* **19**, 283-7 (2014).
- (20) Barron, J.J., Tan, H., Spalding, J., Bakst, A.W. & Singer, J. Proton pump inhibitor utilization patterns in infants. *J Pediatr Gastroenterol Nutr* **45**, 421-7 (2007).
- (21) Blank, M.L. & Parkin, L. National Study of Off-label Proton Pump Inhibitor Use Among New Zealand Infants in the First Year of Life (2005-2012). *J Pediatr Gastroenterol Nutr* **65**, 179-84 (2017).
- (22) Rosen, R. *et al.* Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* **66**, 516-54 (2018).
- (23) Gibbons, T.E. & Gold, B.D. The use of proton pump inhibitors in children: a comprehensive review. *Paediatr Drugs* **5**, 25-40 (2003).
- (24) Jones, N.L. *et al.* Joint ESPGHAN/NASPGHAN Guidelines for the Management of *Helicobacter pylori* in Children and Adolescents (Update 2016). *J Pediatr Gastroenterol Nutr* **64**, 991-1003 (2017).
- (25) Dellon, E.S. *et al.* ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* **108**, 679-92; quiz 93 (2013).
- (26) Shakhnovich, V., Ward, R.M. & Kearns, G.L. Failure of proton pump inhibitors to treat GERD in neonates and infants: a question of drug, diagnosis, or design. *Clin Pharmacol Ther* **92**, 388-92 (2012).
- (27) Hassall, E. Over-prescription of acid-suppressing medications in infants: how it came about, why it's wrong, and what to do about it. *J Pediatr* **160**, 193-8 (2012).
- (28) Ummarino, D., Miele, E., Masi, P., Tramontano, A., Staiano, A. & Vandenplas, Y. Impact of antisecretory treatment on respiratory symptoms of gastroesophageal reflux disease in children. *Dis Esophagus* **25**, 671-7 (2012).
- (29) Wasilewska, J., Semeniuk, J., Cudowska, B., Klukowski, M., Debkowska, K. & Kaczmarek, M. Respiratory response to proton pump inhibitor treatment in children with obstructive sleep apnea syndrome and gastroesophageal reflux disease. *Sleep Med* **13**, 824-30 (2012).
- (30) Gieruszczak-Bialek, D., Konarska, Z., Skorka, A., Vandenplas, Y. & Szajewska, H. No effect of proton pump inhibitors on crying and irritability in infants: systematic review of randomized controlled trials. *J Pediatr* **166**, 767-70 e3 (2015).
- (31) Stark, C.M. & Nylund, C.M. Side Effects and Complications of Proton Pump Inhibitors: A Pediatric Perspective. *J Pediatr* **168**, 16-22 (2016).
- (32) Canani, R.B. *et al.* Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* **117**, e817-20 (2006).
- (33) Rosh, J.R. & Hassall, E. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *J Pediatr Gastroenterol Nutr* **43**, 545 (2006).

- (34) Cheungpasitporn, W. *et al.* Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. *Ren Fail* **37**, 1237-41 (2015).
- (35) Lazarus, B. *et al.* Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med* **176**, 238-46 (2016).
- (36) Zhou, B., Huang, Y., Li, H., Sun, W. & Liu, J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. *Osteoporos Int* **27**, 339-47 (2016).
- (37) Writing Committee for the American Lung Association Asthma Clinical Research, C. *et al.* Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* **307**, 373-81 (2012).
- (38) Marier, J.F., Dubuc, M.C., Drouin, E., Alvarez, F., Ducharme, M.P. & Brazier, J.L. Pharmacokinetics of omeprazole in healthy adults and in children with gastroesophageal reflux disease. *Ther Drug Monit* **26**, 3-8 (2004).
- (39) Tran, A. *et al.* Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther* **71**, 359-67 (2002).
- (40) Zhang, W., Kukulka, M., Witt, G., Sutkowski-Markmann, D., North, J. & Atkinson, S. Age-dependent pharmacokinetics of lansoprazole in neonates and infants. *Paediatr Drugs* **10**, 265-74 (2008).
- (41) Knebel, W., Tammara, B., Udata, C., Comer, G., Gastonguay, M.R. & Meng, X. Population pharmacokinetic modeling of pantoprazole in pediatric patients from birth to 16 years. *J Clin Pharmacol* **51**, 333-45 (2011).
- (42) Shimizu, T. *et al.* Oral esomeprazole in Japanese pediatric patients with gastric acid-related disease: Safety, efficacy, and pharmacokinetics. *Pediatr Int* **61**, 87-95 (2019).
- (43) Shakhnovich, V. *et al.* A Population-Based Pharmacokinetic Model Approach to Pantoprazole Dosing for Obese Children and Adolescents. *Paediatr Drugs* **20**, 483-95 (2018).
- (44) Kearns, G.L. *et al.* Single-dose pharmacokinetics of oral and intravenous pantoprazole in children and adolescents. *J Clin Pharmacol* **48**, 1356-65 (2008).
- (45) Litalien, C., Theoret, Y. & Faure, C. Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* **44**, 441-66 (2005).
- (46) Zhao, W., Leroux, S., Biran, V. & Jacqz-Aigrain, E. Developmental pharmacogenetics of CYP2C19 in neonates and young infants: omeprazole as a probe drug. *Br J Clin Pharmacol* **84**, 997-1005 (2018).
- (47) Franciosi, J.P. *et al.* Association Between CYP2C19*17 Alleles and pH Probe Testing Outcomes in Children With Symptomatic Gastroesophageal Reflux. *J Clin Pharmacol* **58**, 89-96 (2018).
- (48) Franciosi, J.P. *et al.* Association between CYP2C19 extensive metabolizer phenotype and childhood anti-reflux surgery following failed proton pump inhibitor medication treatment. *Eur J Pediatr* **177**, 69-77 (2018).
- (49) Molina-Infante, J. *et al.* Long-Term Loss of Response in Proton Pump Inhibitor-Responsive Esophageal Eosinophilia Is Uncommon and Influenced by CYP2C19 Genotype and Rhinoconjunctivitis. *Am J Gastroenterol* **110**, 1567-75 (2015).
- (50) Mougey, E.B. *et al.* CYP2C19 and STAT6 Variants Influence the Outcome of Proton Pump Inhibitor Therapy in Pediatric Eosinophilic Esophagitis. *J Pediatr Gastroenterol Nutr* **69**, 581-7 (2019).

- (51) Lima, J.J. *et al.* Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. *J Pediatr* **163**, 686-91 (2013).
- (52) Bernal, C.J. *et al.* CYP2C19 Phenotype and Risk of Proton Pump Inhibitor-Associated Infections. *Pediatrics* **144**, (2019).
- (53) Cicali, E.J. *et al.* Novel Implementation of Genotype-Guided Proton Pump Inhibitor Medication Therapy in Children: A Pilot, Randomized, Multisite Pragmatic Trial. *Clin Transl Sci* **12**, 172-9 (2019).
- (54) Tang, M. *et al.* Genotype tailored treatment of mild symptomatic acid reflux in children with uncontrolled asthma (GenARA): Rationale and methods. *Contemp Clin Trials* **78**, 27-33 (2019).
- (55) Lima, J.J. & Franciosi, J.P. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene-drug pairs. *Pharmacogenomics* **15**, 1405-16 (2014).
- (56) Ieiri, I. *et al.* Pharmacokinetics of omeprazole (a substrate of CYP2C19) and comparison with two mutant alleles, C gamma P2C19m1 in exon 5 and C gamma P2C19m2 in exon 4, in Japanese subjects. *Clin Pharmacol Ther* **59**, 647-53 (1996).
- (57) Herrlin, K. *et al.* Bantu Tanzanians have a decreased capacity to metabolize omeprazole and mephenytoin in relation to their CYP2C19 genotype. *Clin Pharmacol Ther* **64**, 391-401 (1998).
- (58) Furuta, T. *et al.* CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. *Clin Pharmacol Ther* **65**, 552-61 (1999).
- (59) Furuta, T. *et al.* Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. *Clin Pharmacol Ther* **66**, 265-74 (1999).
- (60) Sakai, T. *et al.* CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects. *Pharm Res* **18**, 721-7 (2001).
- (61) Shirai, N. *et al.* Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. *Aliment Pharmacol Ther* **15**, 1929-37 (2001).
- (62) He, N. *et al.* Inhibitory effect of troleandomycin on the metabolism of omeprazole is CYP2C19 genotype-dependent. *Xenobiotica* **33**, 211-21 (2003).
- (63) Yin, O.Q., Tomlinson, B., Chow, A.H., Waye, M.M. & Chow, M.S. Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. *J Clin Pharmacol* **44**, 582-9 (2004).
- (64) Rosemary, J., Adithan, C., Padmaja, N., Shashindran, C.H., Gerard, N. & Krishnamoorthy, R. The effect of the CYP2C19 genotype on the hydroxylation index of omeprazole in South Indians. *Eur J Clin Pharmacol* **61**, 19-23 (2005).
- (65) Ohnishi, A., Murakami, S., Akizuki, S., Mochizuki, J., Echizen, H. & Takagi, I. In vivo metabolic activity of CYP2C19 and CYP3A in relation to CYP2C19 genetic polymorphism in chronic liver disease. *J Clin Pharmacol* **45**, 1221-9 (2005).
- (66) Qiao, H.L. *et al.* Pharmacokinetics of three proton pump inhibitors in Chinese subjects in relation to the CYP2C19 genotype. *Eur J Clin Pharmacol* **62**, 107-12 (2006).
- (67) Shimizu, M. *et al.* Sensitive determination of omeprazole and its two main metabolites in human plasma by column-switching high-performance liquid chromatography: application to pharmacokinetic study in relation to CYP2C19 genotypes. *J Chromatogr B Analyt Technol Biomed Life Sci* **832**, 241-8 (2006).
- (68) Uno, T., Niioka, T., Hayakari, M., Yasui-Furukori, N., Sugawara, K. & Tateishi, T. Absolute bioavailability and metabolism of omeprazole in relation to CYP2C19

