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)

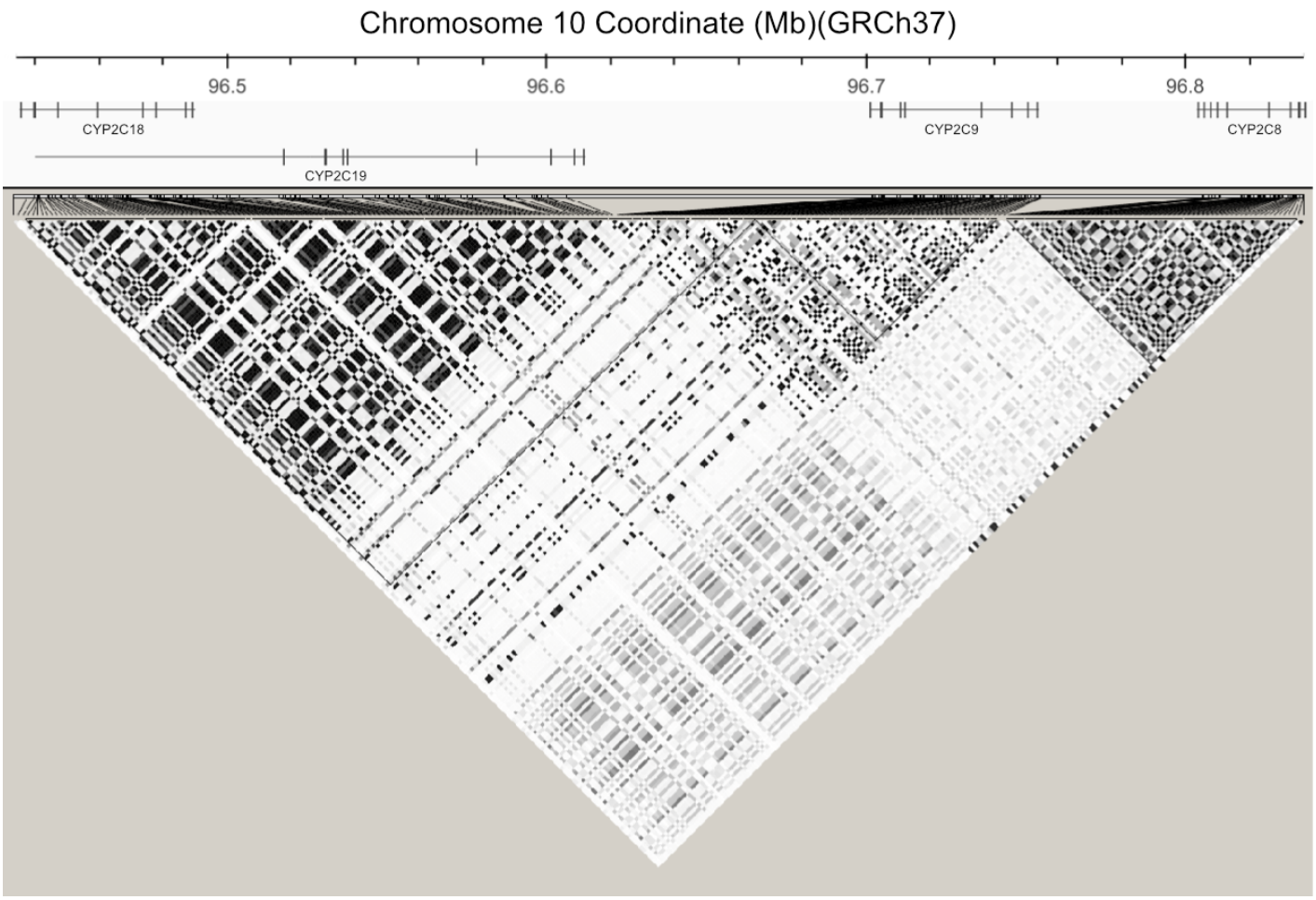

FIGURE S1. LINKAGE DISEQUILIBRIUM (LD) ACROSS *CYP2C* GENES. LD plot was generated in Haploview (189) using data from the 1000 Genomes Project (190). Shading indicates the extent of LD, with darker shading indicating a higher r^2 value.

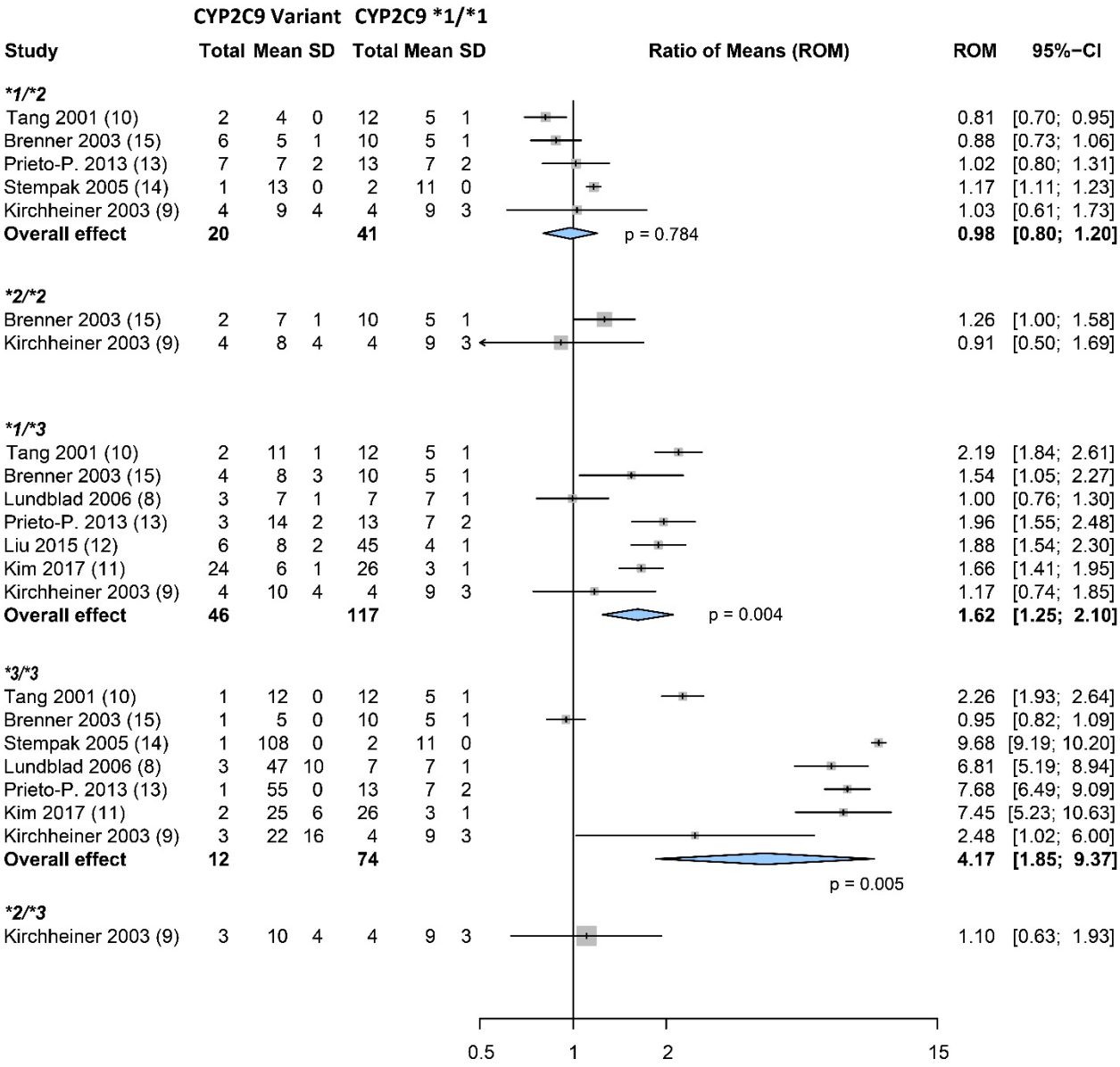

FIGURE S2. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON CELECOXIB EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1*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

