Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2C9* and Nonsteroidal Anti-Inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics due to their lack of addictive potential. However, NSAIDs have the potential to cause serious gastrointestinal, renal, and cardiovascular adverse events. *CYP2C9* polymorphisms influence metabolism and clearance of several drugs in this class, thereby affecting drug exposure and potentially safety. We summarize evidence from the published literature supporting these associations and provide therapeutic recommendations for NSAIDs based on *CYP2C9* genotype (updates at www.cpicpgx.org).

The purpose of this guideline is to provide information for the interpretation of *CYP2C9* genotype tests so that the results can guide dosing and/or use of nonsteroidal anti-inflammatory drugs (NSAIDs). Detailed guidelines for use of NSAIDs as well as cost-effectiveness of *CYP2C9* genotyping are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are periodically updated at www.cpicpgx.org/guidelines/.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2C9* genotype and NSAID (celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lornoxicam, meloxicam, nabumetone, naproxen, piroxicam, tenoxicam, and sulindac) use and *CYP2C8* genotype and ibuprofen, piroxicam, and diclofenac use was conducted (details in **Supplementary Material**). Evidence summarized in **Tables S1–S10**.

GENE: *CYP2C9*

Hepatic CYP2C9 enzyme contributes to the metabolism of many drugs, including several NSAIDs (celecoxib, diclofenac, flurbiprofen, indomethacin, ibuprofen, lornoxicam, meloxicam, nabumetone, naproxen, piroxicam, and tenoxicam). The *CYP2C9* gene is highly polymorphic, with at least 61 variant alleles and multiple sub-alleles (see ***CYP2C9* Allele Definition Table** in refs. 1,2). Differences in allele frequencies have been observed across multiple geographically, racially, and ethnically diverse groups (see ***CYP2C9* Allele Frequency Table** in refs. 1,2). The most commonly reported alleles are categorized into functional groups as follows: Normal function (e.g., *CYP2C9*1*), decreased function (e.g., *CYP2C9*2*, **5*, **8*, and **11*), and no function (e.g., *CYP2C9*3*, **6*, and **13*). Allele function assignments have been made based on available *in vitro* and *in vivo* data, with consideration for their clinical actionability.[1,2] The two most extensively studied variants are *CYP2C9*2* (p.R144C; rs1799853) and *CYP2C9*3* (p.I359L; rs1057910).[3] *In vitro* and clinical studies suggest that the catalytic activity of *CYP2C9* decreased function and no function alleles is substrate-dependent. Therefore, assigning function to *CYP2C9* alleles requires careful evaluation of individual drugs.

Genetic test interpretation

Most clinical laboratories reporting *CYP2C9* genotype use the star (*)-allele nomenclature, in which each allele is defined by a genotype at one or more specific single-nucleotide polymorphisms with variable enzyme activity. The star (*)-allele nomenclature for *CYP2C9* is found at the Pharmacogene Variation (PharmVar) Consortium website (https://www.pharmvar.org/gene/CYP2C9). The combination of alleles is used to determine a patient's diplotype (often also referred to as genotype), which can then be used to infer an individual's predicted metabolizer phenotype (**Table 1**; *CYP2C9* Diplotype to Phenotype Table[1,2]). Each allele functional status is assigned an activity value ranging from 0 to 1 (e.g., 0 for no function, 0.5 for decreased, and 1.0 for normal function), which are summed to calculate the activity score (AS) for each diplotype.[1,2] The CYP2C9 AS has been translated into the phenotype classification system as follows: Individuals with an AS of 0 or 0.5 are poor metabolizers (PMs), those with a score of 1 or 1.5 are intermediate metabolizers (IMs), and those with a score of 2 are normal metabolizers (NMs) (**Table 1**; *CYP2C9* Diplotype to Phenotype Table[1,2]). Because

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Table 1 Assignment of likely CYP2C9 phenotypes based on genotypes

Likely phenotype[a,b]	Activity score	Genotypes	Examples of diplotypes
Normal metabolizer	2	An individual carrying two normal function alleles	*1/*1
Intermediate metabolizer	1.5 1	An individual carrying one normal function allele plus one decreased function allele; OR one normal function allele plus one no function allele OR two decreased function alleles	*1/*2 *1/*3, *2/*2
Poor metabolizer	0.5 0	An individual carrying one no function allele plus one decreased function allele; OR two no function alleles	*2/*3 *3/*3
Indeterminate	n/a	An individual carrying allele combinations with uncertain and/or unknown function alleles	*1/*7, *1/*10, *7/*10, *1/*57

[a]Assignment of allele function and associated citations can be found at https://www.pharmgkb.org/page/cyp2c9RefMaterials (see *CYP2C9* Allele Definition Table and *CYP2C9* Allele Functionality Table in refs. 1,2). For a complete list of *CYP2C9* diplotypes and resulting phenotypes, see the *CYP2C9* Genotype to Phenotype Table in refs. 1,2. [b]See the *CYP2C9* Frequency Table in refs. 1,2 for population-specific allele and phenotype frequencies.

reference laboratories providing clinical *CYP2C9* genotyping may use varying methods to assign phenotypes, it is advisable to note a patient's *CYP2C9* diplotype and to refer to the *CYP2C9* Diplotype to Phenotype Table[1,2] online for a complete list of possible diplotypes and phenotype assignments before making therapeutic decisions about NSAID therapy.