- genotypes following single intravenous and oral administrations. *Eur J Clin Pharmacol* **63**, 143-9 (2007).
- (69) Wang, J.H., Li, P.Q., Fu, Q.Y., Li, Q.X. & Cai, W.W. Cyp2c19 genotype and omeprazole hydroxylation phenotype in Chinese Li population. *Clin Exp Pharmacol Physiol* **34**, 421-4 (2007).
 - (70) Hu, X.P., Xu, J.M., Hu, Y.M., Mei, Q. & Xu, X.H. Effects of CYP2C19 genetic polymorphism on the pharmacokinetics and pharmacodynamics of omeprazole in Chinese people. *J Clin Pharm Ther* **32**, 517-24 (2007).
 - (71) Wang, Y. *et al.* Influence of CYP2C19 on the relationship between pharmacokinetics and intragastric pH of omeprazole administered by successive intravenous infusions in Chinese healthy volunteers. *Eur J Clin Pharmacol* **66**, 563-9 (2010).
 - (72) Shiohira, H., Yasui-Furukori, N., Tateishi, T. & Uno, T. Chiral assay of omeprazole and metabolites and its application to a pharmacokinetics related to CYP2C19 genotypes. *J Chromatogr B Analyt Technol Biomed Life Sci* **879**, 2465-70 (2011).
 - (73) Shiohira, H., Yasui-Furukori, N., Yamada, S., Tateishi, T., Akamine, Y. & Uno, T. Hydroxylation of R(+)- and S(-)-omeprazole after racemic dosing are different among the CYP2C19 genotypes. *Pharm Res* **29**, 2310-6 (2012).
 - (74) Yamada, S., Shiohira, H., Yasui-Furukori, N., Tateishi, T., Akamine, Y. & Uno, T. The (R)-omeprazole hydroxylation index reflects CYP2C19 activity in healthy Japanese volunteers. *Eur J Clin Pharmacol* **69**, 1423-8 (2013).
 - (75) Payan, M., Rouini, M.R., Tajik, N., Ghahremani, M.H. & Tahvilian, R. Hydroxylation index of omeprazole in relation to CYP2C19 polymorphism and sex in a healthy Iranian population. *Daru* **22**, 81 (2014).
 - (76) Park, S. *et al.* Effects of CYP2C19 Genetic Polymorphisms on PK/PD Responses of Omeprazole in Korean Healthy Volunteers. *J Korean Med Sci* **32**, 729-36 (2017).
 - (77) Chang, M. *et al.* Interphenotype differences in disposition and effect on gastrin levels of omeprazole--suitability of omeprazole as a probe for CYP2C19. *Br J Clin Pharmacol* **39**, 511-8 (1995).
 - (78) Rost, K.L. & Roots, I. Nonlinear kinetics after high-dose omeprazole caused by saturation of genetically variable CYP2C19. *Hepatology* **23**, 1491-7 (1996).
 - (79) Zhou, Q., Yamamoto, I., Fukuda, T., Ohno, M., Sumida, A. & Azuma, J. CYP2C19 genotypes and omeprazole metabolism after single and repeated dosing when combined with clarithromycin. *Eur J Clin Pharmacol* **55**, 43-7 (1999).
 - (80) Kita, T. *et al.* Optimal dose of omeprazole for CYP2C19 extensive metabolizers in anti-*Helicobacter pylori* therapy: pharmacokinetic considerations. *Biol Pharm Bull* **25**, 923-7 (2002).
 - (81) Ieiri, I., Kimura, M., Irie, S., Urae, A., Otsubo, K. & Ishizaki, T. Interaction magnitude, pharmacokinetics and pharmacodynamics of ticlopidine in relation to CYP2C19 genotypic status. *Pharmacogenet Genomics* **15**, 851-9 (2005).
 - (82) Niioka, T., Uno, T., Sugimoto, K., Sugawara, K., Hayakari, M. & Tateishi, T. Estimation of CYP2C19 activity by the omeprazole hydroxylation index at a single point in time after intravenous and oral administration. *Eur J Clin Pharmacol* **63**, 1031-8 (2007).
 - (83) Uno, T., Sugimoto, K., Sugawara, K. & Tateishi, T. The role of cytochrome P2C19 in R-warfarin pharmacokinetics and its interaction with omeprazole. *Ther Drug Monit* **30**, 276-81 (2008).

- (84) Chen, B.L. *et al.* Clopidogrel inhibits CYP2C19-dependent hydroxylation of omeprazole related to CYP2C19 genetic polymorphisms. *J Clin Pharmacol* **49**, 574-81 (2009).
- (85) Chaudhry, A.S., Kochhar, R. & Kohli, K.K. Importance of CYP2C19 genetic polymorphism in the eradication of *Helicobacter pylori* in north Indians. *Indian J Med Res* **130**, 437-43 (2009).
- (86) Rost, K.L., Brosicke, H., Brockmoller, J., Scheffler, M., Helge, H. & Roots, I. Increase of cytochrome P450IA2 activity by omeprazole: evidence by the ¹³C-[N-3-methyl]-caffeine breath test in poor and extensive metabolizers of S-mephenytoin. *Clin Pharmacol Ther* **52**, 170-80 (1992).
- (87) Yasuda, S. *et al.* Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4'-hydroxylation status. *Clin Pharmacol Ther* **58**, 143-54 (1995).
- (88) Tybring, G., Bottiger, Y., Widen, J. & Bertilsson, L. Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. *Clin Pharmacol Ther* **62**, 129-37 (1997).
- (89) Bottiger, Y., Tybring, G., Gotharson, E. & Bertilsson, L. Inhibition of the sulfoxidation of omeprazole by ketoconazole in poor and extensive metabolizers of S-mephenytoin. *Clin Pharmacol Ther* **62**, 384-91 (1997).
- (90) Andersson, T., Holmberg, J., Rohss, K. & Walan, A. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. *Br J Clin Pharmacol* **45**, 369-75 (1998).
- (91) Mihara, K., Svensson, U.S., Tybring, G., Hai, T.N., Bertilsson, L. & Ashton, M. Stereospecific analysis of omeprazole supports artemisinin as a potent inducer of CYP2C19. *Fundam Clin Pharmacol* **13**, 671-5 (1999).
- (92) Tassaneeyakul, W., Vannaprasaht, S. & Yamazoe, Y. Formation of omeprazole sulphone but not 5-hydroxyomeprazole is inhibited by grapefruit juice. *Br J Clin Pharmacol* **49**, 139-44 (2000).
- (93) Chang, M., Dahl, M.L., Tybring, G., Gotharson, E. & Bertilsson, L. Use of omeprazole as a probe drug for CYP2C19 phenotype in Swedish Caucasians: comparison with S-mephenytoin hydroxylation phenotype and CYP2C19 genotype. *Pharmacogenetics* **5**, 358-63 (1995).
- (94) Marinac, J.S. *et al.* Determination of CYP2C19 phenotype in black Americans with omeprazole: correlation with genotype. *Clin Pharmacol Ther* **60**, 138-44 (1996).
- (95) Shu, Y. *et al.* 5-hydroxylation of omeprazole by human liver microsomal fractions from Chinese populations related to CYP2C19 gene dose and individual ethnicity. *J Pharmacol Exp Ther* **295**, 844-51 (2000).
- (96) Kim, M.J., Bertino, J.S., Jr., Gaedigk, A., Zhang, Y., Sellers, E.M. & Nafziger, A.N. Effect of sex and menstrual cycle phase on cytochrome P450 2C19 activity with omeprazole used as a biomarker. *Clin Pharmacol Ther* **72**, 192-9 (2002).
- (97) Kearns, G.L. *et al.* Omeprazole disposition in children following single-dose administration. *J Clin Pharmacol* **43**, 840-8 (2003).
- (98) Hunfeld, N.G. *et al.* Effect of CYP2C19*2 and *17 mutations on pharmacodynamics and kinetics of proton pump inhibitors in Caucasians. *Br J Clin Pharmacol* **65**, 752-60 (2008).