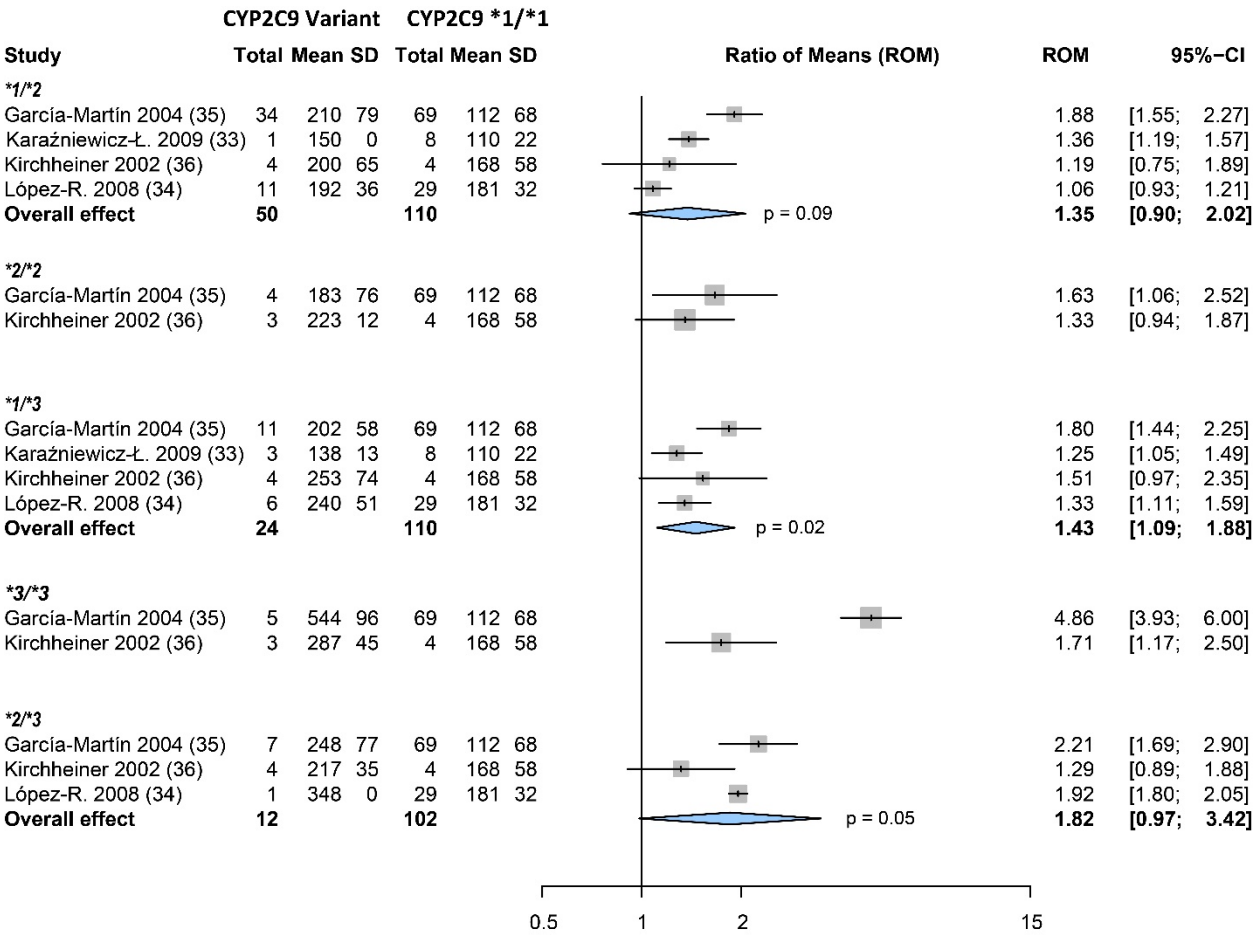

FIGURE S3. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON IBUPROFEN EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1*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

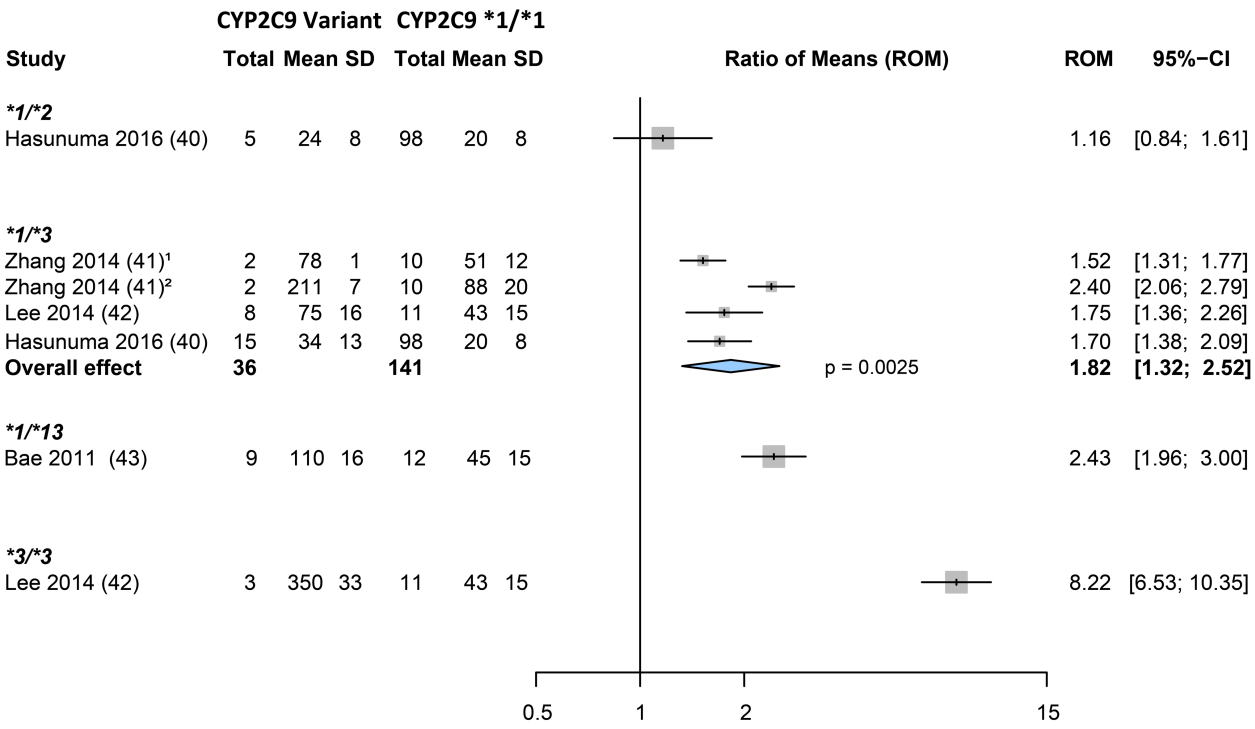

FIGURE S4. META-ANALYSIS OF THE EFFECT OF *CYP2C9* GENOTYPES ON MELOXICAM EXPOSURE. Mean area under the curve (AUC) was extracted from each study and compared across genotype groups using a random effects model. Results are expressed as the ratio of mean (ROM) AUC for variant allele carriers to *CYP2C9*1/*1*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

REFERENCES

(1) Kalman, L.V. *et al.* Pharmacogenetic allele nomenclature: International workgroup recommendations for test result reporting. *Clin Pharmacol Ther* **99**, 172-85 (2016).