Of note, **Table 1** denotes a change to the prior genotype to phenotype translation table[4] for diplotypes containing *CYP2C9*2* and other decreased function alleles. The phenotype group for *CYP2C9*2/*2* (AS = 1) is now translated into the IM phenotype group (originally translated to PM). This change is based on data from multiple substrates (flurbiprofen, celecoxib, phenytoin, and warfarin) showing a similar effect of *CYP2C9*1/*3* (AS = 1) and *CYP2C9*2/*2* on metabolic ratio and dose requirements (warfarin).[5–7] Furthermore, *CYP2C9*3* and alleles with similar clinical effect and function were assigned a clinical function as "no function" with an activity value of 0 (previously decreased function). This is based on *CYP2C9*3/*3*, which is the diplotype with the lowest clinically actionable activity; thus, the *CYP2C9*3* allele receives a "no function" assignment. Other alleles with similarly low function will also be classified as "no function."

Currently, clinical laboratories rarely sequence the entire *CYP2C9* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine common haplotypes (also referred to as alleles) using the star-allele (*) nomenclature system. Tables on the CPIC and PharmGKB websites contain a list of *CYP2C9* alleles, the specific combination of variants that can be used to determine each allele, allele functional status, and frequency across major ethnic populations as reported in the literature.[1,2]

Available genetic test options

See the Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/) for more information on commercially available clinical testing options.

Incidental findings

No diseases or conditions have been consistently or strongly linked to variation in *CYP2C9* independent of drug metabolism and response. CYP2C9 IMs and PMs may be predisposed to serious bleeding during warfarin therapy and increased risk of phenytoin-related toxicities.[4,8]

Other considerations

CYP2C9 is located within a cluster of *CYP2C* genes (*CYP2C18*, *CYP2C19*, *CYP2C9*, and *CYP2C8*) on chromosome 10 (**Figure S1**), which evolved from a common ancestral *CYP* gene through duplication events.[9] Importantly, the *CYP2C9*2* allele is in strong linkage disequilibrium with the *CYP2C8*3* allele (**Table S11**), such that > 80% of individuals who carry the *CYP2C9*2* allele also carry the *CYP2C8*3* allele in many populations.[10] This may be of clinical relevance for drugs that are substrates for both CYP2C8 and CYP2C9, such as diclofenac and ibuprofen.

DRUG: NSAIDS

Background

NSAIDs are among the most commonly used analgesics due to their lack of addictive potential.[11] They are also one of the most diverse classes of clinically available drugs, with > 40 chemically distinct compounds marketed worldwide. The principal therapeutic effect of NSAIDs occurs via inhibition of prostaglandin biosynthesis from arachidonic acid by the prostaglandin G/H synthases 1 and 2, also known as cyclooxygenases (COX).[12] Most NSAIDs are reversible inhibitors of both the COX-1 and COX-2 isoforms. Celecoxib, meloxicam, and diclofenac are selective COX-2 inhibitors.

Millions of older adults consume NSAIDs regularly for chronic pain,[13] whereas short-term use is prevalent in those experiencing acute pain and musculoskeletal injuries.[14,15] NSAIDs are commonly used in pediatric patients to reduce fever and ameliorate pain and in preterm infants or neonates with patent ductus arteriosus as an attempt to induce closure of the ductus.

Hepatic biotransformation, often via cytochrome P450 isoforms CYP2C9, 1A2, and 3A4 (**Table S12**), and renal excretion are the principal routes of clearance of the majority of NSAIDs. The activity of CYP enzymes is influenced by genetic variation, age, sex, circadian variation, disease, and interacting drugs that are CYP substrates, inhibitors, or inducers.[16] Thus, variability in the metabolism of NSAIDs can have a considerable impact

on drug exposure. Several NSAIDs undergo enterohepatic recycling, thus amplifying interindividual variability in drug exposure.

Although several NSAIDs are considered safe for over-the-counter use, they have the potential to cause serious complications, including gastrointestinal (GI) bleeding (1–2% per year of regular users), hypertension (up to 5% per year of regular users), myocardial infarction (up to 1% per year), heart failure (up to 1% per year), and renal damage; arrhythmias and sudden cardiac death have also been observed in rare cases.[11] With the large population exposure to NSAIDs, these adverse events may have considerable public health and economic impacts, although this is difficult to quantify particularly for cardiovascular adverse effects, given the background prevalence of cardiovascular disease in the general population.[17]

Individual risk factors, such as older age, concomitant drug use, or pre-existing disease, have been associated with the occurrence of adverse events; however, our understanding of the molecular mechanisms—including genetic predisposition—that result in complications in some patients, but not others, is limited. Importantly, NSAID adverse events are largely on-target adverse events caused by the inhibition of COX-1 or COX-2 in tissues in which they fulfill physiological functions, such as the GI tract, kidneys, and cardiovascular system,[18] resulting in an increased risk of complications with increased drug doses or exposure.[12] This has been borne out in a meta-analysis that demonstrated the dose-dependency of cardiovascular complications related to celecoxib.[19]