- (99) Roman, M. *et al.* Evaluation of the relationship between polymorphisms in CYP2C19 and the pharmacokinetics of omeprazole, pantoprazole and rabeprazole. *Pharmacogenomics* **15**, 1893-901 (2014).
- (100) Sim, S.C. *et al.* A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther* **79**, 103-13 (2006).
- (101) Baldwin, R.M. *et al.* Increased omeprazole metabolism in carriers of the CYP2C19*17 allele; a pharmacokinetic study in healthy volunteers. *Br J Clin Pharmacol* **65**, 767-74 (2008).
- (102) Ishizawa, Y., Yasui-Furukori, N., Takahata, T., Sasaki, M. & Tateishi, T. The effect of aging on the relationship between the cytochrome P450 2C19 genotype and omeprazole pharmacokinetics. *Clin Pharmacokinet* **44**, 1179-89 (2005).
- (103) Kuhlmann, J.B., Wensing, G. & Kuhlmann, J. Correlation of genotype, phenotype, and mRNA expression of CYP2D6 and CYP2C19 in peripheral blood leukocytes (PBLs). *Int J Clin Pharmacol Ther* **52**, 143-50 (2014).
- (104) Nazir, S., Iqbal, Z., Ahmad, L., Shah, Y. & Nasir, F. Pharmacokinetics of omeprazole and its metabolites in three phases of menstrual cycle. *Eur J Drug Metab Pharmacokinet* **40**, 13-22 (2015).
- (105) Nazir, S., Iqbal, Z., Ahmad, L. & Ahmad, S. Variation in pharmacokinetics of omeprazole and its metabolites by gender and CYP2C19 genotype in Pakistani male and female subjects. *Pak J Pharm Sci* **29**, 887-94 (2016).
- (106) Denisenko, N.P. *et al.* Urine metabolic ratio of omeprazole in relation to CYP2C19 polymorphisms in Russian peptic ulcer patients. *Pharmgenomics Pers Med* **10**, 253-9 (2017).
- (107) Roh, H.K., Dahl, M.L., Tybring, G., Yamada, H., Cha, Y.N. & Bertilsson, L. CYP2C19 genotype and phenotype determined by omeprazole in a Korean population. *Pharmacogenetics* **6**, 547-51 (1996).
- (108) Sagar, M., Seensalu, R., Tybring, G., Dahl, M.L. & Bertilsson, L. CYP2C19 genotype and phenotype determined with omeprazole in patients with acid-related disorders with and without *Helicobacter pylori* infection. *Scand J Gastroenterol* **33**, 1034-8 (1998).
- (109) Roh, H.K. *et al.* Omeprazole treatment of Korean patients: effects on gastric pH and gastrin release in relation to CYP2C19 geno- and phenotypes. *Basic Clin Pharmacol Toxicol* **95**, 112-9 (2004).
- (110) Isaza, C., Henao, J., Martinez, J.H., Sepulveda Arias, J.C. & Beltran, L. Phenotype-genotype analysis of CYP2C19 in Colombian mestizo individuals. *BMC Clin Pharmacol* **7**, 6 (2007).
- (111) Koukoulou, M. *et al.* Study of the effect of CYP2C19 polymorphisms on omeprazole pharmacokinetics by utilizing validated LC-MS/MS and Real Time-PCR methods. *J Chromatogr B Analyt Technol Biomed Life Sci* **1047**, 173-9 (2017).
- (112) Xavier, A.S., Kumar, S.V., Sundaram, R., Francis, J. & Shewade, D.G. Effect of antituberculosis treatment on CYP2C19 enzyme activity in genetically polymorphic South Indian Tamilian population. *Fundam Clin Pharmacol* **30**, 607-15 (2016).
- (113) Kearns, G.L., Leeder, J.S. & Gaedigk, A. Impact of the CYP2C19*17 allele on the pharmacokinetics of omeprazole and pantoprazole in children: evidence for a differential effect. *Drug Metab Dispos* **38**, 894-7 (2010).

- (114) Chwiesko, A. *et al.* Effects of different omeprazole dosing on gastric pH in non-variceal upper gastrointestinal bleeding: A randomized prospective study. *J Dig Dis* **17**, 588-99 (2016).
- (115) Hanioka, N., Tsuneto, Y., Saito, Y., Maekawa, K., Sawada, J. & Narimatsu, S. Influence of CYP2C19*18 and CYP2C19*19 alleles on omeprazole 5-hydroxylation: in vitro functional analysis of recombinant enzymes expressed in *Saccharomyces cerevisiae*. *Basic Clin Pharmacol Toxicol* **102**, 388-93 (2008).
- (116) Lee, S.J., Kim, W.Y., Kim, H., Shon, J.H., Lee, S.S. & Shin, J.G. Identification of new CYP2C19 variants exhibiting decreased enzyme activity in the metabolism of S-mephenytoin and omeprazole. *Drug Metab Dispos* **37**, 2262-9 (2009).
- (117) Wang, H. *et al.* Evaluation of the effects of 20 nonsynonymous single nucleotide polymorphisms of CYP2C19 on S-mephenytoin 4'-hydroxylation and omeprazole 5'-hydroxylation. *Drug Metab Dispos* **39**, 830-7 (2011).
- (118) Langae, T.Y. *et al.* The influence of the CYP2C19*10 allele on clopidogrel activation and CYP2C19*2 genotyping. *Pharmacogenet Genomics* **24**, 381-6 (2014).
- (119) Dai, D.P. *et al.* In vitro functional analysis of 24 novel CYP2C19 variants recently found in the Chinese Han population. *Xenobiotica* **45**, 1030-5 (2015).
- (120) Lau, P.S., Leong, K.V., Ong, C.E., Dong, A.N. & Pan, Y. In Vitro Functional Characterisation of Cytochrome P450 (CYP) 2C19 Allelic Variants CYP2C19*23 and CYP2C19*24. *Biochem Genet* **55**, 48-62 (2017).
- (121) Zendehdel, N. *et al.* Role of cytochrome P450 2C19 genetic polymorphisms in the therapeutic efficacy of omeprazole in Iranian patients with erosive reflux esophagitis. *Arch Iran Med* **13**, 406-12 (2010).
- (122) Ando, T. *et al.* A comparative study on endoscopic ulcer healing of omeprazole versus rabeprazole with respect to CYP2C19 genotypic differences. *Dig Dis Sci* **50**, 1625-31 (2005).
- (123) Ando, T., Ishikawa, T., Kokura, S., Naito, Y., Yoshida, N. & Yoshikawa, T. Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype. *Dig Dis Sci* **53**, 933-7 (2008).
- (124) Hizawa, K. *et al.* Late-onset life threatening hemorrhage of omeprazole-resistant duodenal ulcer managed by interventional radiology: report of a case. *Intern Med* **45**, 861-3 (2006).
- (125) Okamura, Y., Takeno, S., Takahashi, Y., Moroga, T., Yamashita, S. & Kawahara, K. Refractory ulcer of reconstructed gastric tube after esophagectomy: a case report. *Ann Thorac Cardiovasc Surg* **19**, 136-9 (2013).
- (126) Fukaya, M., Abe, T. & Nagino, M. Rapid progressive long esophageal stricture caused by gastroesophageal reflux disease after pylorus-preserving pancreaticoduodenectomy. *BMC Surg* **16**, 19 (2016).
- (127) Ji, S. *et al.* Comparison of the efficacy of rabeprazole 10 mg and omeprazole 20 mg for the healing rapidity of peptic ulcer diseases. *J Gastroenterol Hepatol* **21**, 1381-7 (2006).
- (128) Ohkusa, T. *et al.* Effect of CYP2C19 polymorphism on the safety and efficacy of omeprazole in Japanese patients with recurrent reflux oesophagitis. *Aliment Pharmacol Ther* **21**, 1331-9 (2005).
- (129) Furuta, T. *et al.* Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. *Ann Intern Med* **129**, 1027-30 (1998).

