Supplement to:

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

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

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

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

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

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

Clinical	CYP2C19 NMs have a decreased healing rate of ulcers when treated with omeprazole.	Hizawa, *et al.* 2006 (124)	Weak
Clinical	CYP2C19 IMs have a decreased healing rate of ulcers when treated with omeprazole compared to CYP2C19 NMs.	Okamura, *et al.* 2013 (125)	Weak
Clinical	CYP2C19 RMs have a decreased healing rate of reflux when treated with omeprazole compared to CYP2C19 NMs.	Fukaya, *et al.* 2016 (126)	Weak
Clinical	CYP2C19 PMs are not associated with healing rate of ulcers when treated with omeprazole as compared to IMs+NMs.	Ji, *et al.* 2006 (127)	Weak
Clinical	*CYP2C19* is not associated with healing rate of reflux when treated with omeprazole when comparing PMs vs IMs vs NMs.	Ohkusa, *et al.* 2005 (128)	Weak
***H. pylori* eradication**			
Clinical	CYP2C19 PMs are associated with an increased *H. pylori* eradication rate when treated with omeprazole as compared to IMs.	Furuta, *et al.* 1998 (129) Lin, *et al.* 2017 (130)	Weak
Clinical	CYP2C19 PMs are associated with an increased *H. pylori* eradication rate when treated with omeprazole as compared to NMs.	Furuta, *et al.* 1998 (129) Chaudhry, *et al.* 2009 (85) Lin, *et al.* 2017 (130)	Moderate
Clinical	CYP2C19 IMs are associated with an increased *H. pylori* eradication rate when treated with omeprazole as compared to NMs	Furuta, *et al.* 1998 (129) Sapone, *et al.* 2003 (131) Miehlke, *et al.* 2006 (132) Sezgin, *et al.* 2014 (133) Lin, *et al.* 2017 (130)	Weak
Clinical	CYP2C19 PMs are associated with increased *H. pylori* eradication rate when treated with omeprazole as compared to IMs+NMs.	Tanigawara, *et al.*1999 (134) Miwa, *et al.* 2001 (135) Yang, *et al.* 2011 (136)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased *H. pylori* eradication rate when treated with omeprazole as compared to NMs.	Sheu, *et al.* 2005 (137) Hong, *et al.* 2016 (138)	Moderate
Clinical	*CYP2C19* is associated with *H. pylori* eradication rate when treated with omeprazole when comparing PMs vs IMs vs NMs.	Furuta, *et al.*1998 (129) Dojo, *et al.* 2001 (139) Inaba, *et al.* 2002 (140) Higuchi, *et al.* 2006 (141) Zhang, *et al.* 2010 (142) Nabinger, *et al.* 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, *et al.*1999 (58) Shirai, *et al.*2001 (61) Shimatani, *et al.* 2003 (144) Hu, *et al.* 2007 (70) Wang, *et al.* 2010 (71) Sahara, *et al.* 2013 (145) Sugimoto, *et al.* 2014 (146) Park, *et al.* 2017 (76)	Moderate
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with omeprazole as compared to NMs.	Furuta, *et al.* 1999 (58) Shirai, *et al.* 2001 (61) Shimatani, *et al.*2003 (144) Sugimoto, *et al.* 2006 (147) Hu, *et al.* 2007 (70) Wang, *et al.* 2010 (71) Furuta, *et al.* 2010 (148) Sahara, *et al.* 2013 (145) Sugimoto, *et al.* 2014 (146) Park, *et al.* 2017 (76)	Moderate
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with omeprazole as compared to NMs.	Furuta, *et al.* 1999 (58) Adachi, *et al.* 2000 (149) Sagar, *et al.* 2000 (150) Sagar, *et al.* 2000 (151) Sagar, *et al.* 2000 (150) Shirai, *et al.* 2001 (61) Sugimoto, *et al.* 2006 (147) Hu, *et al.* 2007 (70) Hunfeld, *et al.* 2008 (98) Sahara, *et al.* 2013 (145) Sugimoto, *et al.* 2014 (146)	Moderate
Clinical	CYP2C19 NMs are not associated with altered acid secretion indices when treated with omeprazole as compared to RMs	Hunfeld, *et al.*2008 (98) Chwiesko, *et al.* 2016 (114)	Weak
Clinical	CYP2C19 PMs have better acid secretion indices when treated with omeprazole as compared to IMs+NMs.	Yang, *et al.* 2011 (136)	Weak

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

[a]Rating 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, *et al.* 2001 (60) Ieiri, *et al.* 2001(155) Furuta, *et al.* 2001 (156) Shirai, *et al.* 2002 (157) Furuta, *et al.* 2002 (158) Schwab, *et al.* 2004 (159) Miura, *et al.* 2004 (160) Uno, *et al.* 2005 (161) Saito, *et al.* 2005 (162) Uno, *et al.* 2005 (163) Qiao, *et al.* 2006 (66) Xu, *et al.* 2010 (164) Zhang, *et al.* 2011 (165) Gumus, *et al.* 2012 (166) Li, *et al.* 2014 (167)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of lansoprazole as compared to NMs.	Ko, *et al.* 1999 (168) Sakai, *et al.* 2001 (60) Ieiri, *et al.* 2001 (155) Furuta, *et al.* 2001 (156) Shirai, *et al.* 2002 (157) Kim, *et al.* 2002 (169) Furuta, *et al.* 2002 (158) Hu, *et al.* 2004 (170) Schwab, *et al.* 2004 (159) Miura, *et al.* 2004 (160) Uno, *et al.* 2005 (161) Saito, *et al.* 2005 (162)	High

