Supplemental Material

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for C*YP2C9* and Nonsteroidal Anti-inflammatory Drugs

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CPIC UPDATES

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published in full on www.cpicpgx.org. Information will be reviewed and updated periodically on that website.

LITERATURE REVIEW

The PubMed® database (1966 to July 2018) was searched for the following keywords: (celecoxib OR diclofenac OR flurbiprofen OR ibuprofen OR meloxicam OR naproxen OR piroxicam OR tenoxicam OR sulindac OR nabumetone OR indomethacin) AND (CYP2C9 OR cytochrome p450 2c9) AND English[Language]) NOT review[Publication Type]. Using these search terms, 465 publications were identified. Due to the high linkage disequilibrium between *CYP2C8*3* and *CYP2C9*2* (**Table S11, Figure S1**), additional searches were conducted using the search terms: (diclofenac OR ibuprofen OR piroxicam) AND (CYP2C8 OR cytochrome p450 2c8). 91 articles were identified. Study inclusion criteria included publications that incorporated analyses for the association between *CYP2C9* genotypes and nonsteroidal anti-inflammatory drugs (NSAIDs) pharmacokinetic and pharmacodynamic parameters as well as clinical outcomes. Non-English manuscripts were excluded. Following the application of these inclusion and exclusion criteria, 138 publications were reviewed and included in the evidence table (**Table S1**).

AVAILABLE GENETIC TEST OPTIONS

Commercially available genetic testing options change over time. Below is some information that may assist in evaluating options.

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (1). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see ***CYP2C9* Allele Definition Table**, ***CYP2C9* Allele Functionality Table** and ***CYP2C9* Allele Frequency Table** (https://cpicpgx.org/cpic-guideline-for-nsaids-based-on-CYP2C9-genotype/) adhere to

these allele nomenclature standards (1). Moreover, the ***CYP2C9* Allele Definition Table**, ***CYP2C9* Allele Functionality Table**, and ***CYP2C9* 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. Furthermore, the Association for Molecular Pathology and College of American Pathologists have published a joint 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 *CYP2C9* (2).

The Genetic Testing Registry (GTR) provides a central location for voluntary submission of genetic test information by laboratories and is available at http://www.ncbi.nlm.nih.gov/gtr/.

LINKING GENETIC VARIABILITY TO VARIABILITY IN DRUG-RELATED PHENOTYPES

Celecoxib. Celecoxib biotransformation to its primary metabolite, hydroxycelecoxib, is predominantly catalyzed by CYP2C9 (3-5). CYP3A4 plays a minor role (3, 6) (see PharmGKB celecoxib pathway; https://www.pharmgkb.org/pathway/PA165816736 (7)). The *CYP2C9*3* no function variant causes a marked decrease in celecoxib metabolism *in vitro* and *in vivo,* and is associated with a significant increase in celecoxib plasma exposure and half-life *in vivo* (5, 8-14). The magnitude of the effects appears largest in CYP2C9 poor metabolizers (9, 11) (**Figure S2**). In contrast, the decreased function *CYP2C9*2* variant is not associated with differences in celecoxib exposure or clearance (9, 10, 13, 15).

Flurbiprofen. Flurbiprofen has been used as a phenotypic probe of CYP2C9 metabolism. No function *CYP2C9* alleles, including *CYP2C9*3,* cause significantly decreased flurbiprofen metabolism *in vitro*, whereas the effect of *CYP2C9*2* is modest (16-18). *In vivo, CYP2C9*3* is associated with decreased flurbiprofen metabolism and clearance and

increased plasma exposure, whereas *CYP2C9*2* is not associated with altered flurbiprofen exposure (19-22).

Lornoxicam. Lornoxicam 5'hydroxylation is predominantly catalyzed by CYP2C9, and *in vitro* studies have shown that the no function *CYP2C9*3* and **13* alleles markedly decrease intrinsic clearance, whereas *CYP2C9*2* has little effect (23, 24). The *in vivo* effect of the *CYP2C9*3* and **13* alleles are associated with reduced clearance, increased plasma concentrations, and a prolonged half-life (23, 25); the impact of the *CYP2C9*2* allele has not been studied *in vivo* (26, 27).

Ibuprofen. Ibuprofen is usually available as a racemic mixture containing R (-) and S (+) ibuprofen. CYP2C9 is the major enzyme involved in the hydroxylation of S (+) ibuprofen, whereas R (-) ibuprofen hydroxylation is catalyzed by CYP2C8 and CYP2C9 (28-30) (see PharmGKB Ibuprofen pathway; https://www.pharmgkb.org/pathway/PA166041114 (31)). The *CYP2C9*3* allele is associated with decreased clearance, increased plasma concentration and prolonged half-life of the R (-) and S (+) enantiomers *in vivo* (32-36), whereas the effect of *CYP2C9*2* is moderate, more pronounced with R (-) ibuprofen, and likely impacted by linkage disequilibrium with the decreased function *CYP2C8*3* variant allele (33-37) (**Figure S3**).

Meloxicam. Meloxicam hydroxylation is catalyzed mainly by CYP2C9, and to a minor extent by CYP3A4 (38). The no function *CYP2C9* alleles *CYP2C9*3* and *CYP2C9*13* are associated with decreased meloxicam metabolism, decreased clearance, and increased plasma concentrations *in vivo*, and the magnitude of these effects was largest in CYP2C9 poor metabolizers (39-43). The *CYP2C9*2* decreased function allele appears to be associated with a modest decrease in meloxicam metabolism and clearance (39, 40) (**Figure S4**).

Piroxicam and tenoxicam. Piroxicam and tenoxicam intrinsic clearance are also markedly decreased by the *CYP2C9*3* allele *in vitro* (44). Although the number of available *in vivo* studies is very limited, the *CYP2C9*2* and **3* alleles are each associated

with reduced piroxicam clearance and higher plasma concentrations, with observation of a dramatic prolongation in half-life to 420 hours in a single *CYP2C9*3/*3* subject (45, 46). The published evidence with tenoxicam is scarce. The *CYP2C9*3* allele is also associated with increased plasma tenoxicam concentrations *in vivo,* whereas the effect of *CYP2C9*2* is less pronounced (44, 47, 48).

Diclofenac. Diclofenac 4'hydroxylation is predominantly catalyzed by CYP2C9, and used as a phenotypic probe of CYP2C9 metabolic activity (4). Diclofenac undergoes metabolism by multiple other pathways (see PharmGKB pathway; https://www.pharmgkb.org/pathway/PA166163705)), including 5-hydroxylation by CYP2C8 (49) and acyl glucuronidation by UGT2B7 (50). *CYP2C9* no function alleles, such as *CYP2C9*3*, significantly decrease diclofenac 4-hydroxylation *in vitro* and *in vivo* (17, 44, 51-58); however, these effects on diclofenac metabolism did not translate into altered diclofenac pharmacokinetics *in vivo* such that *CYP2C9*3* is not associated with decreased diclofenac oral clearance or increased plasma concentrations (59-62). The *CYP2C9*2* allele also is not associated with altered diclofenac pharmacokinetics (59, 60).

Other NSAIDs that do not rely on CYP2C9-mediated metabolism as their primary clearance pathway *in vivo* include aspirin, naproxen (UGT2B7, CYP1A2), sulindac (multiple pathways), etoricoxib (CYP3A4), parecoxib (CYP3A4), and valdecoxib (CYP3A4) (63).