- (130) Lin, Y.A. *et al.* Effect of CYP2C19 Gene Polymorphisms on Proton Pump Inhibitor, Amoxicillin, and Levofloxacin Triple Therapy for Eradication of *Helicobacter Pylori*. *Med Sci Monit* **23**, 2701-7 (2017).
- (131) Sapone, A. *et al.* The clinical role of cytochrome p450 genotypes in *Helicobacter pylori* management. *Am J Gastroenterol* **98**, 1010-5 (2003).
- (132) Miehlke, S. *et al.* Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* **24**, 395-403 (2006).
- (133) Sezgin, O., Barlas, I.O., Ucbilek, E., Yengel, E. & Altintas, E. Modified sequential *Helicobacter pylori* eradication therapy using high dose omeprazole and amoxicillin in the initial phase in the extensive metaboliser Turkish patients for CYP2C19 polymorphism is ineffective. *Acta Gastroenterol Belg* **77**, 3-7 (2014).
- (134) Tanigawara, Y. *et al.* CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. *Clin Pharmacol Ther* **66**, 528-34 (1999).
- (135) Miwa, H., Misawa, H., Yamada, T., Nagahara, A., Ohtaka, K. & Sato, N. Clarithromycin resistance, but not CYP2C-19 polymorphism, has a major impact on treatment success in 7-day treatment regimen for cure of *H. pylori* infection: a multiple logistic regression analysis. *Dig Dis Sci* **46**, 2445-50 (2001).
- (136) Yang, J.C. *et al.* Role of omeprazole dosage and cytochrome P450 2C19 genotype in patients receiving omeprazole-amoxicillin dual therapy for *Helicobacter pylori* eradication. *Pharmacotherapy* **31**, 227-38 (2011).
- (137) Sheu, B.S. *et al.* Esomeprazole 40 mg twice daily in triple therapy and the efficacy of *Helicobacter pylori* eradication related to CYP2C19 metabolism. *Aliment Pharmacol Ther* **21**, 283-8 (2005).
- (138) Hong, J. *et al.* Antibiotic resistance and CYP2C19 polymorphisms affect the efficacy of concomitant therapies for *Helicobacter pylori* infection: an open-label, randomized, single-centre clinical trial. *J Antimicrob Chemother* **71**, 2280-5 (2016).
- (139) Dojo, M., Azuma, T., Saito, T., Ohtani, M., Muramatsu, A. & Kuriyama, M. Effects of CYP2C19 gene polymorphism on cure rates for *Helicobacter pylori* infection by triple therapy with proton pump inhibitor (omeprazole or rabeprazole), amoxycillin and clarithromycin in Japan. *Dig Liver Dis* **33**, 671-5 (2001).
- (140) Inaba, T. *et al.* Randomized open trial for comparison of proton pump inhibitors in triple therapy for *Helicobacter pylori* infection in relation to CYP2C19 genotype. *J Gastroenterol Hepatol* **17**, 748-53 (2002).
- (141) Higuchi, K. *et al.* Efficacy and safety of *Helicobacter pylori* eradication therapy with omeprazole, amoxicillin and high- and low-dose clarithromycin in Japanese patients: a randomised, double-blind, multicentre study. *Clin Drug Investig* **26**, 403-14 (2006).
- (142) Zhang, L., Mei, Q., Li, Q.S., Hu, Y.M. & Xu, J.M. The effect of cytochrome P2C19 and interleukin-1 polymorphisms on *H. pylori* eradication rate of 1-week triple therapy with omeprazole or rabeprazole, amoxycillin and clarithromycin in Chinese people. *J Clin Pharm Ther* **35**, 713-22 (2010).
- (143) Nabinger, D.D. *et al.* Influence of CYP2C19 on *Helicobacter pylori* eradication in Brazilian patients with functional dyspepsia. *Genet Mol Res* **15**, (2016).
- (144) Shimatani, T., Inoue, M., Kuroiwa, T., Horikawa, Y., Mieno, H. & Nakamura, M. Effect of omeprazole 10 mg on intragastric pH in three different CYP2C19 genotypes,

- compared with omeprazole 20 mg and lafutidine 20 mg, a new H₂-receptor antagonist. *Aliment Pharmacol Ther* **18**, 1149-57 (2003).
- (145) Sahara, S. *et al.* Twice-daily dosing of esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily omeprazole, rabeprazole or lansoprazole. *Aliment Pharmacol Ther* **38**, 1129-37 (2013).
 - (146) Sugimoto, M. *et al.* Comparison of acid inhibition with standard dosages of proton pump inhibitors in relation to CYP2C19 genotype in Japanese. *Eur J Clin Pharmacol* **70**, 1073-8 (2014).
 - (147) Sugimoto, M., Furuta, T., Shirai, N., Ikuma, M., Hishida, A. & Ishizaki, T. Initial 48-hour acid inhibition by intravenous infusion of omeprazole, famotidine, or both in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther* **80**, 539-48 (2006).
 - (148) Furuta, K. *et al.* Relationship between the acid-inhibitory effects of two proton pump inhibitors and CYP2C19 genotype in Japanese subjects: a randomized two-way crossover study. *J Int Med Res* **38**, 1473-83 (2010).
 - (149) Adachi, K. *et al.* CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. *Aliment Pharmacol Ther* **14**, 1259-66 (2000).
 - (150) Sagar, M., Bertilsson, L., Stridsberg, M., Kjellin, A., Mardh, S. & Seensalu, R. Omeprazole and CYP2C19 polymorphism: effects of long-term treatment on gastrin, pepsinogen I, and chromogranin A in patients with acid related disorders. *Aliment Pharmacol Ther* **14**, 1495-502 (2000).
 - (151) Sagar, M., Tybring, G., Dahl, M.L., Bertilsson, L. & Seensalu, R. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. *Gastroenterology* **119**, 670-6 (2000).
 - (152) Helsby, N.A. *et al.* Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP2C19 phenotype. *Br J Clin Pharmacol* **69**, 516-9 (2010).
 - (153) Dury, S., Nardi, J., Gozalo, C., Lebargy, F. & Deslee, G. Agranulocytosis induced by proton pump inhibitors. *J Clin Gastroenterol* **46**, 859 (2012).
 - (154) Lutz, M. *et al.* Visual disorders associated with omeprazole and their relation to CYP2C19 polymorphism. *Pharmacogenetics* **12**, 73-5 (2002).
 - (155) Ieiri, I. *et al.* Comparison of the kinetic disposition of and serum gastrin change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism. *Eur J Clin Pharmacol* **57**, 485-92 (2001).
 - (156) Furuta, T., Shirai, N., Xiao, F., Ohashi, K. & Ishizaki, T. Effect of high-dose lansoprazole on intragastric pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19. *Clin Pharmacol Ther* **70**, 484-92 (2001).
 - (157) Shirai, N. *et al.* Comparison of lansoprazole and famotidine for gastric acid inhibition during the daytime and night-time in different CYP2C19 genotype groups. *Aliment Pharmacol Ther* **16**, 837-46 (2002).
 - (158) Furuta, T. *et al.* Effect of cytochrome P4502C19 genotypic differences on cure rates for gastroesophageal reflux disease by lansoprazole. *Clin Pharmacol Ther* **72**, 453-60 (2002).
 - (159) Schwab, M., Schaeffeler, E., Klotz, U. & Treiber, G. CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of *Helicobacter pylori*. *Clin Pharmacol Ther* **76**, 201-9 (2004).