Linking genetic variability to variability in drug-related phenotypes

Substantial evidence links *CYP2C9* genotypes with phenotypic variability in CYP2C9 metabolism and plasma NSAID concentrations, with the majority of studies conducted in healthy volunteers (**Tables S1–S9**). Application of a grading system to evidence linking genotypic with pharmacokinetic variability indicates a moderate to high quality of evidence for most NSAIDs. The quality of evidence linking genotype to NSAID therapeutic response and adverse events was graded as weak in most cases (**Tables S1–S9**). See the **Supplementary Material** for additional summaries for each drug covered in this guideline. Although clinical evidence linking genetic variation in *CYP2C9* to an increased rate of adverse events with NSAIDs use is scarce, several studies have established an association between *CYP2C9* decreased function and no function alleles and elevated NSAID exposure (**Figures 1** and **S2**). Because most NSAID adverse events are dose-dependent, on-target adverse events involving COX inhibition,[19–23] it is reasonable to assume that elevated exposure increases the risk of adverse events.

Therapeutic recommendations

NSAIDs may be used on a chronic, short-term, or as needed (PRN) basis. Although data on risks associated with short-term or PRN NSAID consumption vs. chronic use are limited, the risks of upper GI bleeding and myocardial infarction are thought to be similar among new and chronic NSAID users.[24,25] Thus, these recommendations can be considered and applied regardless of treatment duration. In addition, as some short-acting NSAIDs (e.g., low-dose ibuprofen) can be purchased over-the-counter in some countries, clinicians need to be aware that these recommendations also apply to these drugs.

CYP2C9 IM and PM phenotypes affect systemic plasma concentrations of NSAIDs by decreasing metabolic clearance and consequently prolonging plasma elimination half-life. Therefore, therapeutic recommendations are broadly organized according to the NSAID plasma elimination half-life in NMs. Where more than two studies reported plasma concentration area under the curve (AUC), a meta-analysis was conducted to estimate the average impact of *CYP2C9* genotype on drug exposure (**Figures 1** and **S2–S4**).

Celecoxib, flurbiprofen, ibuprofen, and lornoxicam. **Table 2** summarizes the therapeutic recommendations for celecoxib, flurbiprofen, ibuprofen, and lornoxicam prescribing based on CYP2C9 phenotype. These NSAIDs exhibit a short to moderately long elimination half-life in CYP2C9 NMs (celecoxib: 11–16 hours; flurbiprofen: 2–6 hours; ibuprofen: 2–4 hours; and lornoxicam: 3–5 hours).[26–32] Based on current evidence (**Tables S1–S4**), NMs and IMs with an AS of 1.5 are recommended to initiate therapy with the approved starting dose. Despite having mildly reduced metabolism, IMs with an AS of 1.5 do not exhibit significant increases in drug exposure relative to NMs (**Figures S2–S4**). Although study populations sizes were small, a meta-analysis of five studies showed that the *CYP2C9*1/*2* genotype (IM with an AS of 1.5) had no effect on celecoxib exposure (ratio of means 0.98; 95% confidence interval (CI) 0.8–1.2 vs. **1/*1*) and a meta-analysis of four studies suggested that a potential effect on ibuprofen exposure (ratio of means 1.35; 95% CI 0.9–2.0 vs. **1/*1*; $P = 0.09$) would be mild if it exists. Given the wide therapeutic index of NSAIDs, dose reductions would not be recommended.

CYP2C9 IMs with an AS of 1 have reduced metabolism and are expected to exhibit a prolonged drug half-life and higher plasma concentrations compared to NMs, which may increase probability of toxicities. A meta-analysis of 7 small studies showed a ~ 60% increase of celecoxib AUC (ratio of means 1.62; 95% CI 1.25–2.10 **1/*3* vs. **1/*1*; $P = 0.004$), and an analysis of four studies of ibuprofen showed an increase in AUC of ~ 40% (ratio of means 1.43; 95% CI 1.09–1.88 **1/*3* vs. **1/*1*; $P = 0.02$). Insufficient data exist for formal meta-analyses of flurbiprofen and lornoxicam, and recommendations are based on evaluating each study individually. For IMs with an AS of 1, it is recommended to initiate NSAID therapy with the lowest recommended starting dose and titrate to clinical effect with close monitoring for adverse events, such as elevated blood pressure and kidney dysfunction during course of therapy. Regarding ibuprofen use, it should be taken into consideration that, although the *CYP2C9*2* allele alone might not cause a clinically relevant reduction in clearance, its strong linkage with the decreased function *CYP2C8*3* allele may result in impaired R (-) ibuprofen hydroxylation and increased exposure to the parent drug.