(2) Pratt, V.M. *et al.* Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn*, (2019).

(3) Tang, C., Shou, M., Mei, Q., Rushmore, T.H. & Rodrigues, A.D. Major role of human liver microsomal cytochrome P450 2C9 (CYP2C9) in the oxidative metabolism of celecoxib, a novel cyclooxygenase-II inhibitor. *J Pharmacol Exp Ther* **293**, 453-9 (2000).

(4) Murayama, N. *et al.* Assessment of multiple cytochrome P450 activities in metabolically inactivated human liver microsomes and roles of P450 2C isoforms in reaction phenotyping studies. *Biopharmaceutics & drug disposition* **39**, 116-21 (2018).

(5) Sandberg, M., Yasar, U., Stromberg, P., Hoog, J.O. & Eliasson, E. Oxidation of celecoxib by polymorphic cytochrome P450 2C9 and alcohol dehydrogenase. *British journal of clinical pharmacology* **54**, 423-9 (2002).

(6) Rodrigues, A.D., Yang, Z., Chen, C., Pray, D., Kim, S. & Sinz, M. Is celecoxib an inducer of cytochrome P450 3A4 in subjects carrying the CYP2C9*3 allele? *Clin Pharmacol Ther* **80**, 298-301; author reply -02 (2006).

(7) Gong, L., Thorn, C.F., Bertagnolli, M.M., Grosser, T., Altman, R.B. & Klein, T.E. Celecoxib pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenetics and genomics* **22**, 310-8 (2012).

(8) Lundblad, M.S., Ohlsson, S., Johansson, P., Lafolie, P. & Eliasson, E. Accumulation of celecoxib with a 7-fold higher drug exposure in individuals homozygous for CYP2C9*3. *Clin Pharmacol Ther* **79**, 287-8 (2006).

(9) Kirchheiner, J., Stormer, E., Meisel, C., Steinbach, N., Roots, I. & Brockmoller, J. Influence of CYP2C9 genetic polymorphisms on pharmacokinetics of celecoxib and its metabolites. *Pharmacogenetics* **13**, 473-80 (2003).

(10) Tang, C. *et al.* In-vitro metabolism of celecoxib, a cyclooxygenase-2 inhibitor, by allelic variant forms of human liver microsomal cytochrome P450 2C9: correlation with CYP2C9 genotype and in-vivo pharmacokinetics. *Pharmacogenetics* **11**, 223-35 (2001).

(11) Kim, S.H. *et al.* Effects of CYP2C9 genetic polymorphisms on the pharmacokinetics of celecoxib and its carboxylic acid metabolite. *Arch Pharm Res* **40**, 382-90 (2017).

(12) Liu, R. *et al.* Influence of genetic polymorphisms on the pharmacokinetics of celecoxib and its two main metabolites in healthy Chinese subjects. *Eur J Pharm Sci* **79**, 13-9 (2015).

(13) Prieto-Perez, R. *et al.* Evaluation of the relationship between polymorphisms in CYP2C8 and CYP2C9 and the pharmacokinetics of celecoxib. *J Clin Pharmacol* **53**, 1261-7 (2013).

(14) Stempak, D., Bukaveckas, B.L., Linder, M., Koren, G. & Baruchel, S. Cytochrome P450 2C9 genotype: impact on celecoxib safety and pharmacokinetics in a pediatric patient. *Clin Pharmacol Ther* **78**, 309-10 (2005).

(15) Brenner, S.S. *et al.* Influence of age and cytochrome P450 2C9 genotype on the steady-state disposition of diclofenac and celecoxib. *Clin Pharmacokinet* **42**, 283-92 (2003).

(16) Wang, L. *et al.* Effect of CYP2C9 genetic polymorphism on the metabolism of flurbiprofen in vitro. *Drug Dev Ind Pharm* **41**, 1363-7 (2015).

(17) Yamazaki, H. *et al.* Comparative studies on the catalytic roles of cytochrome P450 2C9 and its Cys- and Leu-variants in the oxidation of warfarin, flurbiprofen, and diclofenac by human liver microsomes. *Biochemical pharmacology* **56**, 243-51 (1998).
(18) Tracy, T.S., Hutzler, J.M., Haining, R.L., Rettie, A.E., Hummel, M.A. & Dickmann, L.J. Polymorphic variants (CYP2C9*3 and CYP2C9*5) and the F114L active site mutation of CYP2C9: effect on atypical kinetic metabolism profiles. *Drug Metab Dispos* **30**, 385-90 (2002).
(19) Swar, B.D. *et al.* Evaluation of cytochrome P450 2C9 activity in normal, healthy, adult Western Indian population by both phenotyping and genotyping. *Indian J Pharmacol* **48**, 248-51 (2016).
(20) Lee, Y.J. *et al.* Effects of CYP2C9*1/*3 genotype on the pharmacokinetics of flurbiprofen in Korean subjects. *Arch Pharm Res* **38**, 1232-7 (2015).
(21) Lee, C.R., Pieper, J.A., Frye, R.F., Hinderliter, A.L., Blaisdell, J.A. & Goldstein, J.A. Differences in flurbiprofen pharmacokinetics between CYP2C9*1/*1, *1/*2, and *1/*3 genotypes. *European journal of clinical pharmacology* **58**, 791-4 (2003).
(22) Lee, C.R., Pieper, J.A., Frye, R.F., Hinderliter, A.L., Blaisdell, J.A. & Goldstein, J.A. Tolbutamide, flurbiprofen, and losartan as probes of CYP2C9 activity in humans. *J Clin Pharmacol* **43**, 84-91 (2003).
(23) Guo, Y. *et al.* Role of CYP2C9 and its variants (CYP2C9*3 and CYP2C9*13) in the metabolism of lornoxicam in humans. *Drug Metab Dispos* **33**, 749-53 (2005).
(24) Iida, I. *et al.* Catalytic roles of CYP2C9 and its variants (CYP2C9*2 and CYP2C9*3) in lornoxicam 5'-hydroxylation. *Drug Metab Dispos* **32**, 7-9 (2004).
(25) Choi, C.I., Kim, M.J., Jang, C.G., Park, Y.S., Bae, J.W. & Lee, S.Y. Effects of the CYP2C9*1/*13 genotype on the pharmacokinetics of lornoxicam. *Basic Clin Pharmacol Toxicol* **109**, 476-80 (2011).
(26) Liu, Y.L. *et al.* Effect of the CYP2C9*3 allele on lornoxicam metabolism. *Clin Chim Acta* **364**, 287-91 (2006).
(27) Zhang, Y., Zhong, D., Si, D., Guo, Y., Chen, X. & Zhou, H. Lornoxicam pharmacokinetics in relation to cytochrome P450 2C9 genotype. *British journal of clinical pharmacology* **59**, 14-7 (2005).
(28) Chang, S.Y. *et al.* Confirmation that cytochrome P450 2C8 (CYP2C8) plays a minor role in (S)-(+)- and (R)-(-)-ibuprofen hydroxylation in vitro. *Drug metabolism and disposition: the biological fate of chemicals* **36**, 2513-22 (2008).
(29) McGinnity, D.F., Parker, A.J., Soars, M. & Riley, R.J. Automated definition of the enzymology of drug oxidation by the major human drug metabolizing cytochrome P450s. *Drug metabolism and disposition: the biological fate of chemicals* **28**, 1327-34 (2000).
(30) Hamman, M.A., Thompson, G.A. & Hall, S.D. Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. *Biochemical pharmacology* **54**, 33-41 (1997).
(31) Mazaleuskaya, L.L. *et al.* PharmGKB summary: ibuprofen pathways. *Pharmacogenetics and genomics* **25**, 96-106 (2015).
(32) Ochoa, D. *et al.* Effect of gender and CYP2C9 and CYP2C8 polymorphisms on the pharmacokinetics of ibuprofen enantiomers. *Pharmacogenomics* **16**, 939-48 (2015).
(33) Karazniewicz-Lada, M., Luczak, M. & Glowka, F. Pharmacokinetic studies of enantiomers of ibuprofen and its chiral metabolites in humans with different variants of