LEVELS OF EVIDENCE

The evidence summarized in **Supplemental Table S1-S12** is graded using a scale modified slightly from Valdes et al. (64)

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 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.

STRENGTH OF DOSING RECOMMENDATIONS

CPIC's dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data (**Supplemental Tables S1-S12**) as well as on some existing disease-specific consensus guidances (65-67). Some of the factors that are taken into account in evaluating the evidence supporting dosage recommendations include: *in vivo* clinical outcome data for NSAIDs, *in vivo* pharmacokinetic and pharmacodynamic data for NSAIDs, *in vitro* enzyme activity of expressed wild-type or variant-containing *CYP2C9*, *in vitro* CYP2C9 enzyme activity from tissues isolated from individuals of known *CYP2C9* genotypes, *in vivo* pre-clinical pharmacokinetic and pharmacodynamic studies, and *in vitro* studies of CYP2C9 protein stability.
Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just four categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (68):

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 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."

OTHER CONSIDERATIONS

Variation in other genes may also influence outcomes of NSAID therapy, but the evidence is insufficient to recommend using these variants to guide NSAID dosing at this time. Several NSAIDs, including ibuprofen, diclofenac, and piroxicam (28, 49, 69), are metabolized by CYP2C8, and clearance of these agents may be altered in individuals who carry decreased function alleles for *CYP2C8* (e.g. *CYP2C8*3* or *CYP2C8*4*). Several studies have investigated the impact of the *CYP2C8*3* allele (rs11572080 and rs10509681) (**Tables S1-S11**). As noted above, the *CYP2C8*3* allele is in strong linkage disequilibrium with the *CYP2C9*2* allele (**Figure S1)**, and the number of individuals in these studies who carried only *CYP2C8*3* was insufficient to dissect the relative contribution of this variant from that of *CYP2C9*2*. The *CYP2C8*4* allele (rs1058930) also exhibited decreased metabolism of ibuprofen and diclofenac *in vitro* (28, 70, 71), but there are limited data describing the role of this variant on pharmacokinetics or outcomes *in vivo* (54, 72).

The impact of genetic variation in the drug targets, COX-1 (*PTGS1*) and COX-2 (*PTGS2*), on the outcomes of NSAID therapy has also been investigated. The results of studies evaluating these gene-drug interactions in the context of cancer prevention (73-79), prevention of cardiovascular events with low-dose aspirin (80-84), analgesic response (85), risk of adverse cardiovascular events (86, 87) or liver toxicity (88) are conflicting, and the reported associations have not been replicated in independent cohorts. Thus, additional research is necessary to clarify whether these variants should be incorporated into clinical decision making.

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN EHR WITH CDS

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (89-93). See https://cpicpgx.org/cpic-guideline-for-nsaids-based-on-CYP2C9-genotype/ for resources to support the adoption of CPIC guidelines within an EHR. 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 the use of *CYP2C9* genotype results to guide NSAID use and use in an EHR.

Effectively incorporating 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 (94, 95). 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**). 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 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 (89, 96).

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 full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2C9* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems for genes relevant to the CPIC guideline (see https://www.pharmgkb.org/page/CYP2C9RefMaterials.

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 provides gene-drug specific tables that offer 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 drugs relevant to the CPIC

guideline (see https://cpicpgx.org/cpic-guideline-for-nsaids-based-on-CYP2C9-genotype/).

EFFECT SIZE ESTIMATION USING META-ANALYSES

Meta-analyses were performed to assess the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on systemic exposure for each of the NSAIDs metabolized by CYP2C9. Sample sizes and reported AUC data were extracted from clinical pharmacokinetic studies reviewed for this guideline. Studies were excluded from the meta-analysis if 1) plasma drug concentrations were not measured, 2) mean and standard deviation of AUC was not reported or could not be estimated, 3) *CYP2C9*2* or *CYP2C9*3* genotypes were not reported. If less than three studies could be identified that contributed data to at least one genotype comparison for a given NSAID, the meta-analysis was not performed. This resulted in meta-analyses for celecoxib, ibuprofen, and meloxicam (**Figures S2-S4**). The effect of each variant *CYP2C9* diplotype (*CYP2C9*1/*3*, *CYP2C9*3/*3,* *CYP2C9*1/*2*, *CYP2C9*2/*2*, and *CYP2C9*2/*3*) relative to *CYP2C9*1/*1* was determined using a random effects model with Hartung-Knapp adjustment. The results are reported as the ratio of the mean (ROM) AUC in the variant diplotype to that of the *CYP2C9*1/*1* control group. This allowed pooling of studies regardless of dose or number of doses administered. Statistical analyses were performed using R software package meta.

SUPPLEMENTAL TABLE S1. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH CELECOXIB PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	CYP2C9 is the major enzyme involved in the formation of hydroxycelecoxib, which is the primary celecoxib metabolite.	Tang, *et al*. (2000) (3) Sandberg, *et al*. (2002) (5) Murayama, *et al*. (2018) (4)	High
In vitro	CYP3A4 plays a minor role in celecoxib metabolism.	Tang, *et al*. (2000) (3) Rodrigues, *et al*. (2006) (6)	High
In vitro Clinical	Celecoxib inhibits the metabolism of CYP2D6 substrates both *in vitro* and *in vivo*.	Werner, *et al*. (2003) (97)	Moderate
In vitro	*CYP2C9*2* exhibits decreased CYP2C9 catalytic activity and decreased metabolism of celecoxib.	Tang, *et al*. (2001) (10) Sandberg , *et al*. (2002) (5)	Weak
In vitro	*CYP2C9*3* exhibits substantially decreased CYP2C9 catalytic activity and decreased metabolism of celecoxib.	Tang, *et al*. (2001) (10) Sandberg, *et al*. (2002) (5)	High
Clinical	*CYP2C9*3* is associated with decreased celecoxib metabolism (increased celecoxib plasma concentration and decreased oral clearance).	Tang, *et al*. (2001) (10) Brenner, *et al*. (2003) (15) Kirchheiner, *et al*. (2003) (9) Fries, *et al*. (2006) (98) Lundblad, *et al*. (2006) (8) Prieto-Perez, *et al*. (2013) (13) Liu, *et al*. (2015) (12) Kim, *et al*. (2017) (11) Stempak, *et al*. (2005) (14)	High
Clinical	*CYP2C9*2* is not associated with decreased celecoxib metabolism (increased celecoxib plasma concentration and decreased oral clearance).	Tang, *et al*. (2001) (10) Brenner, *et al*. (2003) (15) Kirchheiner, *et al*. (2003) (9) Fries, *et al*. (2006) (98) Prieto-Perez, *et al*. (2013) (13)	Moderate

Clinical	*CYP2C9*13* is associated with decreased celecoxib metabolism (increased celecoxib plasma concentration and decreased oral clearance).	Kim, *et al*. (2017) (11)	Weak
Clinical	Impaired celecoxib metabolism due to *CYP2C9* decreased function alleles may be associated with increased toxicity of celecoxib therapy.	Stempak, *et al*. (2005) (14) Chan, *et al*. (2009) (99) Gupta, *et al*. (2015) (100)	Weak
Clinical	*CYP2C9*3* is associated with enhanced efficacy/response to celecoxib or with the protective effect of celecoxib on colorectal adenoma risk.	Murto, *et al*. (2015) (101) Chan, *et al*. (2009) (99)	Weak
Clinical	CYP2C9 poor metabolizers have higher plasma celecoxib exposure compared to normal metabolizers.	Werner, *et al*. (2002) (102)	Weak