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

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

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

		Nishino, *et al.* 2011 (204) Sahara, *et al.* 2013 (145) Sugimoto, *et al.* 2014 (146)	
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with lansoprazole as compared to NMs.	Furuta, *et al.* 2001 (156) Shirai, *et al.* 2002 (157) Furuta, *et al.* 2005 (202) Howden, *et al.* 2006 (174) Hunfeld, *et al.* 2008 (98) Sahara, *et al.* 2013 (145) Sugimoto, *et al.* 2014 (146)	High
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with lansoprazole as compared to IMs+NMs.	Hata, *et al.* 2013 (205)	Moderate
Other			
Clinical	CYP2C19 PMs+IMs are associated with decreased asthma control when treated with lansoprazole as compared to NMs.	Lang, *et al.* 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, *et al.* 2013 (51)	Weak

[a]Rating 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, *et al.* 2009 (207) Furuta, *et al.* 2009 (203) Furuta, *et al.* 2010 (208) Thacker, *et al.* 2011 (209) Thacker, *et al.* 2013 (210)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of pantoprazole as compared to NMs.	Choi, *et al.* 2009 (211) Shao, *et al.* 2009 (212) Furuta, *et al.* 2009 (203) Furuta, *et al.* 2010 (208) Ward, *et al.* 2010 (213)	High
Clinical	CYP2C19 PMs (as determined by phenotyping) have decreased metabolism of pantoprazole as compared to NMs.	Andersson, *et al.* 1998 (90)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to NMs.	Kearns, *et al.* 2008 (44) Furuta, *et al.* 2009 (203) Furuta, *et al.* 2010 (208) Hunfeld, *et al.* 2010 (214) Gawronska-Szklarz, *et al.* 2012 (215) Roman, *et al.* 2014 (99)	High
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to RMs.	Roman, *et al.* 2014 (99)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of pantoprazole as compared to UMs.	Roman, *et al.* 2014 (99)	Moderate
Clinical	CYP2C19 NMs are not associated with altered metabolism of pantoprazole as compared to RMs.	Hunfeld, *et al.* 2008 (98) Roman, *et al.* 2014 (99)	Weak
Clinical	CYP2C19 NMs are associated with decreased metabolism of pantoprazole as compared to UMs.	Gawronska-Szklarz, *et al.* 2012 (215)	Weak

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

Clinical	CYP2C19 PMs are not associated with altered *H. pylori* eradication rate when treated with pantoprazole as compared to IMs+NMs.	Kang*, et al.* 2008 (225) Lee*, et al.* 2014 (226)	Weak
Clinical	CYP2C19 PMs+IMs are associated with increased *H. pylori* eradication rate when treated with pantoprazole as compared to NMs.	Kurzawski, *et al*. 2006 (224) Ormeci, *et al.* 2016 (227)	Moderate
Clinical	CYP2C19 PMs+IMs are not associated with altered *H. pylori* eradication rate when treated with pantoprazole as compared to NMs+RMs+UMs.	Gawronska-Szklarz, *et al*. 2010 (220)	Weak
Clinical	*CYP2C19* is **not** associated with *H. pylori* eradication rate when treated with pantoprazole when comparing PMs vs IMs vs NMs.	Hsu, *et al*. 2015 (228)	Moderate
Clinical	*CYP2C19* is not associated with *H. pylori* eradication rate when treated with pantoprazole when comparing PMs+IMs vs NMs vs RMs+UMs.	Karaca, *et al*. 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*, et al.* 2007 (229)	Weak
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with pantoprazole as compared to NMs.	Oh*, et al.* 2007 (229)	Weak
Clinical	CYP2C19 IMs are associated with better acid secretion indices when treated with pantoprazole as compared to NMs.	Oh*, et al.* 2007 (229) Hunfeld*, et al.* 2010 (214)	Moderate
Clinical	CYP2C19 NMs are not associated with altered acid secretion indices when treated with pantoprazole as compared to RMs.	Hunfeld*, et al.* 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*, et al.* 2012 (221)	Moderate