genes coding CYP2C8 and CYP2C9 isoenzymes. *Xenobiotica; the fate of foreign compounds in biological systems* **39**, 476-85 (2009).
(34) Lopez-Rodriguez, R. *et al.* Influence of CYP2C8 and CYP2C9 polymorphisms on pharmacokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen in healthy volunteers. *Pharmacological research* **58**, 77-84 (2008).
(35) Garcia-Martin, E., Martinez, C., Tabares, B., Frias, J. & Agundez, J.A. Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. *Clin Pharmacol Ther* **76**, 119-27 (2004).
(36) Kirchheiner, J., Meineke, I., Freytag, G., Meisel, C., Roots, I. & Brockmoller, J. Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. *Clin Pharmacol Ther* **72**, 62-75 (2002).
(37) Martinez, C., Garcia-Martin, E., Blanco, G., Gamito, F.J., Ladero, J.M. & Agundez, J.A. The effect of the cytochrome P450 CYP2C8 polymorphism on the disposition of (R)-ibuprofen enantiomer in healthy subjects. *British journal of clinical pharmacology* **59**, 62-9 (2005).
(38) Chesne, C., Guyomard, C., Guillouzo, A., Schmid, J., Ludwig, E. & Sauter, T. Metabolism of Meloxicam in human liver involves cytochromes P4502C9 and 3A4. *Xenobiotica; the fate of foreign compounds in biological systems* **28**, 1-13 (1998).
(39) Aoyama, T. *et al.* Pharmacokinetics and Pharmacodynamics of Meloxicam in East Asian Populations: The Role of Ethnicity on Drug Response. *CPT Pharmacometrics Syst Pharmacol* **6**, 823-32 (2017).
(40) Hasunuma, T. *et al.* Absence of ethnic differences in the pharmacokinetics of moxifloxacin, simvastatin, and meloxicam among three East Asian populations and Caucasians. *British journal of clinical pharmacology* **81**, 1078-90 (2016).
(41) Zhang, M. *et al.* Effect of CYP2C9*3 mutant variants on meloxicam pharmacokinetics in a healthy Chinese population. *Genet Mol Res* **13**, 831-7 (2014).
(42) Lee, H.I. *et al.* Strongly increased exposure of meloxicam in CYP2C9*3/*3 individuals. *Pharmacogenet Genomics* **24**, 113-7 (2014).
(43) Bae, J.W., Choi, C.I., Jang, C.G. & Lee, S.Y. Effects of CYP2C9*1/*13 on the pharmacokinetics and pharmacodynamics of meloxicam. *Br J Clin Pharmacol* **71**, 550-5 (2011).
(44) Takanashi, K., Tainaka, H., Kobayashi, K., Yasumori, T., Hosakawa, M. & Chiba, K. CYP2C9 Ile359 and Leu359 variants: enzyme kinetic study with seven substrates. *Pharmacogenetics* **10**, 95-104 (2000).
(45) Perini, J.A. & Suarez-Kurtz, G. Impact of CYP2C9*3/*3 genotype on the pharmacokinetics and pharmacodynamics of piroxicam. *Clin Pharmacol Ther* **80**, 549-51 (2006).
(46) Perini, J.A., Vianna-Jorge, R., Brogliato, A.R. & Suarez-Kurtz, G. Influence of CYP2C9 genotypes on the pharmacokinetics and pharmacodynamics of piroxicam. *Clin Pharmacol Ther* **78**, 362-9 (2005).
(47) Peiro, A.M. *et al.* Pharmacogenetic relevance of the CYP2C9*3 allele in a tenoxicam bioequivalence study performed on Spaniards. *Pharmacological research* **59**, 62-8 (2009).
(48) Vianna-Jorge, R., Perini, J.A., Rondinelli, E. & Suarez-Kurtz, G. CYP2C9 genotypes and the pharmacokinetics of tenoxicam in Brazilians. *Clin Pharmacol Ther* **76**, 18-26 (2004).

(49) Bort, R., Mace, K., Boobis, A., Gomez-Lechon, M.J., Pfeifer, A. & Castell, J. Hepatic metabolism of diclofenac: role of human CYP in the minor oxidative pathways. *Biochemical pharmacology* **58**, 787-96 (1999).
(50) Kuehl, G.E., Lampe, J.W., Potter, J.D. & Bigler, J. Glucuronidation of nonsteroidal anti-inflammatory drugs: identifying the enzymes responsible in human liver microsomes. *Drug metabolism and disposition: the biological fate of chemicals* **33**, 1027-35 (2005).
(51) Xia, M.M. *et al.* The role of CYP2C9 genetic polymorphisms in the oxidative metabolism of diclofenac in vitro. *Pharmazie* **69**, 898-903 (2014).
(52) Llerena, A. *et al.* Interethnic differences in the relevance of CYP2C9 genotype and environmental factors for diclofenac metabolism in Hispanics from Cuba and Spain. *The pharmacogenomics journal* **14**, 229-34 (2014).
(53) Zi, J. *et al.* Effects of CYP2C9*3 and CYP2C9*13 on Diclofenac Metabolism and Inhibition-based Drug-Drug Interactions. *Drug Metab Pharmacokinet* **25**, 343-50 (2010).
(54) Dorado, P., Cavaco, I., Caceres, M.C., Piedade, R., Ribeiro, V. & Llerena, A. Relationship between CYP2C8 genotypes and diclofenac 5-hydroxylation in healthy Spanish volunteers. *European journal of clinical pharmacology* **64**, 967-70 (2008).
(55) Guo, Y., Wang, Y., Si, D., Fawcett, P.J., Zhong, D. & Zhou, H. Catalytic activities of human cytochrome P450 2C9*1, 2C9*3 and 2C9*13. *Xenobiotica; the fate of foreign compounds in biological systems* **35**, 853-61 (2005).
(56) Dorado, P., Berecz, R., Caceres, M.C., Conzalez, I. & Llerena, A. Reproducibility over time of the urinary diclofenac/4'-OH diclofenac ratio among different CYP2C9 genotypes. *Eur J Drug Metab Pharmacokinet* **28**, 213-5 (2003).
(57) Dorado, P., Berecz, R., Caceres, M.C. & A, L.L. Analysis of diclofenac and its metabolites by high-performance liquid chromatography: relevance of CYP2C9 genotypes in diclofenac urinary metabolic ratios. *J Chromatogr B Analyt Technol Biomed Life Sci* **789**, 437-42 (2003).
(58) Dickmann, L.J. *et al.* Identification and functional characterization of a new CYP2C9 variant (CYP2C9*5) expressed among African Americans. *Mol Pharmacol* **60**, 382-7 (2001).
(59) Kirchheiner, J., Meineke, I., Steinbach, N., Meisel, C., Roots, I. & Brockmoller, J. Pharmacokinetics of diclofenac and inhibition of cyclooxygenases 1 and 2: no relationship to the CYP2C9 genetic polymorphism in humans. *British journal of clinical pharmacology* **55**, 51-61 (2003).
(60) Yasar, U. *et al.* The role of CYP2C9 genotype in the metabolism of diclofenac in vivo and in vitro. *European journal of clinical pharmacology* **57**, 729-35 (2001).
(61) Morin, S. *et al.* Is diclofenac a valuable CYP2C9 probe in humans? *European journal of clinical pharmacology* **56**, 793-7 (2001).
(62) Shimamoto, J. *et al.* Lack of differences in diclofenac (a substrate for CYP2C9) pharmacokinetics in healthy volunteers with respect to the single CYP2C9*3 allele. *Eur J Clin Pharmacol* **56**, 65-8 (2000).
(63) Grosser, T., Theken, K.N. & FitzGerald, G.A. Cyclooxygenase Inhibition: Pain, Inflammation, and the Cardiovascular System. *Clin Pharmacol Ther* **102**, 611-22 (2017).
(64) Valdes, R., Payne, D.A. & Linder, M.W. Laboratory analysis and application of pharmacogenetics to clinical practice. *The National Academy of Clinical Biochemistry (NACB) - Laboratory Medicine Practice Guidelines* 2010.