SUPPLEMENTAL TABLE S2. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH FLURBIPROFEN PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	CYP2C9 is the major metabolizing enzyme for flurbiprofen	Yamazaki, *et al*. (1998) (17) Tracy, *et al*. (1996) (103) Tracy, *et al*. (1995) (104) Tracy , *et al*. 2002) (18)	High
In vitro	*CYP2C9*3* and other *CYP2C9* alleles (*CYP2C9*5, *8, *13, *16, *19, *23, *31, *39, *42, *45* and **52*) exhibit significantly decreased CYP2C9 catalytic activity and decreased metabolism of flurbiprofen.	Wang, *et al*. (2015) (16) Yamazaki, *et al*. (1998) (17) Tracy, *et al*. (2002) (18)	High
In vitro	*CYP2C9*2* exhibits moderately decreased metabolism of flurbiprofen.	Wang, *et al*. (2015) (16) Yamazaki, *et al*. (1998) (17)	High
In vitro	Using flurbiprofen as a substrate, other *CYP2C9* alleles (*CYP2C9*11, *14, *27, *29, *36, *40, *41, *49* and **55*) exhibit lower catalytic activity than *CYP2C9*2*, but higher than *CYP2C9*3*.	Wang, *et al*. (2015) (16)	Moderate
In vitro	Using flurbiprofen as a substrate, other *CYP2C9* alleles (*CYP2C9*34, *37, *38, *44, *46, *47, *48, *50, *51* and **54*) exhibit lower catalytic activity than *CYP2C9*1*, but higher than *CYP2C9*2*.	Wang, *et al*. (2015) (16)	Moderate
Clinical	*CYP2C9*3* is associated with decreased flurbiprofen metabolism (increased flurbiprofen plasma concentration and decreased oral clearance).	Swar, *et al*. (2016) (19) Lee, *et al*. (2015) (20) Daali, *et al*. (2012) (105) Lee, *et al*. (2003) (21) Lee, *et al*. (2003) (22)	High
Clinical	*CYP2C9*2* is not associated with decreased flurbiprofen metabolism.	Vogl, *et al*. (2015) (106) (107) Swar, *et al*. (2016) (19) Daali, *et al*. (2012) (105) Lee, *et al*. (2003) (21) Lee, *et al*. (2003) (22)	Moderate

SUPPLEMENTAL TABLE S3. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH LORNOXICAM PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	Lornoxicam 5-hydroxylation is catalyzed exclusively by CYP2C9	Bonnabry, *et al*. (1996) (108)	Moderate
In vitro	*CYP2C9*3* and *CYP2C9*13* exhibit significantly decreased metabolism of lornoxicam.	Guo, *et al*. (2005) (23) Iida, *et al*. (2004) (24)	Moderate
In vitro	*CYP2C9*2* does not exhibit decreased lornoxicam metabolism.	Iida, *et al*. (2004) (24)	Weak
Clinical	*CYP2C9*3* is associated with decreased lornoxicam metabolism (increased lornoxicam plasma concentration and decreased oral clearance).	Choi, *et al*. (2011) (25) Liu, *et al*. (2006) (26) Guo, *et al*. (2005) (23) Zhang, *et al*. (2005) (27)	Moderate
Clinical	*CYP2C9*13* is associated with decreased lornoxicam metabolism (increased lornoxicam plasma concentration and decreased oral clearance).	Choi, *et al*. (2011) (25) Guo, *et al*. (2005) (23) Zhang, *et al*. (2005) (27)	High

SUPPLEMENTAL TABLE S4. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH IBUPROFEN PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	CYP2C9 is the major metabolizing enzyme for S (+) ibuprofen and R (-) ibuprofen hydroxylation. CYP2C8 also plays a minor role.	Chang, *et al*. (2008) (28) McGinnity, *et al*. (2000) (29) Hamman, *et al*. (1997) (30)	High
In vitro	*CYP2C9*2* exhibits decreased ibuprofen hydroxylation.	Hamman, *et al*. (1997) (30)	Moderate
Clinical	*CYP2C9*3* is associated with decreased S (+) and R (-) ibuprofen metabolism (increased ibuprofen plasma concentration and decreased oral clearance of S (+) ibuprofen, R (-) ibuprofen, and racemic ibuprofen).	Ochoa, *et al*. (2015) (32) Karaźniewicz-Lada, *et al*. (2009) (33) López-Rodríguez, *et al*. (2008) (34) García-Martín, *et al*. (2004) (35) Kirchheiner, *et al*. (2002) (36)	Moderate
Clinical	*CYP2C9*2* is associated with moderately decreased S (+) ibuprofen metabolism (increased S (+) ibuprofen plasma concentration and decreased oral clearance). *CYP2C9*2* is not associated with decreased R (-) ibuprofen metabolism.	Ochoa, *et al*. (2015) (32) Karaźniewicz-Łada, *et al*. (2009) (33) López-Rodríguez, *et al*. (2008) (34) Martinez, *et al*. (2004) (37) García-Martín, *et al*. (2004) (35) Kirchheiner, *et al*. (2002) (36)	Weak
Clinical	*CYP2C9*3* is associated with increased ibuprofen pharmacodynamic effects (increased maximal inhibition of thromboxane B_2 formation).	López-Rodríguez, *et al*. (2008) (34) Kirchheiner, *et al*. (2002) (36) (109)	Weak
Clinical	*CYP2C9*2* is not associated with increased ibuprofen pharmacodynamic effects	López-Rodríguez, *et al*. (2008) (34) Kirchheiner, *et al*. (2002) (36)	Weak
Clinical	*CYP2C9*2* and *CYP2C9*3* may be associated with increased odds of response to ibuprofen.	Durrmeyer, *et al*. (2010) (110) Samowitz, *et al*. (2006) (109)	Weak

SUPPLEMENTAL TABLE S5. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH MELOXICAM PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	Meloxicam hydroxylation is mainly catalyzed by CYP2C9. CYP3A4 plays a minor role.	Chesné, *et al*. (1998) (38)	Moderate
Clinical	*CYP2C9*3* is associated with significantly decreased meloxicam metabolism (increased meloxicam plasma concentration and decreased oral clearance).	Hasunuma, *et al*. (2016) (40) Zhang, *et al*. (2014) (41) Lee, *et al*. (2014) (42) Aoyama, *et al*. (2017) (39)	Moderate
Clinical	*CYP2C9*3*/**3* genotype is associated with significantly lower meloxicam metabolism compared to *CYP2C9*1/*3*.	Lee, *et al*. (2014) (42) Aoyama, *et al*. (2017) (39)	Moderate
Clinical	*CYP2C9*13* is associated with significantly decreased meloxicam metabolism (increased meloxicam plasma concentration and decreased oral clearance).	Bae, *et al*. (2011) (43)	Moderate
Clinical	*CYP2C9*2* is associated with moderately decreased meloxicam metabolism (increased meloxicam plasma concentration and decreased oral clearance).	Hasunuma, *et al*. (2016) (40) Aoyama, *et al*. (2017) (39)	Weak
Clinical	*CYP2C9*2*/**2* genotype is associated with decreased meloxicam metabolism, while *CYP2C9*1/*2* genotype has a marginal impact.	Hasunuma, *et al*. (2016) (40) Aoyama, *et al*. (2017) (39)	Weak
Clinical	*CYP2C9*3* is associated with increased meloxicam pharmacodynamic effects (increased maximal inhibition of thromboxane B_2 formation).	Lee, *et al*. (2014) (42) Aoyama, *et al*. (2017) (39)	Moderate
Clinical	*CYP2C9*3*/**3* genotype is associated with increased meloxicam pharmacodynamic effects compared to *CYP2C9*1/*3* (increased maximal inhibition of thromboxane B_2 formation).	Lee, *et al*. (2014) (42) Aoyama, *et al*. (2017) (39)	Moderate
Clinical	*CYP2C9*13* is associated with increased meloxicam pharmacodynamic effects (increased maximal inhibition of thromboxane B_2 formation).	Bae, *et al*. (2011) (43)	Weak