- (160) Miura, M. *et al.* Pharmacokinetic differences between the enantiomers of lansoprazole and its metabolite, 5-hydroxylansoprazole, in relation to CYP2C19 genotypes. *Eur J Clin Pharmacol* **60**, 623-8 (2004).
- (161) Uno, T., Yasui-Furukori, N., Takahata, T., Sugawara, K. & Tateishi, T. Determination of lansoprazole and two of its metabolites by liquid-liquid extraction and automated column-switching high-performance liquid chromatography: application to measuring CYP2C19 activity. *J Chromatogr B Analyt Technol Biomed Life Sci* **816**, 309-14 (2005).
- (162) Saito, M. *et al.* Effects of clarithromycin on lansoprazole pharmacokinetics between CYP2C19 genotypes. *Br J Clin Pharmacol* **59**, 302-9 (2005).
- (163) Uno, T., Yasui-Furukori, N., Takahata, T., Sugawara, K. & Tateishi, T. Lack of significant effect of grapefruit juice on the pharmacokinetics of lansoprazole and its metabolites in subjects with different CYP2C19 genotypes. *J Clin Pharmacol* **45**, 690-4 (2005).
- (164) Xu, H.R., Chen, W.L., Li, X.N. & Chu, N.N. The effect of CYP2C19 activity on pharmacokinetics of lansoprazole and its active metabolites in healthy subjects. *Pharm Biol* **48**, 947-52 (2010).
- (165) Zhang, D., Wang, X., Yang, M., Wang, G. & Liu, H. Effects of CYP2C19 polymorphism on the pharmacokinetics of lansoprazole and its main metabolites in healthy Chinese subjects. *Xenobiotica* **41**, 511-7 (2011).
- (166) Gumus, E. *et al.* Evaluation of lansoprazole as a probe for assessing cytochrome P450 2C19 activity and genotype-phenotype correlation in childhood. *Eur J Clin Pharmacol* **68**, 629-36 (2012).
- (167) Li, C.Y. *et al.* A correlative study of polymorphisms of CYP2C19 and MDR1 C3435T with the pharmacokinetic profiles of lansoprazole and its main metabolites following single oral administration in healthy adult Chinese subjects. *Eur J Drug Metab Pharmacokinet* **39**, 121-8 (2014).
- (168) Ko, J.W., Jang, I.J., Shin, J.G., Nam, S.K., Shin, S.G. & Flockhart, D.A. Theophylline pharmacokinetics are not altered by lansoprazole in CYP2C19 poor metabolizers. *Clin Pharmacol Ther* **65**, 606-14 (1999).
- (169) Kim, K.A. *et al.* Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. *Clin Pharmacol Ther* **72**, 90-9 (2002).
- (170) Hu, Y.R., Qiao, H.L. & Kan, Q.C. Pharmacokinetics of lansoprazole in Chinese healthy subjects in relation to CYP2C19 genotypes. *Acta Pharmacol Sin* **25**, 986-90 (2004).
- (171) Niioka, T. *et al.* Estimation of the area under the concentration-time curve of racemic lansoprazole by using limited plasma concentration of lansoprazole enantiomers. *Eur J Clin Pharmacol* **64**, 503-9 (2008).
- (172) Miura, M. *et al.* Correlation between R/S enantiomer ratio of lansoprazole and CYP2C19 activity after single oral and enteral administration. *Chirality* **22**, 635-40 (2010).
- (173) Sohn, D.R., Kwon, J.T., Kim, H.K. & Ishizaki, T. Metabolic disposition of lansoprazole in relation to the S-mephenytoin 4'-hydroxylation phenotype status. *Clin Pharmacol Ther* **61**, 574-82 (1997).
- (174) Howden, C.W. *et al.* Dose-response evaluation of the antisecretory effect of continuous infusion intravenous lansoprazole regimens over 48 h. *Aliment Pharmacol Ther* **23**, 975-84 (2006).
- (175) Miura, M. *et al.* Influence of ABCB1 C3435T polymorphism on the pharmacokinetics of lansoprazole and gastroesophageal symptoms in Japanese renal transplant recipients

- classified as CYP2C19 extensive metabolizers and treated with tacrolimus. *Int J Clin Pharmacol Ther* **44**, 605-13 (2006).
- (176) Zalloum, I., Hakooz, N. & Arafat, T. Genetic polymorphism of CYP2C19 in a Jordanian population: influence of allele frequencies of CYP2C19*1 and CYP2C19*2 on the pharmacokinetic profile of lansoprazole. *Mol Biol Rep* **39**, 4195-200 (2012).
 - (177) Zhang, Y.X., Wei, S.J., Yang, X.Y., Zhang, W.P., Wang, X.Y. & Dang, H.W. Effects of genetic polymorphisms of CYP2C19*2/*3 and MDR1 C3435T on the pharmacokinetics of lansoprazole in healthy Chinese subjects. *Int J Clin Pharmacol Ther* **52**, 850-5 (2014).
 - (178) Katsuki, H., Nakamura, C., Arimori, K., Fujiyama, S. & Nakano, M. Genetic polymorphism of CYP2C19 and lansoprazole pharmacokinetics in Japanese subjects. *Eur J Clin Pharmacol* **52**, 391-6 (1997).
 - (179) Miura, M. *et al.* Influence of CYP2C19 and ABCB1 polymorphisms on plasma concentrations of lansoprazole enantiomers after enteral administration. *Xenobiotica* **40**, 630-6 (2010).
 - (180) Zhang, D. *et al.* Pharmacokinetics of lansoprazole and its main metabolites after single intravenous doses in healthy Chinese subjects. *Xenobiotica* **42**, 1156-62 (2012).
 - (181) Zhang, D. *et al.* Pharmacokinetics of lansoprazole and its main metabolites after single and multiple intravenous doses in healthy Chinese subjects. *Eur J Drug Metab Pharmacokinet* **38**, 209-15 (2013).
 - (182) Yasui-Furukori, N., Saito, M., Uno, T., Takahata, T., Sugawara, K. & Tateishi, T. Effects of fluvoxamine on lansoprazole pharmacokinetics in relation to CYP2C19 genotypes. *J Clin Pharmacol* **44**, 1223-9 (2004).
 - (183) Niioka, T., Yasui-Furukori, N., Uno, T., Sugawara, K., Kaneko, S. & Tateishi, T. Identification of a single time-point for plasma lansoprazole measurement that adequately reflects area under the concentration-time curve. *Ther Drug Monit* **28**, 321-5 (2006).
 - (184) Sakurai, Y. *et al.* Population pharmacokinetics and proton pump inhibitory effects of intravenous lansoprazole in healthy Japanese males. *Biol Pharm Bull* **30**, 2238-43 (2007).
 - (185) Kawamura, M. *et al.* Cytochrome P450 2C19 polymorphism influences the preventive effect of lansoprazole on the recurrence of erosive reflux esophagitis. *J Gastroenterol Hepatol* **22**, 222-6 (2007).
 - (186) Furuta, T. *et al.* CYP2C19 genotype is associated with symptomatic recurrence of GERD during maintenance therapy with low-dose lansoprazole. *Eur J Clin Pharmacol* **65**, 693-8 (2009).
 - (187) Yoshizawa, Y. *et al.* Factors associated with healing of artificial ulcer after endoscopic submucosal dissection with reference to *Helicobacter pylori* infection, CYP2C19 genotype, and tumor location: Multicenter randomized trial. *Dig Endosc* **28**, 162-72 (2016).
 - (188) Kawamura, M. *et al.* The effects of lansoprazole on erosive reflux oesophagitis are influenced by CYP2C19 polymorphism. *Aliment Pharmacol Ther* **17**, 965-73 (2003).
 - (189) Okudaira, K., Furuta, T., Shirai, N., Sugimoto, M. & Miura, S. Concomitant dosing of famotidine with a triple therapy increases the cure rates of *Helicobacter pylori* infections in patients with the homozygous extensive metabolizer genotype of CYP2C19. *Aliment Pharmacol Ther* **21**, 491-7 (2005).

- (190) Isomoto, H. *et al.* Lafutidine, a novel histamine H₂-receptor antagonist, vs lansoprazole in combination with amoxicillin and clarithromycin for eradication of *Helicobacter pylori*. *Helicobacter* **8**, 111-9 (2003).
- (191) Furuta, T. *et al.* Influence of CYP2C19 polymorphism and *Helicobacter pylori* genotype determined from gastric tissue samples on response to triple therapy for H pylori infection. *Clin Gastroenterol Hepatol* **3**, 564-73 (2005).
- (192) Furuta, T. *et al.* Effect of MDR1 C3435T polymorphism on cure rates of *Helicobacter pylori* infection by triple therapy with lansoprazole, amoxicillin and clarithromycin in relation to CYP 2C19 genotypes and 23S rRNA genotypes of H. pylori. *Aliment Pharmacol Ther* **26**, 693-703 (2007).
- (193) Suzuki, T. *et al.* Influence of smoking and CYP2C19 genotypes on H. pylori eradication success. *Epidemiol Infect* **135**, 171-6 (2007).
- (194) Settin, A., Abdalla, A.F., Al-Hussaini, A.S., El-Baz, R. & Galal, A. Cure rate of *Helicobacter pylori* infection in Egyptian children related to CYP2C19 gene polymorphism. *Indian J Gastroenterol* **33**, 330-5 (2014).
- (195) Ozdil, B., Akkiz, H., Bayram, S., Bekar, A., Akgollu, E. & Sandikci, M. Influence of CYP2C19 functional polymorphism on *Helicobacter pylori* eradication. *Turk J Gastroenterol* **21**, 23-8 (2010).
- (196) Kawabata, H. *et al.* Effect of different proton pump inhibitors, differences in CYP2C19 genotype and antibiotic resistance on the eradication rate of *Helicobacter pylori* infection by a 1-week regimen of proton pump inhibitor, amoxicillin and clarithromycin. *Aliment Pharmacol Ther* **17**, 259-64 (2003).
- (197) Liou, J.M. *et al.* Sequential therapy for 10 days versus triple therapy for 14 days in the eradication of *Helicobacter pylori* in the community and hospital populations: a randomised trial. *Gut* **65**, 1784-92 (2016).
- (198) Liou, J.M. *et al.* Levofloxacin Sequential Therapy vs Levofloxacin Triple Therapy in the Second-Line Treatment of *Helicobacter pylori*: A Randomized Trial. *Am J Gastroenterol* **111**, 381-7 (2016).
- (199) Hagiwara, T. *et al.* Improvement in symptoms after H₂-receptor antagonist-based therapy for eradication of H pylori infection. *World J Gastroenterol* **13**, 3836-40 (2007).
- (200) Sugimoto, M. *et al.* Evidence that the degree and duration of acid suppression are related to *Helicobacter pylori* eradication by triple therapy. *Helicobacter* **12**, 317-23 (2007).
- (201) Srinarong, C., Siramolpiwat, S., Wongcha-um, A., Mahachai, V. & Vilaichone, R.K. Improved eradication rate of standard triple therapy by adding bismuth and probiotic supplement for *Helicobacter pylori* treatment in Thailand. *Asian Pac J Cancer Prev* **15**, 9909-13 (2014).
- (202) Furuta, T. *et al.* Effect of concomitant dosing of famotidine with lansoprazole on gastric acid secretion in relation to CYP2C19 genotype status. *Aliment Pharmacol Ther* **22**, 67-74 (2005).
- (203) Furuta, T. *et al.* [13C]-pantoprazole breath test to predict CYP2C19 phenotype and efficacy of a proton pump inhibitor, lansoprazole. *Aliment Pharmacol Ther* **30**, 294-300 (2009).
- (204) Nishino, M. *et al.* Preventive effects of lansoprazole and famotidine on gastric mucosal injury induced by low-dose aspirin in *Helicobacter pylori*-negative healthy volunteers. *J Clin Pharmacol* **51**, 1079-86 (2011).