(65) Antman, E.M. *et al.* Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation* **115**, 1634-42 (2007).
(66) Fda. *FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes*. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory>. Accessed 09/2005 2019.
(67) NSAIDAWARE. *The Alliance for Rational Use of NSAIDs* <http://nsaidalliance.com/>. Accessed 09/05 2019.
(68) Adolescents, P.o.A.G.f.A.a. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 1-166 (2011).
(69) Mancy, A. *et al.* Diclofenac and its derivatives as tools for studying human cytochromes P450 active sites: particular efficiency and regioselectivity of P450 2Cs. *Biochemistry* **38**, 14264-70 (1999).
(70) Lazarska, K.E., Dekker, S.J., Vermeulen, N.P.E. & Commandeur, J.N.M. Effect of UGT2B7*2 and CYP2C8*4 polymorphisms on diclofenac metabolism. *Toxicology letters* **284**, 70-8 (2018).
(71) Yu, L., Shi, D., Ma, L., Zhou, Q. & Zeng, S. Influence of CYP2C8 polymorphisms on the hydroxylation metabolism of paclitaxel, repaglinide and ibuprofen enantiomers in vitro. *Biopharmaceutics & drug disposition* **34**, 278-87 (2013).
(72) Daly, A.K., Aithal, G.P., Leathart, J.B., Swainsbury, R.A., Dang, T.S. & Day, C.P. Genetic susceptibility to diclofenac-induced hepatotoxicity: contribution of UGT2B7, CYP2C8, and ABCC2 genotypes. *Gastroenterology* **132**, 272-81 (2007).
(73) Andersen, V. & Vogel, U. Systematic review: interactions between aspirin, and other nonsteroidal anti-inflammatory drugs, and polymorphisms in relation to colorectal cancer. *Alimentary pharmacology & therapeutics* **40**, 147-59 (2014).
(74) Barry, E.L. *et al.* Cyclooxygenase-2 polymorphisms, aspirin treatment, and risk for colorectal adenoma recurrence--data from a randomized clinical trial. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **18**, 2726-33 (2009).
(75) Cross, J.T., Poole, E.M. & Ulrich, C.M. A review of gene-drug interactions for nonsteroidal anti-inflammatory drug use in preventing colorectal neoplasia. *The pharmacogenomics journal* **8**, 237-47 (2008).
(76) Makar, K.W. *et al.* COX-1 (PTGS1) and COX-2 (PTGS2) polymorphisms, NSAID interactions, and risk of colon and rectal cancers in two independent populations. *Cancer causes & control : CCC* **24**, 2059-75 (2013).
(77) Nagao, M., Sato, Y. & Yamauchi, A. A meta-analysis of PTGS1 and PTGS2 polymorphisms and NSAID intake on the risk of developing cancer. *PLoS One* **8**, e71126 (2013).
(78) Nan, H. *et al.* Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants. *Jama* **313**, 1133-42 (2015).
(79) Ulrich, C.M. *et al.* PTGS2 (COX-2) -765G > C promoter variant reduces risk of colorectal adenoma among nonusers of nonsteroidal anti-inflammatory drugs. *Cancer*

epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology **14**, 616-9 (2005).
(80) Cai, H. *et al.* Association between PTGS1 polymorphisms and functional outcomes in Chinese patients with stroke during aspirin therapy: Interaction with smoking. *Journal of the neurological sciences* **376**, 211-5 (2017).
(81) Cao, L. *et al.* Impacts of COX-1 gene polymorphisms on vascular outcomes in patients with ischemic stroke and treated with aspirin. *Gene* **546**, 172-6 (2014).
(82) Clappers, N. *et al.* The C50T polymorphism of the cyclooxygenase-1 gene and the risk of thrombotic events during low-dose therapy with acetyl salicylic acid. *Thrombosis and haemostasis* **100**, 70-5 (2008).
(83) Sharma, V., Kaul, S., Al-Hazzani, A., Alshatwi, A.A., Jyothy, A. & Munshi, A. Association of COX-2 rs20417 with aspirin resistance. *Journal of thrombosis and thrombolysis* **35**, 95-9 (2013).
(84) Voora, D., Horton, J., Shah, S.H., Shaw, L.K. & Newby, L.K. Polymorphisms associated with in vitro aspirin resistance are not associated with clinical outcomes in patients with coronary artery disease who report regular aspirin use. *American heart journal* **162**, 166-72 e1 (2011).
(85) Lee, Y.S., Kim, H., Wu, T.X., Wang, X.M. & Dionne, R.A. Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. *Clin Pharmacol Ther* **79**, 407-18 (2006).
(86) McGettigan, P. *et al.* The risk of coronary thrombosis with cyclo-oxygenase-2 inhibitors does not vary with polymorphisms in two regions of the cyclo-oxygenase-2 gene. *British journal of clinical pharmacology* **72**, 707-14 (2011).
(87) St Germaine, C.G., Bogaty, P., Boyer, L., Hanley, J., Engert, J.C. & Brophy, J.M. Genetic polymorphisms and the cardiovascular risk of non-steroidal anti-inflammatory drugs. *The American journal of cardiology* **105**, 1740-5 (2010).
(88) Lucena, M.I., Garcia-Martin, E., Daly, A.K., Blanca, M., Andrade, R.J. & Agundez, J.A.G. Next-Generation Sequencing of PTGS Genes Reveals an Increased Frequency of Non-synonymous Variants Among Patients With NSAID-Induced Liver Injury. *Front Genet* **10**, 134 (2019).
(89) Shuldiner, A.R. *et al.* The Pharmacogenomics Research Network Translational Pharmacogenetics Program: overcoming challenges of real-world implementation. *Clin Pharmacol Ther* **94**, 207-10 (2013).
(90) Wilke, R.A. *et al.* The emerging role of electronic medical records in pharmacogenomics. *Clin Pharmacol Ther* **89**, 379-86 (2011).
(91) Peterson, J.F. *et al.* Electronic health record design and implementation for pharmacogenomics: a local perspective. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 833-41 (2013).
(92) Gottesman, O. *et al.* The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 761-71 (2013).
(93) Kullo, I.J., Jarvik, G.P., Manolio, T.A., Williams, M.S. & Roden, D.M. Leveraging the electronic health record to implement genomic medicine. *Genetics in medicine : official journal of the American College of Medical Genetics* **15**, 270-1 (2013).