Clinical	*CYP2C9*3* may be associated with increased risk of meloxicam toxicity.	Ishihara, *et al*. (2014) (111)	Weak

SUPPLEMENTAL TABLE S6. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH PIROXICAM PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	*CYP2C9*3* exhibits significantly decreased CYP2C9 catalytic activity and decreased metabolism of piroxicam.	Takanashi, *et al*. (2000) (44)	Moderate
Clinical	*CYP2C9*2* and *CYP2C9*3* are associated with decreased piroxicam metabolism (increased piroxicam plasma concentration and decreased oral clearance).	Perini, *et al*. (2006) (45) Perini, *et al*. (2005) (46)	Moderate
Clinical	*CYP2C9*2* and *CYP2C9*3* are associated with increased piroxicam pharmacodynamic effects (increased maximal inhibition of thromboxane B_2 formation).	Perini, *et al*. (2006) (45) Calvo, *et al*. (2017) (112)	Moderate
Clinical	*CYP2C9*2* and **3* were not associated with increased odds of response to piroxicam.	Calvo, *et al*. (2017) (112)	Weak

SUPPLEMENTAL TABLE S7. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH TENOXICAM PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
In vitro	*CYP2C9*3* exhibits decreased CYP2C9 catalytic activity and decreased metabolism of tenoxicam.	Takanashi, *et al*. (2000) (44)	Moderate
Clinical	*CYP2C9*3* is associated with decreased tenoxicam metabolism (increased tenoxicam plasma concentration and decreased oral clearance).	Peiro, *et al*. (2009) (47) Vianna-Jorge, *et al*. (2004) (48)	Moderate
Clinical	*CYP2C9*2* may be associated with increased tenoxicam plasma concentration and decreased oral clearance, but the effect is less pronounced than *CYP2C9*3*.	Vianna-Jorge, *et al*. (2004) (48) Peiro, *et al*. (2009) (47)	Weak

SUPPLEMENTAL TABLE S8. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH NSAID PHENOTYPE

Type of experimental model	Major findings	References	Level of evidence
Clinical	*CYP2C9* genotypes are not associated with NSAID efficacy (risk of adenoma, colorectal cancer, ovarian cancer, bladder cancer).	Poole, *et al*. (2009) (113) McGreavey, *et al*. (2005) (114) Jaja, *et al*. (2015) (115) Barry, *et al*. (2013) (116) Pinheiro, *et al*. (2010) (117) Siemes, *et al*. (2009) (118) Fortuny, *et al*. (2006) (119) Wang, *et al*. (2017) (120) Scherer, *et al*. (2014) (121)	Weak
Clinical	*CYP2C9*3* may be associated with increased risk of NSAID gastrointestinal toxicity (bleeding, ulcer).	Figueiras, *et al*. (2016) (122) Carbonell, *et al*.(2010) (123) Blanco, *et al*. (2008) (124) Pilotto, *et al*. (2007) (125) Vonkeman, *et al*. (2006) (126) Martinez, *et al*. (2004) (127) Martin, *et al*. (2001) (128) Ishihara, *et al*. (2014) (111)	Weak
Clinical	*CYP2C9*2* is not associated with increased risk of NSAID gastrointestinal toxicity (bleeding, ulcer).	Figueiras, *et al*. (2016) (122) Carbonell, *et al*. (2010) (123) Ma, *et al*. (2008) (129) Blanco, *et al*. (2008) (124) Pilotto, *et al*. (2007) (125) Vonkeman, *et al*. (2006) (126) Martinez, *et al*. (2004) (127) Martin, *et al*. (2001) (128)	Weak

SUPPLEMENTAL TABLE S9. EVIDENCE LINKING *CYP2C9* GENOTYPE WITH ACECLOFENAC, ASPIRIN, DICLOFENAC, INDOMETHACIN, LUMIRACOXIB, METAMIZOLE, NABUMETONE AND NAPROXEN PHENOTYPE (NO RECOMMENDATION PROVIDED IN GUIDELINE)

Type of experimental model	Major findings	References	Level of evidence
Aceclofenac			
In vitro	CYP2C9 is the major metabolizing enzyme for aceclofenac.	Bort, *et al*. (1996) (130)	Weak
Aspirin			
Clinical	*CYP2C9*2* and *CYP2C9*3* are not associated with increased risk of aspirin toxicity (gastrointestinal complaints, ulcer, urticaria).	Palikhe, *et al*. (2011) (131) Shiotani , *et al*. (2009) (132) Van Oijen, *et al*. (2005) (133) Jalil, *et al*. (2015) (134)	Moderate
Clinical	*CYP2C9*2* and *CYP2C9*3* are not associated with the protective effect of aspirin on colon adenoma risk.	Bigler, *et al*. (2001) (135) Chan, *et al*. (2004) (136) Barry, *et al*. (2013) (116)	Moderate
Diclofenac			
In vitro	CYP2C9 is the major metabolizing enzyme for diclofenac 4'hydroxylation. CYP2C8 and CYP3A4 play a minor role. UGT2B7 plays a major role in diclofenac acyl glucuronidation.	Murayama, *et al*. (2018) (4) den Braver, *et al*. (2016) (137) Grillo, *et al*. (2008) (138) Yan, *et al*. (2005) (139) Kuehl, et al. (2005) (50) Bort, *et al*. (1999) (49) Mancy, et al. (1999)(69) Shen, *et al*. (1999) (140) Tang, *et al*. (1999) (141) Yamazaki, *et al*. (1998) (17) Transon, *et al*. (1996) (142) Leemann, *et al*. (1993) (143)	High
In vitro	*CYP2C9*3* and other *CYP2C9* alleles (*CYP2C9*5, *8, *13,* and **35*) exhibit significantly decreased	Xia, *et al*. (2014) (51) Zi, *et al*. (2010) (53) Maekawa, *et al*. (2009) (144)	High