- (205) Hata, S. *et al.* Intragastric acidity during the first day following administration of low-dose proton pump inhibitors: a randomized crossover study. *Clin Res Hepatol Gastroenterol* **37**, 296-301 (2013).
- (206) Lang, J.E. *et al.* Lansoprazole Is Associated with Worsening Asthma Control in Children with the CYP2C19 Poor Metabolizer Phenotype. *Ann Am Thorac Soc* **12**, 878-85 (2015).
- (207) Desta, Z. *et al.* Rapid identification of the hepatic cytochrome P450 2C19 activity using a novel and noninvasive [¹³C]pantoprazole breath test. *J Pharmacol Exp Ther* **329**, 297-305 (2009).
- (208) Furuta, T., Iwaki, T. & Umemura, K. [¹³C]pantoprazole breath test as a predictor of the anti-platelet function of clopidogrel. *Eur J Clin Pharmacol* **66**, 457-63 (2010).
- (209) Thacker, D.L., Modak, A., Nguyen, P.D., Flockhart, D.A. & Desta, Z. Stereoselective pharmacokinetics of stable isotope (+/-)-[¹³C]-pantoprazole: Implications for a rapid screening phenotype test of CYP2C19 activity. *Chirality* **23**, 904-9 (2011).
- (210) Thacker, D.L., Modak, A., Flockhart, D.A. & Desta, Z. Is (+)-[¹³C]-pantoprazole better than (+/-)-[¹³C]-pantoprazole for the breath test to evaluate CYP2C19 enzyme activity? *J Breath Res* **7**, 016001 (2013).
- (211) Choi, K.D. *et al.* Optimal dose of intravenous pantoprazole in patients with peptic ulcer bleeding requiring endoscopic hemostasis in Korea. *J Gastroenterol Hepatol* **24**, 1617-24 (2009).
- (212) Shao, J.G., Jiang, W., Li, K.Q., Lu, J.R. & Sun, Y.Y. Blood concentration of pantoprazole sodium is significantly high in hepatogenic peptic ulcer patients, especially those with a poor CYP2C19 metabolism. *J Dig Dis* **10**, 55-60 (2009).
- (213) Ward, R.M. *et al.* Single-dose, multiple-dose, and population pharmacokinetics of pantoprazole in neonates and preterm infants with a clinical diagnosis of gastroesophageal reflux disease (GERD). *Eur J Clin Pharmacol* **66**, 555-61 (2010).
- (214) Hunfeld, N.G. *et al.* A comparison of the acid-inhibitory effects of esomeprazole and pantoprazole in relation to pharmacokinetics and CYP2C19 polymorphism. *Aliment Pharmacol Ther* **31**, 150-9 (2010).
- (215) Gawronska-Szklarz, B. *et al.* CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. *Eur J Clin Pharmacol* **68**, 1267-74 (2012).
- (216) Tanaka, M. *et al.* Metabolic disposition of pantoprazole, a proton pump inhibitor, in relation to S-mephenytoin 4'-hydroxylation phenotype and genotype. *Clin Pharmacol Ther* **62**, 619-28 (1997).
- (217) Tanaka, M. *et al.* Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-mephenytoin. *Clin Pharmacol Ther* **69**, 108-13 (2001).
- (218) Shakhnovich, V. *et al.* Obese Children Require Lower Doses of Pantoprazole Than Nonobese Peers to Achieve Equal Systemic Drug Exposures. *J Pediatr* **193**, 102-8 e1 (2018).
- (219) Karaca, R.O. *et al.* Effects of Genetic Polymorphisms of Cytochrome P450 Enzymes and MDR1 Transporter on Pantoprazole Metabolism and Helicobacter pylori Eradication. *Basic Clin Pharmacol Toxicol* **120**, 199-206 (2017).
- (220) Gawronska-Szklarz, B., Siuda, A., Kurzawski, M., Bielicki, D., Marlicz, W. & Drozdziak, M. Effects of CYP2C19, MDR1, and interleukin 1-B gene variants on the eradication rate

- of *Helicobacter pylori* infection by triple therapy with pantoprazole, amoxicillin, and metronidazole. *Eur J Clin Pharmacol* **66**, 681-7 (2010).
- (221) Sheu, B.S., Cheng, H.C., Yeh, Y.C. & Chang, W.L. CYP2C19 genotypes determine the efficacy of on-demand therapy of pantoprazole for reflux esophagitis as Los-Angeles grades C and D. *J Gastroenterol Hepatol* **27**, 104-9 (2012).
 - (222) Chen, W.Y., Chang, W.L., Tsai, Y.C., Cheng, H.C., Lu, C.C. & Sheu, B.S. Double-dosed pantoprazole accelerates the sustained symptomatic response in overweight and obese patients with reflux esophagitis in Los Angeles grades A and B. *Am J Gastroenterol* **105**, 1046-52 (2010).
 - (223) Oh, J.H. *et al.* Effects of CYP2C19 and MDR1 genotype on the eradication rate of *Helicobacter pylori* infection by triple therapy with pantoprazole, amoxycillin and clarithromycin. *J Gastroenterol Hepatol* **24**, 294-8 (2009).
 - (224) Kurzawski, M., Gawronska-Szklarz, B., Wrzesniewska, J., Siuda, A., Starzynska, T. & Drozdziak, M. Effect of CYP2C19*17 gene variant on *Helicobacter pylori* eradication in peptic ulcer patients. *Eur J Clin Pharmacol* **62**, 877-80 (2006).
 - (225) Kang, J.M. *et al.* Effect of the CYP2C19 polymorphism on the eradication rate of *Helicobacter pylori* infection by 7-day triple therapy with regular proton pump inhibitor dosage. *J Gastroenterol Hepatol* **23**, 1287-91 (2008).
 - (226) Lee, J.Y. *et al.* Factors affecting first-line triple therapy of *Helicobacter pylori* including CYP2C19 genotype and antibiotic resistance. *Dig Dis Sci* **59**, 1235-43 (2014).
 - (227) Ormeci, A. *et al.* Effect of cytochrome P450 2C19 polymorphisms on the *Helicobacter pylori* eradication rate following two-week triple therapy with pantoprazole or rabeprazole. *Eur Rev Med Pharmacol Sci* **20**, 879-85 (2016).
 - (228) Hsu, P.I. *et al.* A Randomized Controlled Study Comparing Reverse Hybrid Therapy and Standard Triple Therapy for *Helicobacter pylori* Infection. *Medicine (Baltimore)* **94**, e2104 (2015).
 - (229) Oh, J.H. *et al.* Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. *J Gastroenterol Hepatol* **22**, 1429-34 (2007).
 - (230) Sun, L.N. *et al.* Impact of Gastric H(+)/K(+)-ATPase rs2733743 on the Intragastric pH-Values of Dexlansoprazole Injection in Chinese Subjects. *Front Pharmacol* **8**, 670 (2017).
 - (231) Grabowski, B. & Lee, R.D. Absorption, distribution, metabolism and excretion of [14C]dexlansoprazole in healthy male subjects. *Clin Drug Investig* **32**, 319-32 (2012).
 - (232) Lou, H.Y., Chang, C.C., Sheu, M.T., Chen, Y.C. & Ho, H.O. Optimal dose regimens of esomeprazole for gastric acid suppression with minimal influence of the CYP2C19 polymorphism. *Eur J Clin Pharmacol* **65**, 55-64 (2009).
 - (233) Hunfeld, N.G., Touw, D.J., Mathot, R.A., van Schaik, R.H. & Kuipers, E.J. A comparison of the acid-inhibitory effects of esomeprazole and rabeprazole in relation to pharmacokinetics and CYP2C19 polymorphism. *Aliment Pharmacol Ther* **35**, 810-8 (2012).
 - (234) Yi, S. *et al.* A novel K⁺ competitive acid blocker, YH4808, sustains inhibition of gastric acid secretion with a faster onset than esomeprazole: randomised clinical study in healthy volunteers. *Aliment Pharmacol Ther* **46**, 337-46 (2017).
 - (235) Sheu, B.S., Chang, W.L., Cheng, H.C., Kao, A.W. & Lu, C.C. Body mass index can determine the healing of reflux esophagitis with Los Angeles Grades C and D by esomeprazole. *Am J Gastroenterol* **103**, 2209-14 (2008).