(94) Hicks, J.K. *et al.* A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. *Clin Pharmacol Ther* **92**, 563-6 (2012).
(95) Hoffman, J.M. *et al.* Developing knowledge resources to support precision medicine: principles from the Clinical Pharmacogenetics Implementation Consortium (CPIC). *J Am Med Inform Assoc* **23**, 796-801 (2016).
(96) Pulley, J.M. *et al.* Operational Implementation of Prospective Genotyping for Personalized Medicine: The Design of the Vanderbilt PREDICT Project. *Clin Pharmacol Ther* **92**, 87-95 (2012).
(97) Werner, U., Werner, D., Rau, T., Fromm, M.F., Hinz, B. & Brune, K. Celecoxib inhibits metabolism of cytochrome P450 2D6 substrate metoprolol in humans. *Clin Pharmacol Ther* **74**, 130-7 (2003).
(98) Fries, S. *et al.* Marked interindividual variability in the response to selective inhibitors of cyclooxygenase-2. *Gastroenterology* **130**, 55-64 (2006).
(99) Chan, A.T. *et al.* Cytochrome P450 2C9 variants influence response to celecoxib for prevention of colorectal adenoma. *Gastroenterology* **136**, 2127-36 e1 (2009).
(100) Gupta, A., Zheng, L., Ramanujam, V. & Gallagher, J. Novel Use of Pharmacogenetic Testing in the Identification of CYP2C9 Polymorphisms Related to NSAID-Induced Gastropathy. *Pain Med* **16**, 866-9 (2015).
(101) Murto, K. *et al.* Celecoxib pharmacogenetics and pediatric adenotonsillectomy: a double-blinded randomized controlled study. *Can J Anaesth* **62**, 785-97 (2015).
(102) Werner, U., Werner, D., Pahl, A., Mundkowski, R., Gillich, M. & Brune, K. Investigation of the pharmacokinetics of celecoxib by liquid chromatography-mass spectrometry. *Biomed Chromatogr* **16**, 56-60 (2002).
(103) Tracy, T.S., Marra, C., Wrighton, S.A., Gonzalez, F.J. & Korzekwa, K.R. Studies of flurbiprofen 4'-hydroxylation. Additional evidence suggesting the sole involvement of cytochrome P450 2C9. *Biochemical pharmacology* **52**, 1305-9 (1996).
(104) Tracy, T.S., Rosenbluth, B.W., Wrighton, S.A., Gonzalez, F.J. & Korzekwa, K.R. Role of cytochrome P450 2C9 and an allelic variant in the 4'-hydroxylation of (R)- and (S)-flurbiprofen. *Biochemical pharmacology* **49**, 1269-75 (1995).
(105) Daali, Y. *et al.* Oral flurbiprofen metabolic ratio assessment using a single-point dried blood spot. *Clin Pharmacol Ther* **91**, 489-96 (2012).
(106) Vogl, S., Lutz, R.W., Schonfelder, G. & Lutz, W.K. CYP2C9 genotype vs. metabolic phenotype for individual drug dosing--a correlation analysis using flurbiprofen as probe drug. *PLoS One* **10**, e0120403 (2015).
(107) Vogl, S., Lutz, R.W., Schonfelder, G. & Lutz, W.K. Correction: CYP2C9 genotype vs. metabolic phenotype for individual drug dosing--a correlation analysis using flurbiprofen as probe drug. *PLoS One* **10**, e0126329 (2015).
(108) Bonnabry, P., Leemann, T. & Dayer, P. Role of human liver microsomal CYP2C9 in the biotransformation of lornoxicam. *European journal of clinical pharmacology* **49**, 305-8 (1996).
(109) Samowitz, W.S. *et al.* Interactions between CYP2C9 and UGT1A6 polymorphisms and nonsteroidal anti-inflammatory drugs in colorectal cancer prevention. *Clin Gastroenterol Hepatol* **4**, 894-901 (2006).
(110) Durrmeyer, X. *et al.* Are cytochrome P450 CYP2C8 and CYP2C9 polymorphisms associated with ibuprofen response in very preterm infants? *PLoS One* **5**, e12329 (2010).

(111) Ishihara, M. *et al.* Risk factors of symptomatic NSAID-induced small intestinal injury and diaphragm disease. *Alimentary pharmacology & therapeutics* **40**, 538-47 (2014).
(112) Calvo, A.M., Zupelari-Goncalves, P., Dionisio, T.J., Brozoski, D.T., Faria, F.A. & Santos, C.F. Efficacy of piroxicam for postoperative pain after lower third molar surgery associated with CYP2C8*3 and CYP2C9. *J Pain Res* **10**, 1581-9 (2017).
(113) Poole, E.M., Bigler, J., Whitton, J., Sibert, J.G., Potter, J.D. & Ulrich, C.M. C-reactive protein genotypes and haplotypes, polymorphisms in NSAID-metabolizing enzymes, and risk of colorectal polyps. *Pharmacogenetics and genomics* **19**, 113-20 (2009).
(114) McGreavey, L.E. *et al.* No evidence that polymorphisms in CYP2C8, CYP2C9, UGT1A6, PPARdelta and PPARgamma act as modifiers of the protective effect of regular NSAID use on the risk of colorectal carcinoma. *Pharmacogenetics and genomics* **15**, 713-21 (2005).
(115) Jaja, C. *et al.* Preemptive Genotyping of CYP2C8 and CYP2C9 Allelic Variants Involved in NSAIDs Metabolism for Sickle Cell Disease Pain Management. *Clin Transl Sci* **8**, 272-80 (2015).
(116) Barry, E.L. *et al.* CYP2C9 variants increase risk of colorectal adenoma recurrence and modify associations with smoking but not aspirin treatment. *Cancer causes & control : CCC* **24**, 47-54 (2013).
(117) Pinheiro, S.P. *et al.* Interaction between use of non-steroidal anti-inflammatory drugs and selected genetic polymorphisms in ovarian cancer risk. *Int J Mol Epidemiol Genet* **1**, 320-31 (2010).
(118) Siemes, C. *et al.* No modification of the beneficial effect of NSAIDs on colorectal cancer by CYP2C9 genotype. *Neth J Med* **67**, 134-41 (2009).
(119) Fortuny, J. *et al.* Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **15**, 1696-702 (2006).
(120) Wang, Y., Yi, X.D. & Lu, H.L. Influence of CYP2C9 and COX-2 Genetic Polymorphisms on Clinical Efficacy of Non-Steroidal Anti-Inflammatory Drugs in Treatment of Ankylosing Spondylitis. *Med Sci Monit* **23**, 1775-82 (2017).
(121) Scherer, D. *et al.* Genetic variation in UGT genes modify the associations of NSAIDs with risk of colorectal cancer: colon cancer family registry. *Genes Chromosomes Cancer* **53**, 568-78 (2014).
(122) Figueiras, A. *et al.* CYP2C9 variants as a risk modifier of NSAID-related gastrointestinal bleeding: a case-control study. *Pharmacogenetics and genomics* **26**, 66-73 (2016).
(123) Carbonell, N. *et al.* CYP2C9*3 Loss-of-Function Allele Is Associated With Acute Upper Gastrointestinal Bleeding Related to the Use of NSAIDs Other Than Aspirin. *Clin Pharmacol Ther* **87**, 693-8 (2010).
(124) Blanco, G. *et al.* Interaction of CYP2C8 and CYP2C9 genotypes modifies the risk for nonsteroidal anti-inflammatory drugs-related acute gastrointestinal bleeding. *Pharmacogenetics and genomics* **18**, 37-43 (2008).
(125) Pilotto, A. *et al.* Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. *Gastroenterology* **133**, 465-71 (2007).
(126) Vonkeman, H.E., van de Laar, M.A., van der Palen, J., Brouwers, J.R. & Vermes, I. Allele variants of the cytochrome P450 2C9 genotype in white subjects from The