	CYP2C9 catalytic activity and decreased metabolism of diclofenac.	Guo, *et al*. (2005) (55) Yasar, *et al*. (2001) (60) Dickmann, *et al*. (2001) (58) Ieiri, *et al*. (2000) (145) Takanashi, *et al*. (2000) (44) Yamazaki, *et al*. (1998) (17) Crespi, *et al*. (1997) (146) Zhou, *et al*. (2006) (147) Lee, *et al*. (2014) (148) Maekawa, *et al*. (2009) (144)	
In vitro	*CYP2C9*2* does not exhibit significantly decreased diclofenac metabolism.	Xia, *et al*. (2014) (51) Crespi, *et al*. (1997) (146) Luo, *et al*. (2014) (149) Yasar, *et al*. (2001) (60) Yamazaki, *et al*. (1998) (17)	Moderate
In vitro	Using diclofenac as a substrate, other *CYP2C9* alleles (*CYP2C9*25, *26, *28, *30,* and **33*) exhibit significantly decreased or absent CYP2C9 catalytic activity.	Maekawa, *et al*. (2006) (150) Maekawa, *et al*. (2009) (144)	Moderate
In vitro	*CYP2C9*58* (P337T) exhibited moderately decreased metabolism of diclofenac.	Luo, *et al*. (2014) (149)	Weak
Clinical	*CYP2C9*3* is associated with decreased diclofenac metabolism (higher diclofenac to 4'hydroxy-diclofenac metabolic ratio in urine).	Llerena, *et al*. (2014) (52) Dorado, *et al*. (2008) (54) Dorado, *et al*. (2003) (56) Dorado, *et al*. (2003) (57)	Weak
Clinical	*CYP2C9*3* is not associated with increased diclofenac plasma concentration or decreased oral clearance.	Kirchheiner, *et al*. (2003) (59) Morin, *et al*. (2001) (61) Shimamoto, *et al*. (2000) (62) Yasar, *et al*. (2001) (60)	Weak
Clinical	*CYP2C9*2* is not associated with decreased diclofenac metabolism (diclofenac to 4'hydroxy-diclofenac metabolic ratio in urine).	Llerena, *et al*. (2014) (52) Dorado, *et al*. (2003) (57) Dorado, *et al*. (2003) (151)	Weak

Clinical	*CYP2C9*2* is not associated with increased diclofenac plasma concentrations or decreased oral clearance.	Kirchheiner, *et al*. (2003) (59) Morin, *et al*. (2001) (61) Yasar, *et al*. (2001) (60)	Weak
Clinical	*CYP2C9*3* may be associated with increased risk of diclofenac toxicity.	Ishihara, *et al*. (2014) (111) Aithal, *et al*. (2000) (152)	Weak
Indomethacin			
In vitro	Indomethacin O-demethylation is catalyzed predominantly by CYP2C9.	Nakajima, *et al*. (1998) (153)	Moderate
Clinical	*CYP2C9*3/*3* genotype was observed in a case of indomethacin-associated bleeding.	Zarza, *et al*. (2003) (154)	Weak
Clinical	*CYP2C9* rs2153628 and *CYP2C9*2* may be associated with increased odds of response to indomethacin.	Smith, *et al*. (2017) (155)	Weak
Lumiracoxib			
In vitro	Lumiracoxib hydroxylation is catalyzed predominantly by CYP2C9.	Li, et al. (2008) (91)	Moderate
Metamizole			
Clinical	*CYP2C9*3* is associated with moderately decreased metamizole metabolism.	Martínez, *et al*. (2014) (156)	Moderate
Clinical	*CYP2C9*2* is not associated with decreased metamizole metabolism.	Martínez, *et al*. (2014) (156)	Weak
Clinical	*CYP2C9* genotype is not associated with the risk of developing anaphylaxis in patients treated with metamizole.	García-Martín, *et al*. (2015) (157)	Weak
Nabumetone			
In vitro	Nabumetone metabolism is mainly mediated by CYP2C9.	Matsumoto, *et al*. (2011) (158)	Moderate
Naproxen			
In vitro	CYP2C9 plays a major role in naproxen demethylation. UGT2B7 plays a major role in naproxen acyl glucuronidation. CYP1A2 also plays a role in naproxen metabolism. CYP2C8 may play a minor role.	Bowalgaha, et al. (2005) (159) Tracy, *et al*. (1997) (160) Miners, *et al*. (1996) (161) Rodrigues, *et al.* (1996) (162)	High

In vitro	*CYP2C9*2* and *CYP2C9*3* exhibit decreased (S)-naproxen demethylation.	Wei, *et al*. (2007) (163)	Moderate
Clinical	*CYP2C9*3* is not associated with increased naproxen plasma concentrations or decreased oral clearance	Bae, *et al*. (2009) (164)	Weak

SUPPLEMENTAL TABLE S10. EVIDENCE LINKING *CYP2C8* GENOTYPE WITH IBUPROFEN AND DICLOFENAC PHENOTYPE (NO RECOMMENDATION PROVIDED IN GUIDELINE)

Type of experimental model	Major findings	References	Level of evidence
Ibuprofen			
In vitro	CYP2C8 plays a minor role in ibuprofen metabolism as compared to CYP2C9.	Chang, *et al*. (2008) (28) Yu, *et al*. (2013) (71)	Moderate
In vitro	*CYP2C8*3* and *CYP2C8*4* alleles exhibit decreased CYP2C8 catalytic activity and decreased ibuprofen metabolism.	Chang, *et al*. (2008) (28) Yu, *et al*. (2013) (71)	Weak
Clinical	*CYP2C8*3* is associated with decreased metabolism of ibuprofen (increased ibuprofen plasma concentrations and decreased oral clearance, especially for R (-) ibuprofen).	Martinez, *et al*. (2005) (37) Garcia-Martin, *et al*. (2004) (35) Karatzniewicz-Lada, *et al*. (2009) (33) Ocha, *et al*. (2015) (32) Lopez-Rodriguez, *et al*. (2008) (34)	Weak
Clinical	*CYP2C8*3* and *CYP2C9*2* are associated with lower ibuprofen dose requirements.	Zajic, *et al*. (2019) (165)	Moderate
Clinical	*CYP2C8* and *CYP2C9* alleles are not associated with ibuprofen response (ductus closure) in preterm neonates.	Durrmeyer, *et al*. (2010) (110)	Weak
Diclofenac			
In vitro	CYP2C9 is the major enzyme responsible for the formation of 4'-hydroxy diclofenac. CYP2C8 predominantly catalyzes the formation of 5'-hydroxy diclofenac and plays a minor role in the formation of 4'-hydroxy diclofenac.	Mancy, *et al*. (1999) (69) Bort, *et al*. (1999) (49)	Moderate
In vitro	CYP2C8 catalyzes the conversion of diclofenac acyl glucuronide to its 4-hydroxy derivative.	Kumar, *et al*. (2002) (166)	Moderate
In vitro	*CYP2C8*4* exhibited decreased catalytic activity in the 4'-hydroxylation of diclofenac acyl glucuronide.	Lazarska, *et al*. (2018) (70)	Moderate
Clinical	*CYP2C8*3* and *CYP2C8*4* are associated	Dorado, *et al*. (2008) (54)	Weak

	with significantly lower metabolism of diclofenac to its 5-hydroxy-diclofenac metabolite (higher diclofenac/ 5-hydroxy-diclofenac urinary metabolic ratio). No association with 4-hydroxy-diclofenac formation was observed.		
Clinical	*CYP2C8*4* may be associated with increased odds of diclofenac hepatotoxity. *CYP2C8*3* was not associated with hepatotoxicity risk.	Daly, *et al*. (2007) (72)	Weak