- (236) Schwab, M. *et al.* Esomeprazole-induced healing of gastroesophageal reflux disease is unrelated to the genotype of CYP2C19: evidence from clinical and pharmacokinetic data. *Clin Pharmacol Ther* **78**, 627-34 (2005).
- (237) Su, J., Zhou, X., Chen, H., Hao, B., Zhang, W. & Zhang, G. Efficacy of 1st-line bismuth-containing quadruple therapies with levofloxacin or clarithromycin for the eradication of *Helicobacter pylori* infection: A 1-week, open-label, randomized trial. *Medicine (Baltimore)* **96**, e5859 (2017).
- (238) Miehlke, S. *et al.* One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter* **13**, 69-74 (2008).
- (239) Kuo, C.H. *et al.* Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial. *J Antimicrob Chemother* **63**, 1017-24 (2009).
- (240) Kuo, C.H. *et al.* Comparison of 10 day bismuth quadruple therapy with high-dose metronidazole or levofloxacin for second-line *Helicobacter pylori* therapy: a randomized controlled trial. *J Antimicrob Chemother* **68**, 222-8 (2013).
- (241) Saito, Y. *et al.* First-line eradication for *Helicobacter pylori*-positive gastritis by esomeprazole-based triple therapy is influenced by CYP2C19 genotype. *World J Gastroenterol* **21**, 13548-54 (2015).
- (242) Shimoyama, T. *et al.* Randomized Trial Comparing Esomeprazole and Rabeprazole in First-line Eradication Therapy for *Helicobacter pylori* Infection based on the Serum Levels of Pepsinogens. *Intern Med* **56**, 1621-7 (2017).
- (243) Lee, V.W. *et al.* Pharmacogenetics of esomeprazole or rabeprazole-based triple therapy in *Helicobacter pylori* eradication in Hong Kong non-ulcer dyspepsia Chinese subjects. *J Clin Pharm Ther* **35**, 343-50 (2010).
- (244) Pan, X. *et al.* Efficacy and tolerability of first-line triple therapy with levofloxacin and amoxicillin plus esomeprazole or rabeprazole for the eradication of *Helicobacter pylori* infection and the effect of CYP2C19 genotype: a 1-week, randomized, open-label study in Chinese adults. *Clin Ther* **32**, 2003-11 (2010).
- (245) Wu, D.C. *et al.* *Helicobacter pylori* infection: a randomized, controlled study comparing 2 rescue therapies after failure of standard triple therapies. *Medicine (Baltimore)* **90**, 180-5 (2011).
- (246) Liou, J.M. *et al.* Empirical modified sequential therapy containing levofloxacin and high-dose esomeprazole in second-line therapy for *Helicobacter pylori* infection: a multicentre clinical trial. *J Antimicrob Chemother* **66**, 1847-52 (2011).
- (247) Song, Z., Zhou, L., Zhang, J., He, L., Bai, P. & Xue, Y. Hybrid Therapy as First-Line Regimen for *Helicobacter pylori* Eradication in Populations with High Antibiotic Resistance Rates. *Helicobacter* **21**, 382-8 (2016).
- (248) Song, Z., Zhou, L., Zhang, J., He, L., Bai, P. & Xue, Y. Levofloxacin, bismuth, amoxicillin and esomeprazole as second-line *Helicobacter pylori* therapy after failure of non-bismuth quadruple therapy. *Dig Liver Dis* **48**, 506-11 (2016).
- (249) Sahara, S. *et al.* Potent Gastric Acid Inhibition Over 24 Hours by 4-Times Daily Dosing of Esomeprazole 20 mg. *Digestion* **91**, 277-85 (2015).
- (250) Kagami, T. *et al.* Potent acid inhibition by vonoprazan in comparison with esomeprazole, with reference to CYP2C19 genotype. *Aliment Pharmacol Ther* **43**, 1048-59 (2016).

- (251) Li, Z.S., Zhan, X.B., Xu, G.M., Cheng, N.N. & Liao, Z. Effect of esomeprazole and rabeprazole on intragastric pH in healthy Chinese: an open, randomized crossover trial. *J Gastroenterol Hepatol* **22**, 815-20 (2007).
- (252) Horai, Y. *et al.* Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. *Aliment Pharmacol Ther* **15**, 793-803 (2001).
- (253) Sugimoto, M. *et al.* Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther* **76**, 290-301 (2004).
- (254) Hu, Y.M., Xu, J.M., Mei, Q., Xu, X.H. & Xu, S.Y. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotype in healthy Chinese subjects. *Acta Pharmacol Sin* **26**, 384-8 (2005).
- (255) Hu, Y.M., Mei, Q., Xu, X.H., Hu, X.P., Hu, N.Z. & Xu, J.M. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphism in Chinese Hans. *World J Gastroenterol* **12**, 4750-3 (2006).
- (256) Uno, T., Shimizu, M., Yasui-Furukori, N., Sugawara, K. & Tateishi, T. Different effects of fluvoxamine on rabeprazole pharmacokinetics in relation to CYP2C19 genotype status. *Br J Clin Pharmacol* **61**, 309-14 (2006).
- (257) Miura, M. *et al.* Enantioselective disposition of rabeprazole in relation to CYP2C19 genotypes. *Br J Clin Pharmacol* **61**, 315-20 (2006).
- (258) Shimizu, M., Uno, T., Yasui-Furukori, N., Sugawara, K. & Tateishi, T. Effects of clarithromycin and verapamil on rabeprazole pharmacokinetics between CYP2C19 genotypes. *Eur J Clin Pharmacol* **62**, 597-603 (2006).
- (259) Yamano, H.O., Matsushita, H.O. & Yanagiwara, S. Plasma concentration of rabeprazole after 8-week administration in gastroesophageal reflux disease patients and intragastric pH elevation. *J Gastroenterol Hepatol* **23**, 534-40 (2008).
- (260) Hayato, S. *et al.* Dose-response relationships of rabeprazole 5, 10, 20, and 40 mg once daily on suppression of gastric acid secretion through the night in healthy Japanese individuals with different CYP2C19 genotypes. *Eur J Clin Pharmacol* **68**, 579-88 (2012).
- (261) Lin, C.J., Yang, J.C., Uang, Y.S., Chern, H.D. & Wang, T.H. Time-dependent amplified pharmacokinetic and pharmacodynamic responses of rabeprazole in cytochrome P450 2C19 poor metabolizers. *Pharmacotherapy* **23**, 711-9 (2003).
- (262) Niioka, T., Uno, T., Yasui-Furukori, N., Shimizu, M., Sugawara, K. & Tateishi, T. Identification of the time-point which gives a plasma rabeprazole concentration that adequately reflects the area under the concentration-time curve. *Eur J Clin Pharmacol* **62**, 855-61 (2006).
- (263) Sheng, Y.C., Wang, K., He, Y.C., Yang, J. & Zheng, Q.S. Effect of CYP2C19 genotypes on the pharmacokinetic/pharmacodynamic relationship of rabeprazole after a single oral dose in healthy Chinese volunteers. *Eur J Clin Pharmacol* **66**, 1165-9 (2010).
- (264) Yang, J.C., Yang, Y.F., Uang, Y.S., Lin, C.J. & Wang, T.H. Pharmacokinetic-pharmacodynamic analysis of the role of CYP2C19 genotypes in short-term rabeprazole-based triple therapy against *Helicobacter pylori*. *Br J Clin Pharmacol* **67**, 503-10 (2009).
- (265) Toda, R., Shiramoto, M., Komai, E., Yoshii, K., Hirayama, M. & Kawabata, Y. Pharmacokinetics and Pharmacodynamics of Azeloprazole Sodium, a Novel Proton Pump Inhibitor, in Healthy Japanese Volunteers. *J Clin Pharmacol* **58**, 425-33 (2018).