[a]Rating 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, *et al.* 2017 (230)	Moderate
Clinical	CYP2C19 PMs are associated with decreased metabolism of dexlansoprazole as compare to NMs.	Sun, *et al.* 2017 (230)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of dexlansoprazole as compared to NMs.	Sun, *et al.* 2017 (230)	Moderate
Clinical	CYP2C19 PMs have decreased metabolism of dexlansoprazole as compared to IMs+NMs.	Grabowski and Lee, *et al.* 2012 (231)	Weak
Efficacy			
Clinical	CYP2C19 PMs are not associated with altered acid secretion indices when treated with dexlansoprazole as compared to IMs.	Sun, *et al.* 2017 (230)	Moderate
Clinical	CYP2C19 PMs are associated with better acid secretion indices when treated with dexlansoprazole as compared to NMs.	Sun, *et al.* 2017 (230)	Moderate
Clinical	CYP2C19 IMs are not associated with altered acid secretion indices when treated with dexlansoprazole as compared to NMs.	Sun, *et al.* 2017 (230)	Weak

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

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

[a]Rating 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, *et al.* 2001 (252) Ieiri, *et al.* 2001 (155) Sugimoto, *et al.* 2004 (253) Hu, *et al.*2005 (254) Hu, *et al.* 2006 (255) Qiao, *et al.* 2006 (66) Uno, *et al.* 2006 (256) Miura, *et al.* 2006 (257) Shimizu, *et al.* 2006 (258) Yamano, *et al.* 2008 (259) Hayato, *et al.* 2012 (260)	High
Clinical	CYP2C19 PMs are associated with decreased metabolism of rabeprazole as compared to NMs.	Horai, *et al.* 2001 (252) Ieiri, *et al.* 2001 (155) Shirai, *et al.* 2001 (61) Lin, *et al.* 2003 (261) Sugimoto, *et al.* 2004 (253) Hu, *et al.* 2005 (254) Qiao, *et al.* 2006 (66) Uno, *et al.* 2006 (256) Miura, *et al.* 2006 (257) Shimizu, *et al.* 2006 (258) Niioka, *et al.* 2006 (262) Hu, *et al.* 2006 (255) Yamano, *et al.* 2008 (259) Sheng, *et al.* 2010 (263) Hayato, *et al.* 2012 (260)	High

Clinical	CYP2C19 PMs (as determined by phenotyping) are associated with decreased metabolism of rabeprazole as compared to NMs.	Yasuda, *et al.* 1995 (87)	Moderate
Clinical	CYP2C19 IMs are associated with decreased metabolism of rabeprazole as compared to NMs.	Horai, *et al.* 2001 (252) Ieiri, *et al.* 2001 (155) Sugimoto, *et al.* 2004 (253) Hu, *et al.* 2005 (254) Hu, *et al.* 2006 (255) Yamano, *et al.* 2008 (259) Sheng, *et al.* 2010 (263) Hunfeld, *et al.* 2012 (233) Hayato, *et al.* 2012 (260) Roman, *et al.* 2014 (99)	Weak
Clinical	CYP2C19 IMs are associated with decreased metabolism of rabeprazole as compared to RMs.	Roman, *et al.* 2014 (99)	Weak
Clinical	CYP2C19 NMs are not associated with altered metabolism of rabeprazole as compared to RMs.	Roman, *et al.* 2014 (99)	Weak
Clinical	CYP2C19 PMs are associated with decreased metabolism of rabeprazole as compared to IMs+NMs.	Yang, *et al.* 2009 (264)	Moderate
Clinical	CYP2C19 is associated with rabeprazole metabolism when comparing PMs vs IMs vs NMs.	Toda, *et al.* 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, *et al.* 2006 (127)	Moderate
Clinical	CYP2C19 is not associated with remission of reflux when treated with rabeprazole when comparing PMs vs IMs vs NMs.	Kinoshita, *et al.* 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, *et al.* 2005 (122) Ando, *et al.* 2008 (123) Nakamura, *et al.* 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, *et al.* 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, *et al.* 2006 (268) Kinoshita, *et al.* 2018 (269)	Moderate

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

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

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

[a]Rating 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, *et al.* 2006 (288)	Weak
Clinical	CYP2C19 IMs have decreased metabolism of lansoprazole and pantoprazole as compared to NMs.	Metz, *et al.* 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, *et al.* 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, *et al.* 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, *et al.* 2017 (289)	Weak
***H. pylori* eradication**			
Clinical	CYP2C19 PMs are not associated with altered *H. pylori* eradication rate when treated with lansoprazole and omeprazole as compared to IMs.	Furuta, *et al.* 2001 (290)	Weak
Clinical	CYP2C19 PMs are not associated with altered *H. pylori* eradication rate when treated with lansoprazole, omeprazole and rabeprazole as compared to IMs.	Take, *et al.* 2003 (291)	Weak
Clinical	CYP2C19 PMs are associated with an increased *H. pylori* eradication rate when treated with lansoprazole and omeprazole as compare to NMs.	Furuta, *et al.* 2001 (290) Furuta, *et al*. 2004 (292)	Moderate

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

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

[a]Rating 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 *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 rapid metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 normal metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 likely intermediate metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 intermediate metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 likely poor metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation
CYP2C19 poor metabolizer	Inconsistent findings regarding the effect of *CYP2C19* genotype on pharmacokinetics and therapeutic response	No recommendation	No recommendation

[a]The 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.
[b]Rating scheme described in the **Supplemental Material**

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