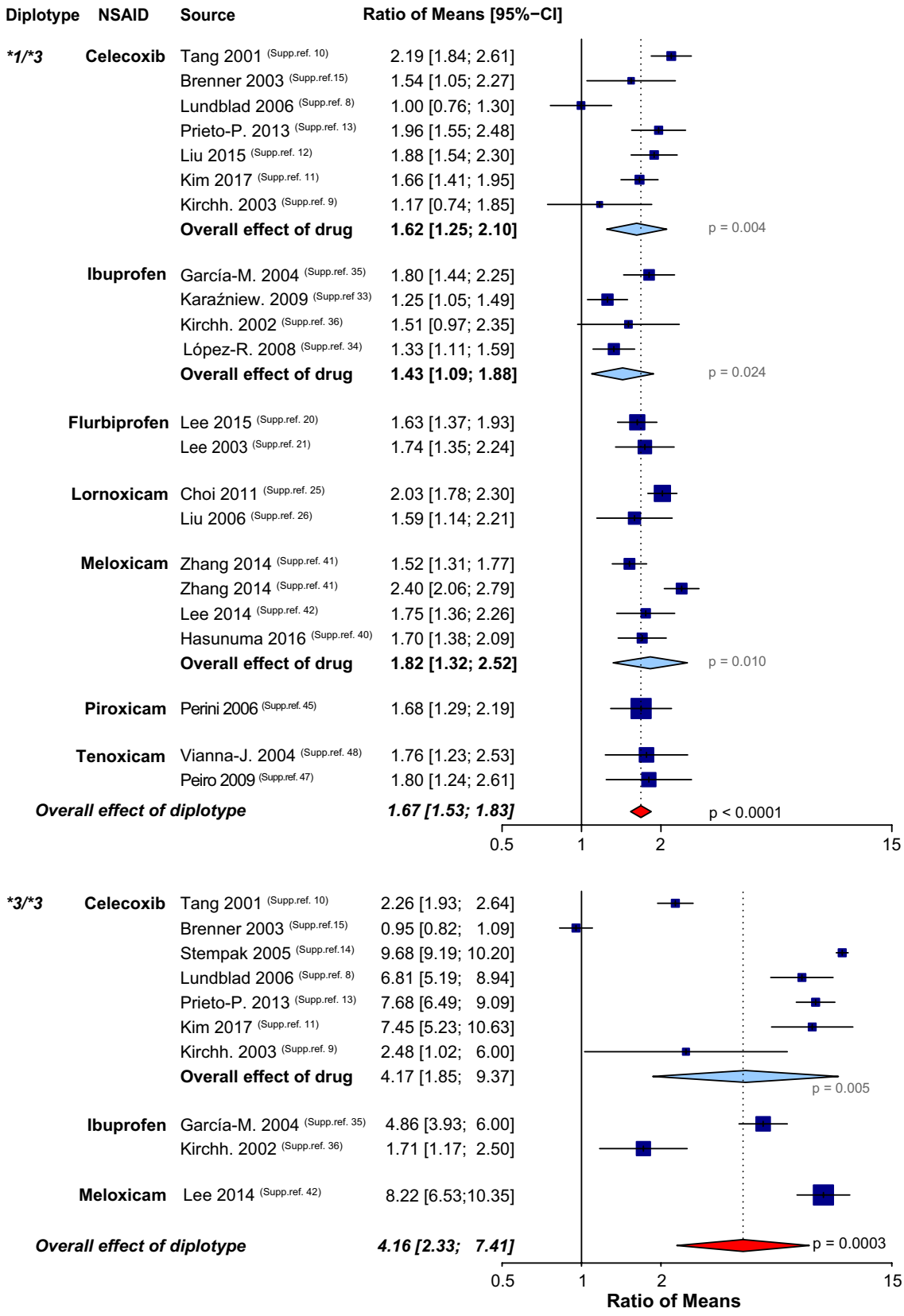

Figure 1 Meta-analysis of the effect of *CYP2C9* variant alleles on nonsteroidal anti-inflammatory drug (NSAID) exposure. Sample sizes and reported area under the curve (AUC) data were extracted from clinical pharmacokinetic studies reviewed for this guideline. Results are expressed as the ratio of mean AUC for variant allele carriers to *CYP2C9*1/*1* controls. Overall effects of individual drugs were only estimated using a random effects model when three or more studies were available for analysis. References shown in parenthesis and methodological details are provided in the **Supplementary Material**. CI, confidence interval.