SUPPLEMENTAL TABLE S11. LINKAGE DISEQUILIBRIUM BETWEEN *CYP2C9*2* AND *CYP2C8*3* ACROSS POPULATIONS (167)

Population	**N**	***CYP2C9*2* Minor Allele Frequency (rs1799853)**	***CYP2C8*3* Minor Allele Frequency (rs11572080 and rs10509681)**	**R^2**	**D'**
All	2504	4.79%	4.57%	0.8501	0.945
African Superpopulation	661	0.83%	0.83%	0.8251	0.9083
Yoruba in Ibadan, Nigeria	108	0.0%	0.0%	NA	NA
Luhya in Webuye, Kenya	99	0.0%	0.0%	NA	NA
Gambian in Western Divisions in the Gambia	113	0.44%	0.44%	1	1
Mende in Sierra Leone	85	0.0%	0.0%	NA	NA
Esan in Nigeria	99	0.0%	0.0%	NA	NA
Americans of African Ancestry in SW USA	61	4.1%	3.28%	0.7932	1
African Caribbeans in Barbados	96	2.6%	3.13%	0.8289	1
Ad mixed American Superpopulation	347	9.94%	9.94%	0.9367	0.9678
Mexican Ancestry from Los Angeles USA	64	10.16%	10.16%	1	1
Puerto Ricans from Puerto Rico	104	13.94%	14.42%	0.9613	1
Colombians from Medellin, Colombia	94	12.23%	11.7%	0.8548	0.9482
Peruvians from Lima, Peru	85	2.35%	2.35%	1	1

East Asian Superpopulation	504	0.1%	0.1%	1	1
Han Chinese in Beijing, China	103	0.0%	0.0%	NA	NA
Japanese in Tokyo, Japan	104	0.0%	0.0%	NA	NA
Southern Han Chinese	105	0.48%	0.48%	1	1
Chinese Dai in Xishuangbanna, China	93	0.0%	0.0%	NA	NA
Kinh in Ho Chi Minh City, Vietnam	99	0.0%	0.0%	NA	NA
European Superpopulation	503	12.43%	11.83%	0.8228	0.9328
Utah Residents (CEPH) with Northern and Western European Ancestry	99	15.15%	13.13%	0.7715	0.9547
Toscani in Italia	107	15.42%	13.08%	0.8257	1
Finnish in Finland	99	8.08%	8.08%	1	1
British in England and Scotland	91	8.79%	9.34%	0.9355	1
Iberian Population in Spain	107	14.02%	14.95%	0.7221	0.8824
South Asian Superpopulation	489	3.48%	2.97%	0.7315	0.9286
Gujarati Indian from Houston, Texas	103	4.85%	3.88%	0.7919	1
Punjabi from Lahore, Pakistan	96	5.21%	4.69%	0.8951	1
Bengali from Bangladesh	86	1.74%	1.74%	0.4366	0.6607
Sri Lankan Tamil from the UK	102	2.94%	1.96%	0.3638	0.7424
Indian Telugu from the UK	102	2.45%	2.45%	1	1

SUPPLEMENTAL TABLE S12. CLINICAL PHARMACOKINETICS OF SELECTED NSAIDS

NSAID chemical class **NSAID**	**T_{max} (h)**	**$T_{1/2}$ (h)**	**Primary route of metabolism (% of total dose) [*oxidative metabolism italicized*]**	**CYP isoforms involved in oxidative metabolism (estimated % of metabolism)**	**References**
Diaryl-substituted pyrazoles					
Celecoxib	2-4	11-16	*methyl hydroxylation (>90%)*	CYP2C9 (70-90%) CYP3A4 CYP2D6	(3, 97, 168-171)
Arylpropionic acids					
Ibuprofen	1-2	2-4 (adults) 1-2 (children) 23-75 (premature infants)	(**S**)-ibuprofen: *2-hydroxylation (~30%)* *3-hydroxylation (~45%)* direct glucuronidation (~15%) (**R**)-enantiomer chiral inversion to (**S**)-ibuprofen (60%) *2-hydroxylation (~10%)* *3-hydroxylation (~20%)* direct glucuronidation (~10%)	CYP2C9 (~50%) CYP2C8 CYP2C19 CYP3A4	(28, 31, 71, 170, 172, 173)
Flurbiprofen	1-2	2-6	*4'-hydroxylation (~75%)* direct glucuronidation (~20%)	CYP2C9 (~50%)	(170, 174)
Naproxen	1.5-3	12-15	direct glucuronidation (~60%) *demethylation (~20%)*	CYP2C9 (~20%) CYP1A2 CYP2C8	(170, 175)
Heteroaryl acids					
Diclofenac	1-2	1-2	direct glucuronidation (~80%)	CYP2C9 (<20%) CYP2C8	(49, 69, 166, 170, 176)

			4'–hydroxylation *5-hydroxylation* *(hydroxylation of glucuronide)*	(CYP2C8)	
Aceclofenac	1-3	4	*4'–hydroxylation (~80%)* *5'–hydroxylation (minor)* Hydrolysis to diclofenac (~10%)	CYP2C9	(130, 177)
Enolic acids					
Meloxicam	4-5	15-20	*5'–hydroxylation*	CYP2C9 (40-60%) CYP3A4	(170, 178)
Piroxicam	2-3	30-86	*5'–hydroxylation (~60%)*	CYP2C9 (~50%)	(170, 179)
Tenoxicam	2	60	*5'–hydroxylation (~60%)* *6'-oxidation (~40%)*	CYP2C9 (~30%)	(170, 179, 180)
Lornoxicam	2-3	3-5	*5'–hydroxylation*	CYP2C9 (>40%)	(108, 170, 181)
Indole and Indene acetic acids					
Indomethacin	0.5-2	4.5-6	*demethylation (~50%)* direct glucuronidation (~20%)	CYP2C9	(182-184)
Sulindac	2 (2[1])	7 (16[1])	reduction to sulfide (active metabolite) *oxidation of active metabolite to sulfoxide*	CYP1A2 CYP3A4 CYP2C9 (minimal)	(170, 185, 186)
Alkalones					
Nabumetone	6-9[2]	22-30[2]	*oxidation to 6-MNA* conjugation (glucuronide / sulfate)	CYP1A2 (formation of 6-MNA) CYP2C9 (metabolism of 6-MNA)	(187)
Aryl-substituted bipyridines					
Etoricoxib	1-2	20	*6'-methyl hydroxylation* *1'-N-oxidation*	CYP3A4 CYP2C9 (<20%)	(170, 188)

[1]Refers to the active metabolite of sulindac, sulindac sulfide

[2]Refers to the active metabolite of nabumetone, 6-methoxy-2-naphthylacetic acid (6-MNA)