Netherlands with serious gastroduodenal ulcers attributable to the use of NSAIDs. *Clin Ther* **28**, 1670-6 (2006).
(127) Martinez, C. *et al.* Genetic predisposition to acute gastrointestinal bleeding after NSAIDs use. *Br J Pharmacol* **141**, 205-8 (2004).
(128) Martin, J.H., Begg, E.J., Kennedy, M.A., Roberts, R. & Barclay, M.L. Is cytochrome P450 2C9 genotype associated with NSAID gastric ulceration? *British journal of clinical pharmacology* **51**, 627-30 (2001).
(129) Ma, J., Yang, X.Y., Qiao, L., Liang, L.Q. & Chen, M.H. CYP2C9 polymorphism in non-steroidal anti-inflammatory drugs-induced gastropathy. *J Dig Dis* **9**, 79-83 (2008).
(130) Bort, R., Ponsoda, X., Carrasco, E., Gomez-Lechon, M.J. & Castell, J.V. Metabolism of aceclofenac in humans. *Drug metabolism and disposition: the biological fate of chemicals* **24**, 834-41 (1996).
(131) Palikhe, N.S., Kim, S.H., Nam, Y.H., Ye, Y.M. & Park, H.S. Polymorphisms of Aspirin-Metabolizing Enzymes CYP2C9, NAT2 and UGT1A6 in Aspirin-Intolerant Urticaria. *Allergy Asthma Immunol Res* **3**, 273-6 (2011).
(132) Shiotani, A. *et al.* The preventive factors for aspirin-induced peptic ulcer: aspirin ulcer and corpus atrophy. *J Gastroenterol* **44**, 717-25 (2009).
(133) van Oijen, M.G. *et al.* Polymorphisms in genes encoding acetylsalicylic acid metabolizing enzymes are unrelated to upper gastrointestinal health in cardiovascular patients on acetylsalicylic acid. *British journal of clinical pharmacology* **60**, 623-8 (2005).
(134) Jalil, N.J. *et al.* The Implication of the Polymorphisms of COX-1, UGT1A6, and CYP2C9 among Cardiovascular Disease (CVD) Patients Treated with Aspirin. *J Pharm Pharm Sci* **18**, 474-83 (2015).
(135) Bigler, J., Whitton, J., Lampe, J.W., Fosdick, L., Bostick, R.M. & Potter, J.D. CYP2C9 and UGT1A6 genotypes modulate the protective effect of aspirin on colon adenoma risk. *Cancer Res* **61**, 3566-9 (2001).
(136) Chan, A.T., Tranah, G.J., Giovannucci, E.L., Hunter, D.J. & Fuchs, C.S. A prospective study of genetic polymorphisms in the cytochrome P-450 2C9 enzyme and the risk for distal colorectal adenoma. *Clin Gastroenterol Hepatol* **2**, 704-12 (2004).
(137) den Braver, M.W., den Braver-Sewradj, S.P., Vermeulen, N.P. & Commandeur, J.N. Characterization of cytochrome P450 isoforms involved in sequential two-step bioactivation of diclofenac to reactive p-benzoquinone imines. *Toxicology letters* **253**, 46-54 (2016).
(138) Grillo, M.P., Ma, J., Teffera, Y. & Waldon, D.J. A novel bioactivation pathway for 2-[2-(2,6-dichlorophenyl)aminophenyl]ethanoic acid (diclofenac) initiated by cytochrome P450-mediated oxidative decarboxylation. *Drug metabolism and disposition: the biological fate of chemicals* **36**, 1740-4 (2008).
(139) Yan, Z., Li, J., Huebert, N., Caldwell, G.W., Du, Y. & Zhong, H. Detection of a novel reactive metabolite of diclofenac: evidence for CYP2C9-mediated bioactivation via arene oxides. *Drug metabolism and disposition: the biological fate of chemicals* **33**, 706-13 (2005).
(140) Shen, S., Marchick, M.R., Davis, M.R., Doss, G.A. & Pohl, L.R. Metabolic activation of diclofenac by human cytochrome P450 3A4: role of 5-hydroxydiclofenac. *Chem Res Toxicol* **12**, 214-22 (1999).

(141) Tang, W., Stearns, R.A., Wang, R.W., Chiu, S.H. & Baillie, T.A. Roles of human hepatic cytochrome P450s 2C9 and 3A4 in the metabolic activation of diclofenac. *Chem Res Toxicol* **12**, 192-9 (1999).
(142) Transon, C., Lecoeur, S., Leemann, T., Beaune, P. & Dayer, P. Interindividual variability in catalytic activity and immunoreactivity of three major human liver cytochrome P450 isozymes. *European journal of clinical pharmacology* **51**, 79-85 (1996).
(143) Leemann, T., Transon, C. & Dayer, P. Cytochrome P450TB (CYP2C): a major monooxygenase catalyzing diclofenac 4'-hydroxylation in human liver. *Life Sci* **52**, 29-34 (1993).
(144) Maekawa, K. *et al.* Substrate-dependent functional alterations of seven CYP2C9 variants found in Japanese subjects. *Drug metabolism and disposition: the biological fate of chemicals* **37**, 1895-903 (2009).
(145) Ieiri, I. *et al.* Catalytic activity of three variants (Ile, Leu, and Thr) at amino acid residue 359 in human CYP2C9 gene and simultaneous detection using single-strand conformation polymorphism analysis. *Ther Drug Monit* **22**, 237-44 (2000).
(146) Crespi, C.L. & Miller, V.P. The R144C change in the CYP2C9*2 allele alters interaction of the cytochrome P450 with NADPH:cytochrome P450 oxidoreductase. *Pharmacogenetics* **7**, 203-10 (1997).
(147) Zhou, Y.H. *et al.* On the human CYP2C9*13 variant activity reduction: a molecular dynamics simulation and docking study. *Biochimie* **88**, 1457-65 (2006).
(148) Lee, M.Y. *et al.* High warfarin sensitivity in carriers of CYP2C9*35 is determined by the impaired interaction with P450 oxidoreductase. *The pharmacogenomics journal* **14**, 343-9 (2014).
(149) Luo, S.B. *et al.* Characterization of a novel CYP2C9 mutation (1009C>A) detected in a warfarin-sensitive patient. *J Pharmacol Sci* **125**, 150-6 (2014).
(150) Maekawa, K. *et al.* Four novel defective alleles and comprehensive haplotype analysis of CYP2C9 in Japanese. *Pharmacogenetics and genomics* **16**, 497-514 (2006).
(151) Dorado, P., Berecz, R., Norberto, M.J., Yasar, U., Dahl, M.L. & A, L.L. CYP2C9 genotypes and diclofenac metabolism in Spanish healthy volunteers. *European journal of clinical pharmacology* **59**, 221-5 (2003).
(152) Aithal, G.P., Day, C.P., Leathart, J.B. & Daly, A.K. Relationship of polymorphism in CYP2C9 to genetic susceptibility to diclofenac-induced hepatitis. *Pharmacogenetics* **10**, 511-8 (2000).
(153) Nakajima, M., Inoue, T., Shimada, N., Tokudome, S., Yamamoto, T. & Kuroiwa, Y. Cytochrome P450 2C9 catalyzes indomethacin O-demethylation in human liver microsomes. *Drug metabolism and disposition: the biological fate of chemicals* **26**, 261-6 (1998).
(154) Zarza, J. Major bleeding during combined treatment with indomethacin and low doses of acenocoumarol in a homozygous patient for 2C9*3 variant of cytochrome p-450 CYP2C9. *Thromb Haemost* **90**, 161-2 (2003).
(155) Smith, C.J., Ryckman, K.K., Bahr, T.M. & Dagle, J.M. Polymorphisms in CYP2C9 are associated with response to indomethacin among neonates with patent ductus arteriosus. *Pediatr Res* **82**, 776-80 (2017).
(156) Martinez, C. *et al.* Gender and functional CYP2C and NAT2 polymorphisms determine the metabolic profile of metamizole. *Biochemical pharmacology* **92**, 457-66 (2014).