Individuals with a CYP2C9 PM phenotype (AS of 0) are expected to have markedly reduced metabolism and are expected to exhibit a pronounced prolongation of drug half-life and increase in plasma concentrations, which may increase the probability and/or severity of toxicities.[19–23] A meta-analysis of 7 small studies showed a ~ 400% increase of celecoxib exposure (ratio of means 4.17; 95% CI 1.85–9.37 **3/*3* vs. **1/*1*; $P = 0.005$; **Figure 1**), whereas insufficient data exist for formal meta-analyses of ibuprofen, flurbiprofen, and lornoxicam. In this case, therapeutic recommendations involve dose reduction or alternative therapies, coupled with careful monitoring for adverse events, which are consistent with the US Food and Drug Administration (FDA) recommendations for celecoxib and flurbiprofen. It is recommended to initiate therapy with 25–50% of the lowest recommended starting dose (i.e., 50–75% dose reduction), and careful dose titration to clinical effect. Because drug half-life is significantly prolonged in these patients, upward dose titration should not occur until after steady-state is reached, taking into consideration the PM half-life for each drug; of course, dosing may be stopped or decreased due to toxicity at any time. Treatment with an alternative therapy could also be considered. This could include NSAIDs not primarily metabolized by CYP2C9 (such as aspirin, ketorolac (approved for short-term use only), metamizole, naproxen, sulindac, etoricoxib, parecoxib, or valdecoxib), or with pharmacokinetic parameters apparently not impacted by *CYP2C9* genetic variants *in vivo* despite CYP2C9 metabolism *in vitro*[33] (diclofenac, weak level of evidence, see **Table S9**). Some of these alternative drugs are not available worldwide (e.g., etoricoxib, metamizole, parecoxib, and valdecoxib) because of the elevated cardiovascular risk associated with COX-2-selective NSAIDs, and some have serious adverse events that need to be considered (e.g., diclofenac and liver toxicity, metamizole, and agranulocytosis). Therefore, individual NSAIDs are not always therapeutically equivalent, and the selection of an alternative agent requires careful consideration of drug properties (e.g., half-life (**Table S12**), potency, metabolism, COX isoenzyme selectivity, and off-target effects) that may affect efficacy and safety.

Meloxicam. **Table 3** summarizes therapeutic recommendations for meloxicam prescribing based on CYP2C9 phenotype. Meloxicam has a longer half-life (15–20 hours; **Table S12**) than celecoxib and ibuprofen; thus, impaired meloxicam metabolism is expected to cause sustained elevations in drug exposure. Recommendations for CYP2C9 NMs and IMs with an AS of 1.5 are similar to the short half-life NSAIDs and include initiation of therapy with the standard dose while using the lowest effective dosage for shortest duration capable to achieve treatment goals. For IMs with an AS of 1, reduced metabolism and increased plasma concentrations are expected that may increase probability of toxicities. A meta-analysis of four small studies showed a ~ 80% increase of meloxicam AUC in IMs with an AS of 1 (ratio of means 1.82; 95% CI 1.32–2.52 **1/*3* vs. **1/*1*; $P = 0.0025$; **Figure 1**). The recommendations are to either initiate therapy with 50% of the lowest recommended starting dose or choose an alternative therapy, consistent with the recommendations in PMs for short half-life NSAIDs (**Table 2**). Upward dose titration should not occur until after steady-state is reached (at least 7 days), and careful monitoring is recommended. CYP2C9 PMs should be prescribed an alternative therapy because markedly prolonged half-life is expected (i.e., > 100 hours).[34] This provides additional guidance to the FDA label recommendations that recommend a lower starting dose in PMs but does not specify the amount of the dose reduction. Recommended alternative therapies are drugs not metabolized by CYP2C9, or with pharmacokinetic parameters not significantly affected by *CYP2C9* genetic variants *in vivo* (see above). Selection of an NSAID with a short half-life (**Table 2**) could also be considered.

Piroxicam and tenoxicam. **Table 4** summarizes therapeutic recommendations for piroxicam and tenoxicam. These drugs have extremely long half-lives (30–86 and 60 hours, respectively), thus amplifying the potential risks in individuals with reduced CYP2C9 metabolism and hampering dose titration strategies due to lack of data. Accordingly, rather than use of a lower starting dose, IMs with an AS of 1 and PMs are recommended to receive an alternative therapy. This includes drugs that are not metabolized by CYP2C9 or significantly affected by *CYP2C9* genetic variants *in vivo*. Selection of an NSAID with a short half-life (**Table 2**) could also be considered.

Aceclofenac, aspirin, diclofenac, indomethacin, lumiracoxib, metamizole, nabumetone, and naproxen. **Table S9** includes evidence linking *CYP2C9* genotype to aceclofenac, aspirin, diclofenac, indomethacin, lumiracoxib, metamizole, nabumetone, and naproxen phenotype. The pharmacokinetics of these drugs are not significantly impacted by *CYP2C9* genetic variants *in vivo* and/or there is insufficient evidence to provide a recommendation to guide clinical practice at this time (CPIC classification of recommendation "no recommendation"; CPIC level C; **Table S20**).

Pediatrics. Data describing the relationship between *CYP2C9* genotype and NSAID systemic exposure and toxicities in pediatric patients are scarce.[35] Because CYP2C9 activity is fully mature by early childhood, it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring. Ultimately, additional research and clinical trials in pediatric patients investigating the association between *CYP2C9* genotype and NSAID systemic exposure and treatment outcomes are needed.