- (266) Kinoshita, Y., Ashida, K., Hongo, M. & Japan Rabeprazole Study Group for, N. Randomised clinical trial: a multicentre, double-blind, placebo-controlled study on the efficacy and safety of rabeprazole 5 mg or 10 mg once daily in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* **33**, 213-24 (2011).
- (267) Nakamura, K. *et al.* Limited Effect of Rebamipide in Addition to Proton Pump Inhibitor (PPI) in the Treatment of Post-Endoscopic Submucosal Dissection Gastric Ulcers: A Randomized Controlled Trial Comparing PPI Plus Rebamipide Combination Therapy with PPI Monotherapy. *Gut Liver* **10**, 917-24 (2016).
- (268) Ariizumi, K. *et al.* Therapeutic effects of 10 mg/day rabeprazole administration on reflux esophagitis was not influenced by the CYP2C19 polymorphism. *J Gastroenterol Hepatol* **21**, 1428-34 (2006).
- (269) Kinoshita, Y., Kusano, M., Iwakiri, K., Fujishiro, M., Tachikawa, N. & Haruma, K. Efficacy and Safety Profile of Z-215 (Azeloprazole Sodium), a Proton Pump Inhibitor, Compared with Rabeprazole Sodium in Patients with Reflux Esophagitis: A Phase II, Multicenter, Randomized, Double-Blind, Comparative Study. *Curr Ther Res Clin Exp* **88**, 26-34 (2018).
- (270) Furuta, T. *et al.* Effects of genotypic differences in CYP2C19 status on cure rates for *Helicobacter pylori* infection by dual therapy with rabeprazole plus amoxicillin. *Pharmacogenetics* **11**, 341-8 (2001).
- (271) Lay, C.S. & Lin, C.J. Correlation of CYP2C19 genetic polymorphisms with *Helicobacter pylori* eradication in patients with cirrhosis and peptic ulcer. *J Chin Med Assoc* **73**, 188-93 (2010).
- (272) Hokari, K. *et al.* Efficacy of triple therapy with rabeprazole for *Helicobacter pylori* infection and CYP2C19 genetic polymorphism. *Aliment Pharmacol Ther* **15**, 1479-84 (2001).
- (273) Hsu, P.I. *et al.* Quadruple rescue therapy for *Helicobacter pylori* infection after two treatment failures. *Eur J Clin Invest* **38**, 404-9 (2008).
- (274) Sugimoto, M. *et al.* Four-times-daily Dosing of Rabeprazole with Sitafloracin, High-Dose Amoxicillin, or Both for Metronidazole-Resistant Infection with *Helicobacter pylori* in Japan. *Helicobacter* **22**, (2017).
- (275) Isomoto, H. *et al.* High-dose rabeprazole-amoxicillin versus rabeprazole-amoxicillin-metronidazole as second-line treatment after failure of the Japanese standard regimen for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* **18**, 101-7 (2003).
- (276) Lee, S.B. *et al.* Efficacy of triple therapy with rabeprazole for *Helicobacter pylori* infection in relation to CYP2C19 genotype. *Korean J Gastroenterol* **42**, 468-75 (2003).
- (277) Kuwayama, H. *et al.* Rabeprazole-based eradication therapy for *Helicobacter pylori*: a large-scale study in Japan. *Aliment Pharmacol Ther* **25**, 1105-13 (2007).
- (278) Sugimoto, M. *et al.* Efficacy of tailored *Helicobacter pylori* eradication treatment based on clarithromycin susceptibility and maintenance of acid secretion. *Helicobacter* **19**, 312-8 (2014).
- (279) Sugimoto, M., Sahara, S., Ichikawa, H., Kagami, T., Uotani, T. & Furuta, T. High *Helicobacter pylori* cure rate with sitafloracin-based triple therapy. *Aliment Pharmacol Ther* **42**, 477-83 (2015).
- (280) Yang, J.C. *et al.* High-dose dual therapy is superior to standard first-line or rescue therapy for *Helicobacter pylori* infection. *Clin Gastroenterol Hepatol* **13**, 895-905 e5 (2015).

- (281) Sugimoto, M. *et al.* Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. *Clin Pharmacol Ther* **77**, 302-11 (2005).
- (282) Sugimoto, M. *et al.* Esophageal mucosal injury with low-dose aspirin and its prevention by rabeprazole. *J Clin Pharmacol* **50**, 320-30 (2010).
- (283) Nishino, M. *et al.* Relationship between low-dose aspirin-induced gastric mucosal injury and intragastric pH in healthy volunteers. *Dig Dis Sci* **55**, 1627-36 (2010).
- (284) Sugimoto, M. *et al.* Rabeprazole 10 mg q.d.s. decreases 24-h intragastric acidity significantly more than rabeprazole 20 mg b.d. or 40 mg o.m., overcoming CYP2C19 genotype. *Aliment Pharmacol Ther* **36**, 627-34 (2012).
- (285) Shimatani, T., Inoue, M., Kuroiwa, T. & Horikawa, Y. Rabeprazole 10 mg twice daily is superior to 20 mg once daily for night-time gastric acid suppression. *Aliment Pharmacol Ther* **19**, 113-22 (2004).
- (286) Kagami, T. *et al.* One-day front-loading with four doses of rabeprazole followed by a standard twice-daily regimen provides sufficient acid inhibition in extensive metabolizers of CYP2C19. *Eur J Clin Pharmacol* **71**, 1467-75 (2015).
- (287) Nuki, Y. *et al.* The influence of CYP2C19 polymorphisms on exacerbating effect of rabeprazole in celecoxib-induced small bowel injury. *Aliment Pharmacol Ther* **46**, 331-6 (2017).
- (288) Metz, D.C., Amer, F., Hunt, B., Vakily, M., Kukulka, M.J. & Samra, N. Lansoprazole regimens that sustain intragastric pH > 6.0: an evaluation of intermittent oral and continuous intravenous infusion dosages. *Aliment Pharmacol Ther* **23**, 985-95 (2006).
- (289) Kawara, F. *et al.* Factors associated with residual gastroesophageal reflux disease symptoms in patients receiving proton pump inhibitor maintenance therapy. *World J Gastroenterol* **23**, 2060-7 (2017).
- (290) Furuta, T. *et al.* Effect of genotypic differences in CYP2C19 on cure rates for *Helicobacter pylori* infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. *Clin Pharmacol Ther* **69**, 158-68 (2001).
- (291) Take, S. *et al.* Interleukin-1beta genetic polymorphism influences the effect of cytochrome P 2C19 genotype on the cure rate of 1-week triple therapy for *Helicobacter pylori* infection. *Am J Gastroenterol* **98**, 2403-8 (2003).
- (292) Furuta, T. *et al.* Polymorphism of interleukin-1beta affects the eradication rates of *Helicobacter pylori* by triple therapy. *Clin Gastroenterol Hepatol* **2**, 22-30 (2004).
- (293) Miki, I. *et al.* Impact of clarithromycin resistance and CYP2C19 genetic polymorphism on treatment efficacy of *Helicobacter pylori* infection with lansoprazole- or rabeprazole-based triple therapy in Japan. *Eur J Gastroenterol Hepatol* **15**, 27-33 (2003).
- (294) Sugimoto, M., Furuta, T., Shirai, N., Ikuma, M., Hishida, A. & Ishizaki, T. Influences of proinflammatory and anti-inflammatory cytokine polymorphisms on eradication rates of clarithromycin-sensitive strains of *Helicobacter pylori* by triple therapy. *Clin Pharmacol Ther* **80**, 41-50 (2006).
- (295) Gawronska-Szklarz, B. *et al.* Effect of CYP2C19 and MDR1 polymorphisms on cure rate in patients with acid-related disorders with *Helicobacter pylori* infection. *Eur J Clin Pharmacol* **61**, 375-9 (2005).
- (296) Kuo, C.H. *et al.* Rabeprazole can overcome the impact of CYP2C19 polymorphism on quadruple therapy. *Helicobacter* **15**, 265-72 (2010).

- (297) Miyoshi, M. *et al.* A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rabeprazole, in dual therapy for *Helicobacter pylori* infection in relation to CYP2C19 genetic polymorphism. *J Gastroenterol Hepatol* **16**, 723-8 (2001).
- (298) Egan, L.J., Myhre, G.M., Mays, D.C., Dierkhising, R.A., Kammer, P.P. & Murray, J.A. CYP2C19 pharmacogenetics in the clinical use of proton-pump inhibitors for gastro-oesophageal reflux disease: variant alleles predict gastric acid suppression, but not oesophageal acid exposure or reflux symptoms. *Aliment Pharmacol Ther* **17**, 1521-8 (2003).
- (299) Shiotani, A. *et al.* Hypergastrinemia in Long-Term Use of Proton Pump Inhibitors. *Digestion* **97**, 154-62 (2018).
- (300) Wada, F. *et al.* Polymorphism of CYP2C19 and gastric emptying in patients with proton pump inhibitor-resistant gastric ulcers. *J Int Med Res* **30**, 413-21 (2002).