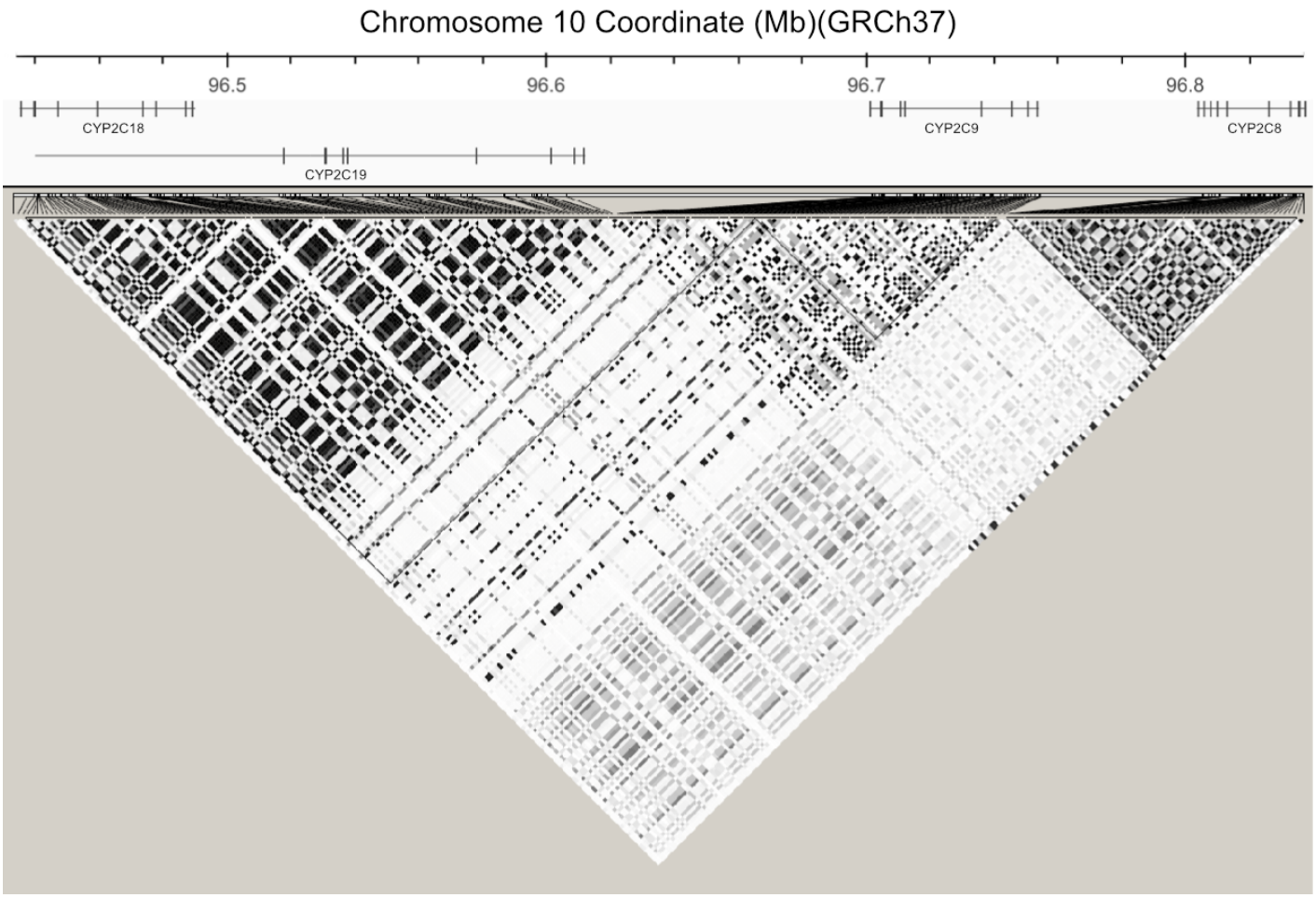

FIGURE S1. LINKAGE DISEQUILIBRIUM (LD) ACROSS *CYP2C* GENES. LD plot was generated in Haploview (189) using data from the 1000 Genomes Project (190). Shading indicates the extent of LD, with darker shading indicating a higher r^2 value.

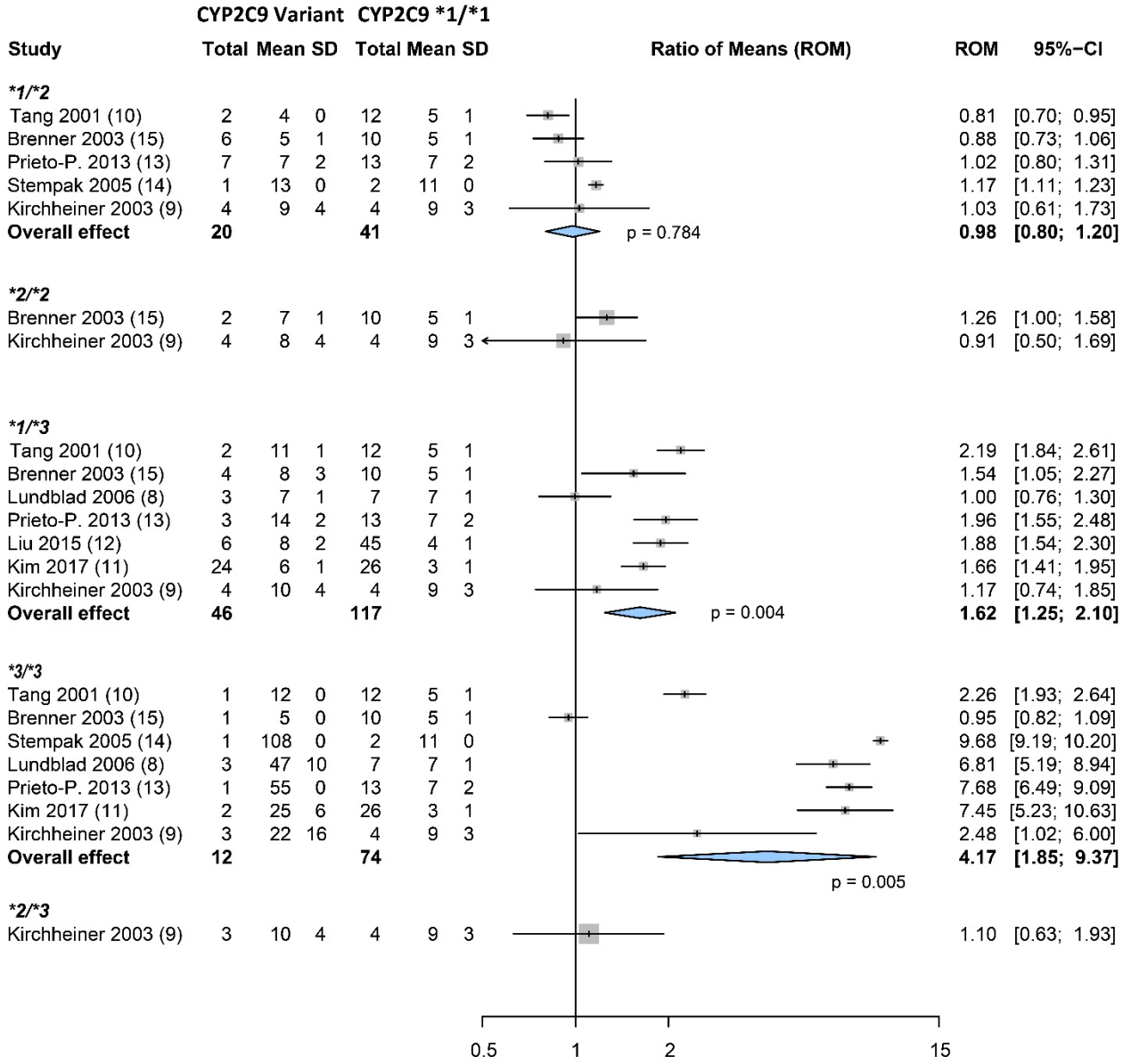

FIGURE S2. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON CELECOXIB EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1* controls. References shown in parenthesis.