Recommendations for incidental findings

See the CPIC guidelines for *CYP2C9* and warfarin and phenytoin for genotype-based recommendations for these drugs.[4,8]

Other considerations

The potential for drug-drug interactions should be considered when initiating NSAID therapy. *CYP2C9* decreased function allele carriers are at higher risk of supratherapeutic International Normalized Ratio or major bleeding with concomitant use of warfarin or other coumarin anticoagulants with NSAIDs compared with NMs.[36–40] Thus, it is recommended that this

Table 2 Therapeutic recommendations for celecoxib, flurbiprofen, lornoxicam, and ibuprofen based on CYP2C9 phenotype

Phenotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Other considerations
CYP2C9 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Strong	
CYP2C9 intermediate metabolizer AS of 1.5	Mildly reduced metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Moderate	IMs might have a higher than normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs, such as hepatic impairment or advanced age. Further caution should be taken with ibuprofen use in individuals carrying the *CYP2C9*2* allele as it is in linkage disequilibrium with *CYP2C8*3* and ibuprofen is also metabolized by CYP2C8.
CYP2C9 intermediate metabolizer AS of 1	Moderately reduced metabolism; higher plasma concentrations may increase probability of toxicities	Initiate therapy with lowest recommended starting dose. Titrate dose upward to clinical effect or maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Carefully monitor adverse events, such as blood pressure and kidney function during course of therapy.	Moderate	IMs might have a higher than normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs, such as hepatic impairment or advanced age. Further caution should be taken with ibuprofen use in individuals carrying the *CYP2C9*2* allele as it is in linkage disequilibrium with *CYP2C8*3* and ibuprofen is also metabolized by CYP2C8.
CYP2C9 poor metabolizer	Significantly reduced metabolism and prolonged half-life; higher plasma concentrations may increase probability and/or severity of toxicities	Initiate therapy with 25–50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 25–50% of the maximum recommended dose with caution. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Upward dose titration should not occur until after steady-state is reached (at least 8 days for celecoxib and 5 days for ibuprofen, flurbiprofen, and lornoxicam after first dose in PMs). Carefully monitor adverse events such as blood pressure and kidney function during course of therapy. Alternatively, consider an alternate therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants *in vivo*.	Moderate	Alternative therapies not primarily metabolized by CYP2C9 include aspirin, ketorolac, naproxen, and sulindac. Selection of therapy will depend on individual patient treatment goals and risks for toxicity.
Indeterminate	N/A	No recommendation	No recommendation	N/A

AS, activity score; IMs, intermediate metabolizers; N/A, not applicable; PMs, poor metabolizers.
[a]Separate drug-specific recommendation tables are available online.[1]

Table 3 Therapeutic recommendations for meloxicam based on CYP2C9 phenotype

Phenotype[a]	Implication	Therapeutic recommendation	Classification of recommendation	Other considerations
CYP2C9 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Strong	
CYP2C9 intermediate metabolizer AS of 1.5	Mildly reduced metabolism	Initiate therapy with recommended starting dose. In accordance with the meloxicam prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Moderate	IMs might have a higher than normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs, such as hepatic impairment or advanced age.
CYP2C9 intermediate metabolizer AS of 1	Moderately reduced metabolism; higher plasma concentrations may increase probability of toxicities	Initiate therapy with 50% of the lowest recommended starting dose. Titrate dose upward to clinical effect or 50% of the maximum recommended dose with caution. In accordance with the meloxicam prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. Upward dose titration should not occur until after steady-state is reached (at least 7 days). Carefully monitor adverse events, such as blood pressure and kidney function during course of therapy. Alternatively, consider alternative therapy. Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants *in vivo* or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (**Table 2**).	Moderate	IMs might have a higher than normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs, such as hepatic impairment or advanced age. Alternative therapies not primarily metabolized by CYP2C9 include aspirin, ketorolac, naproxen, and sulindac. Selection of therapy will depend on individual patient treatment goals and risks for toxicity.
CYP2C9 poor metabolizer	Significantly reduced metabolism and prolonged half-life; higher plasma concentrations may increase probability and/or severity of toxicities	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants *in vivo* or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (**Table 2**).	Moderate	
Indeterminate	N/A	No recommendation	No recommendation	N/A

AS, activity score; IMs, intermediate metabolizers; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drug.
[a]Separate drug-specific recommendation tables are available online.[1]

drug combination be avoided in CYP2C9 IMs and PMs. Variants in other genes, including *CYP2C8* and drug targets, such as *PTGS1* and *PTGS2*, may also influence the outcome of NSAID therapy, but the evidence is insufficient to recommend using these variants to guide NSAID dosing at this time (see **Supplementary Material**).

Implementation of this guideline. The guideline supplement and CPIC website (https://cpicpgx.org/cpic-guideline-for-nsaids-based-on-cyp2c9-genotype/) contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see Resources to Incorporate Pharmacogenetics Into an Electronic Health Record With Clinical Decision Support in the **Supplementary Material**).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefits for patients with existing *CYP2C9* genotyping information are avoiding adverse events in those patients who are CYP2C9 IMs or PMs by making significant reductions in their starting dose or by selecting alternative agents. This may provide an opportunity to prescribe NSAIDs for acute or chronic

Table 4 Therapeutic recommendations for piroxicam and tenoxicam based on CYP2C9 phenotype