(157) Garcia-Martin, E. *et al.* Genetic determinants of metamizole metabolism modify the risk of developing anaphylaxis. *Pharmacogenetics and genomics* **25**, 462-4 (2015).
(158) Matsumoto, K., Nemoto, E., Hasegawa, T., Akimoto, M. & Sugibayashi, K. In vitro characterization of the cytochrome P450 isoforms involved in the metabolism of 6-methoxy-2-napthylacetic acid, an active metabolite of the prodrug nabumetone. *Biol Pharm Bull* **34**, 734-9 (2011).
(159) Bowalgaha, K., Elliot, D.J., Mackenzie, P.I., Knights, K.M., Swedmark, S. & Miners, J.O. S-Naproxen and desmethylnaproxen glucuronidation by human liver microsomes and recombinant human UDP-glucuronosyltransferases (UGT): role of UGT2B7 in the elimination of naproxen. *British journal of clinical pharmacology* **60**, 423-33 (2005).
(160) Tracy, T.S., Marra, C., Wrighton, S.A., Gonzalez, F.J. & Korzekwa, K.R. Involvement of multiple cytochrome P450 isoforms in naproxen O-demethylation. *European journal of clinical pharmacology* **52**, 293-8 (1997).
(161) Miners, J.O., Coulter, S., Tukey, R.H., Veronese, M.E. & Birkett, D.J. Cytochromes P450, 1A2, and 2C9 are responsible for the human hepatic O-demethylation of R- and S-naproxen. *Biochemical pharmacology* **51**, 1003-8 (1996).
(162) Rodrigues, A.D., Kukulka, M.J., Roberts, E.M., Ouellet, D. & Rodgers, T.R. [O-methyl 14C]naproxen O-demethylase activity in human liver microsomes: evidence for the involvement of cytochrome P4501A2 and P4502C9/10. *Drug metabolism and disposition: the biological fate of chemicals* **24**, 126-36 (1996).
(163) Wei, L., Locuson, C.W. & Tracy, T.S. Polymorphic variants of CYP2C9: mechanisms involved in reduced catalytic activity. *Mol Pharmacol* **72**, 1280-8 (2007).
(164) Bae, J.W. *et al.* Effect of CYP2C9*3 allele on the pharmacokinetics of naproxen in Korean subjects. *Arch Pharm Res* **32**, 269-73 (2009).
(165) Zajic, S.C. *et al.* Individuals with CYP2C8 and CYP2C9 reduced metabolism haplotypes self-adjusted ibuprofen dose in the Coriell Personalized Medicine Collaborative. *Pharmacogenetics and genomics* **29**, 49-57 (2019).
(166) Kumar, S. *et al.* Extrapolation of diclofenac clearance from in vitro microsomal metabolism data: role of acyl glucuronidation and sequential oxidative metabolism of the acyl glucuronide. *J Pharmacol Exp Ther* **303**, 969-78 (2002).
(167) Machiela, M.J. & Chanock, S.J. LDlink: a web-based application for exploring population-specific haplotype structure and linking correlated alleles of possible functional variants. *Bioinformatics* **31**, 3555-7 (2015).
(168) Siu, Y.A., Hao, M.H., Dixit, V. & Lai, W.G. Celecoxib is a substrate of CYP2D6: Impact on celecoxib metabolism in individuals with CYP2C9*3 variants. *Drug Metab Pharmacokinet* **33**, 219-27 (2018).
(169) Shi, S. & Klotz, U. Clinical use and pharmacological properties of selective COX-2 inhibitors. *European journal of clinical pharmacology* **64**, 233-52 (2008).
(170) Rodrigues, A.D. Impact of CYP2C9 genotype on pharmacokinetics: are all cyclooxygenase inhibitors the same? *Drug metabolism and disposition: the biological fate of chemicals* **33**, 1567-75 (2005).
(171) Davies, N.M., McLachlan, A.J., Day, R.O. & Williams, K.M. Clinical pharmacokinetics and pharmacodynamics of celecoxib: a selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet* **38**, 225-42 (2000).
(172) Rainsford, K.D. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology* **17**, 275-342 (2009).

(173) Davies, N.M. Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clin Pharmacokinet* **34**, 101-54 (1998).
(174) Davies, N.M. Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet* **28**, 100-14 (1995).
(175) Davies, N.M. & Anderson, K.E. Clinical pharmacokinetics of naproxen. *Clin Pharmacokinet* **32**, 268-93 (1997).
(176) Davies, N.M. & Anderson, K.E. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. *Clin Pharmacokinet* **33**, 184-213 (1997).
(177) Kim, E., Ihm, C. & Kang, W. Modeling of aceclofenac metabolism to major metabolites in healthy volunteers. *Drug Metab Pharmacokinet* **31**, 458-63 (2016).
(178) Gates, B.J., Nguyen, T.T., Setter, S.M. & Davies, N.M. Meloxicam: a reappraisal of pharmacokinetics, efficacy and safety. *Expert Opin Pharmacother* **6**, 2117-40 (2005).
(179) Olkkola, K.T., Brunetto, A.V. & Mattila, M.J. Pharmacokinetics of oxicam nonsteroidal anti-inflammatory agents. *Clin Pharmacokinet* **26**, 107-20 (1994).
(180) Nilsen, O.G. Clinical pharmacokinetics of tenoxicam. *Clin Pharmacokinet* **26**, 16-43 (1994).
(181) Skjodt, N.M. & Davies, N.M. Clinical pharmacokinetics of lornoxicam. A short half-life oxicam. *Clin Pharmacokinet* **34**, 421-8 (1998).
(182) Lucas, S. The Pharmacology of Indomethacin. *Headache* **56**, 436-46 (2016).
(183) Pacifici, G.M. Clinical pharmacology of indomethacin in preterm infants: implications in patent ductus arteriosus closure. *Paediatr Drugs* **15**, 363-76 (2013).
(184) Skeith, K.J. & Jamali, F. Clinical pharmacokinetics of drugs used in juvenile arthritis. *Clin Pharmacokinet* **21**, 129-49 (1991).
(185) Davies, N.M. & Watson, M.S. Clinical pharmacokinetics of sulindac. A dynamic old drug. *Clin Pharmacokinet* **32**, 437-59 (1997).
(186) Brunell, D., Sagher, D., Kesaraju, S., Brot, N. & Weissbach, H. Studies on the metabolism and biological activity of the epimers of sulindac. *Drug metabolism and disposition: the biological fate of chemicals* **39**, 1014-21 (2011).
(187) Davies, N.M. Clinical pharmacokinetics of nabumetone. The dawn of selective cyclo-oxygenase-2 inhibition? *Clin Pharmacokinet* **33**, 404-16 (1997).
(188) Takemoto, J.K., Reynolds, J.K., Remsberg, C.M., Vega-Villa, K.R. & Davies, N.M. Clinical pharmacokinetic and pharmacodynamic profile of etoricoxib. *Clin Pharmacokinet* **47**, 703-20 (2008).
(189) Barrett, J.C. Haploview: Visualization and analysis of SNP genotype data. *Cold Spring Harb Protoc* **2009**, pdb ip71 (2009).
(190) Genomes Project, C. *et al.* A global reference for human genetic variation. *Nature* **526**, 68-74 (2015).