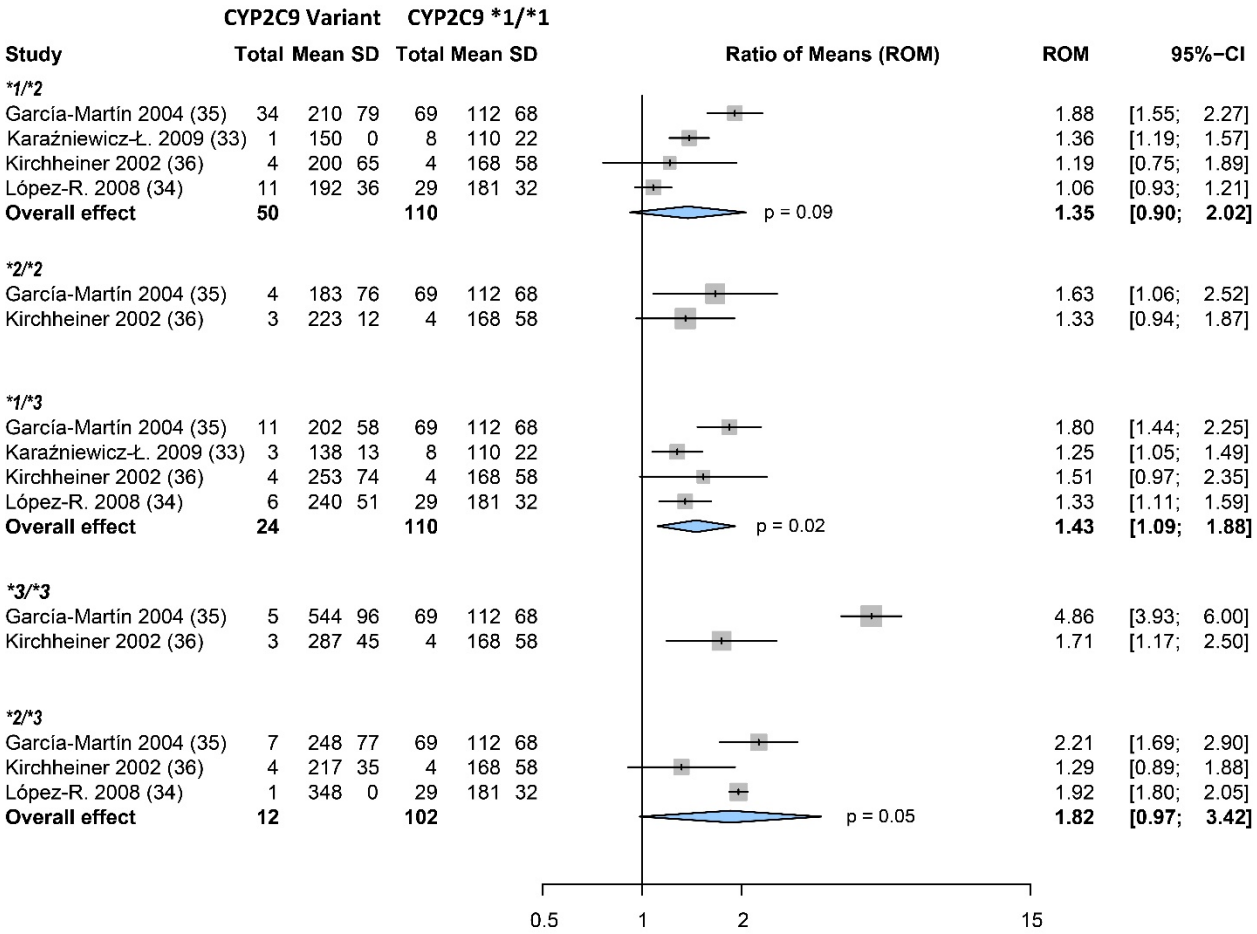

FIGURE S3. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON IBUPROFEN EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1* controls. References shown in parenthesis.

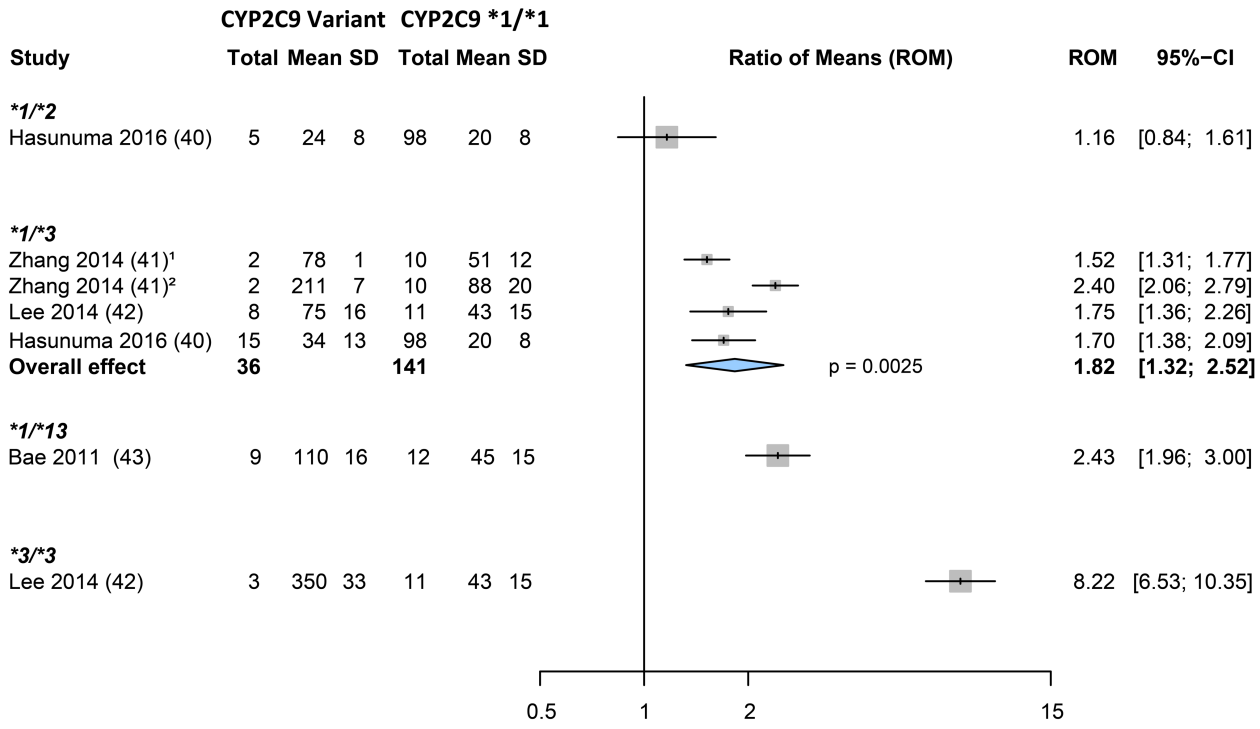

FIGURE S4. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON MELOXICAM EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1* controls. [1]single dose study arm; [2]multiple dose study arm. References shown in parenthesis.

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