Phenotype[a]	Implication	Therapeutic recommendation	Classification of recommendation – piroxicam	Classification of recommendation – tenoxicam	Other considerations
CYP2C9 normal metabolizer	Normal metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Strong	Strong	
CYP2C9 intermediate metabolizer AS of 1.5	Mildly reduced metabolism	Initiate therapy with recommended starting dose. In accordance with the prescribing information, use the lowest effective dosage for shortest duration consistent with individual patient treatment goals.	Moderate	Moderate	IMs might have a higher than normal risk of adverse events especially in individuals with other factors affecting clearance of these drugs such as hepatic impairment or advanced age.
CYP2C9 intermediate metabolizer AS of 1	Moderately reduced metabolism; higher plasma concentrations may increase probability of toxicities	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants *in vivo* or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (**Table 2**).	Moderate	Optional	Alternative therapies not primarily metabolized by CYP2C9 include aspirin, ketorolac, naproxen, and sulindac. Selection of therapy will depend on individual patient treatment goals and risks for toxicity.
CYP2C9 poor metabolizer	Significantly reduced metabolism and prolonged half-life; higher plasma concentrations may increase probability and/or severity of toxicities	Choose an alternative therapy not metabolized by CYP2C9 or not significantly impacted by *CYP2C9* genetic variants *in vivo* or choose an NSAID metabolized by CYP2C9 but with a shorter half-life (**Table 2**).	Moderate	Optional	Alternative therapies not primarily metabolized by CYP2C9 include aspirin, ketorolac, naproxen, and sulindac. Selection of therapy will depend on individual patient treatment goals and risks for toxicity.
Indeterminate	N/A	No recommendation	No recommendation	No recommendation	N/A

AS, activity score; IMs, intermediate metabolizers; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drug.
[a]Separate drug-specific recommendation tables are available online.[1]

pain conditions at genetically informed doses to limit long-term drug exposure and secondary adverse events for patients who may be at increased risk. However, although traditional pharmacogenetic studies have provided evidence associating common *CYP2C9* genetic variation with NSAID pharmacokinetics, there is sparse prospective evidence showing that genetically guided NSAID prescribing improves clinical outcomes. Additionally, study populations were too small to assess interactions between *CYP2C9* genetic variation and other factors potentially affecting drug disposition and risk of adverse reactions, such as sex, race, ethnicity, age, comorbidities, and concomitant medication. Potential risks associated with *CYP2C9* genotyping, which is reliable when performed in qualified laboratories, include errors in genotyping or reporting of genotype.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

Rare *CYP2C9* variants may not be included in the genotype test used, and patients with rare variants may be assigned an NM phenotype based on a default *CYP2C9*1/*1* test result. Thus, an assigned *CYP2C9*1* allele could potentially harbor a decreased or no function variant. Therefore, it is important that genetic test reports include information on which variant alleles were genotyped or which single-nucleotide polymorphisms were interrogated.

As with any diagnostic test, *CYP2C9* genotype is just one factor that clinicians should consider when prescribing NSAIDs to an individual patient. Age, sex, race and ethnicity, liver dysfunction, comorbidities, concomitant medications, genetic linkage disequilibrium with *CYP2C8*, and other undiscovered genetic and environmental factors can all impact the likelihood that a patient will experience adverse events with NSAID therapy. For example, regardless of CYP2C9 phenotype, NSAIDs should be avoided in patients with renal dysfunction or heart failure and in those at high risk of cardiovascular or GI adverse events. NSAIDs should be used with caution in elderly patients, as hepatic CYP2C9 metabolism decreases with older age and these individuals are at greater risk of renal and GI adverse events. Another consideration is the impact of drug-drug interactions. In particular, concomitant use of NSAIDs and agents with antiplatelet or anticoagulant effects should only be with extreme caution, as this can result in an increased risk of bleeding or interfere with platelet inhibition in the case of aspirin. NSAIDs decrease the therapeutic effect of antihypertensive medications and should be used with caution in patients with underlying hypertension.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICTS OF INTEREST

All authors declared no competing interests for this work.

DISCLAIMER

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

1. Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC Guideline for NSAIDs based on CYP2C9 genotype <https://cpicpgx.org/cpic-guideline-for-nsaids-based-on-cyp2c9-genotype/>.
2. Pharmacogenomics Knowledgebase (PharmGKB). Gene-specific Information Tables for CYP2C9 <https://www.pharmgkb.org/page/cyp2c9RefMaterials>.
3. Lee, C.R., Goldstein, J.A. & Pieper, J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* **12**, 251–263 (2002).
4. Caudle, K.E. *et al.* Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. *Clin. Pharmacol. Ther.* **96**, 542–548 (2014).
5. 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).
6. Kusama, M., Maeda, K., Chiba, K., Aoyama, A. & Sugiyama, Y. Prediction of the effects of genetic polymorphism on the pharmacokinetics of CYP2C9 substrates from in vitro data. *Pharm. Res.* **26**, 822–835 (2009).
7. Lindh, J.D., Holm, L., Andersson, M.L. & Rane, A. Influence of CYP2C9 genotype on warfarin dose requirements–a systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* **65**, 365–375 (2009).
8. Johnson, J.A. *et al.* Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetics-guided warfarin dosing: 2017 update. *Clin. Pharmacol. Ther.* **102**, 397–404 (2017).
9. Chaney, M.E., Piontkivska, H. & Tosi, A.J. Retained duplications and deletions of CYP2C genes among primates. *Mol. Phylogenet. Evol.* **125**, 204–212 (2018).
10. Speed, W.C., Kang, S.P., Tuck, D.P., Harris, L.N. & Kidd, K.K. Global variation in CYP2C8-CYP2C9 functional haplotypes. *Pharmacogenomics J.* **9**, 283–290 (2009).
11. Grosser, T., Theken, K.N. & FitzGerald, G.A. Cyclooxygenase inhibition: pain, inflammation, and the cardiovascular system. *Clin. Pharmacol. Ther.* **102**, 611–622 (2017).
12. Grosser, T., Fries, S. & FitzGerald, G.A. Biological basis for the cardiovascular consequences of COX-2 inhibition: therapeutic challenges and opportunities. *J. Clin. Invest.* **116**, 4–15 (2006).
13. Zhou, Y., Boudreau, D.M. & Freedman, A.N. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiol. Drug Saf.* **23**, 43–50 (2014).
14. Gorski, T. *et al.* Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br. J. Sports Med.* **45**, 85–90 (2011).

15. Walker, L.A., Zambraski, E.J. & Williams, R.F. Widespread use of prescription nonsteroidal anti-inflammatory drugs among U.S. army active duty soldiers. *Mil. Med.* **182**, e1709–e1712 (2017).
16. Lin, J.H. & Lu, A.Y. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin. Pharmacokinet.* **35**, 361–390 (1998).
17. Brownstein, J.S., Sordo, M., Kohane, I.S. & Mandl, K.D. The tell-tale heart: population-based surveillance reveals an association of rofecoxib and celecoxib with myocardial infarction. *PLoS One* **2**, e840 (2007).
18. Grosser, T., Yu, Y. & Fitzgerald, G.A. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu. Rev. Med.* **61**, 17–33 (2010).
19. Bhala, N. *et al.* Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* **382**, 769–779 (2013).
20. Solomon, S.D. *et al.* Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* **114**, 1028–1035 (2006).
21. Lanas, A. *et al.* Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. *Gut* **55**, 1731–1738 (2006).
22. Castellsague, J. *et al.* Individual NSAIDs and upper gastrointestinal complications: a systematic review and meta-analysis of observational studies (the SOS project). *Drug Saf.* **35**, 1127–1146 (2012).
23. Huerta, C., Castellsague, J., Varas-Lorenzo, C. & Garcia Rodriguez, L.A. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. *Am. J. Kidney Dis.* **45**, 531–539 (2005).
24. Schjerning Olsen, A.M. *et al.* Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation* **123**, 2226–2235 (2011).
25. Hernandez-Diaz, S. & Garcia-Rodriguez, L.A. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. *Am. J. Med.* **110**(suppl. 3A), 20S–S27 (2001).
26. Ochoa, D. *et al.* Effect of gender and CYP2C9 and CYP2C8 polymorphisms on the pharmacokinetics of ibuprofen enantiomers. *Pharmacogenomics* **16**, 939–948 (2015).
27. Lee, Y.J. *et al.* Effects of CYP2C9*1/*3 genotype on the pharmacokinetics of flurbiprofen in Korean subjects. *Arch. Pharm. Res.* **38**, 1232–1237 (2015).
28. 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**, 476–480 (2011).
29. 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**, 749–753 (2005).
30. 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**, 119–127 (2004).
31. 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**, 473–480 (2003).
32. 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. *Eur. J. Clin. Pharmacol.* **58**, 791–794 (2003).
33. Rodrigues, A.D. Impact of CYP2C9 genotype on pharmacokinetics: are all cyclooxygenase inhibitors the same? *Drug Metab. Dispos.* **33**, 1567–1575 (2005).
34. Lee, H.I. *et al.* Strongly increased exposure of meloxicam in CYP2C9*3/*3 individuals. *Pharmacogenet. Genomics* **24**, 113–117 (2014).
35. 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**, 309–310 (2005).
36. Beinema, M.J., de Jong, P.H., Salden, H.J., van Wijnen, M., van der Meer, J. & Brouwers, J.R. The influence of NSAIDs on coumarin sensitivity in patients with CYP2C9 polymorphism after total hip replacement surgery. *Mol. Diagn. Ther.* **11**, 123–128 (2007).
37. Malhi, H., Atac, B., Daly, A.K. & Gupta, S. Warfarin and celecoxib interaction in the setting of cytochrome P450 (CYP2C9) polymorphism with bleeding complication. *Postgrad. Med. J.* **80**, 107–109 (2004).
38. van Dijk, K.N. *et al.* Potential interaction between acenocoumarol and diclofenac, naproxen and ibuprofen and role of CYP2C9 genotype. *Thromb. Haemost.* **91**, 95–101 (2004).
39. Visser, L.E. *et al.* Allelic variants of cytochrome P450 2C9 modify the interaction between nonsteroidal anti-inflammatory drugs and coumarin anticoagulants. *Clin. Pharmacol. Ther.* **77**, 479–485 (2005).
40. 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**, 161–162 (2003).