Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6*, *OPRM1*, and *COMT* genotype and select opioid therapy

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Word counts:

Text: 3504

References: 54

Figures: 0

Tables: 4

Keywords: CYP2D6, codeine, pharmacogenetics, pharmacogenomics, opioids, hydrocodone, oxycodone, tramadol, genetic testing, OPRM1, COMT

Conflicts of Interest: H.M.D. is a paid consultant for Admera Health and Veritas Genetics. A.A.M. owns stock in Illumina. G.R. received fees for role as medical director for Genomas, Inc. T.C. S is a paid consultant by Indiana University Health and has received travel funding by Tabula Rasa Healthcare.

Funding: This work was funded by the National Institutes of Health (NIH) for CPIC (K.E.C., T.E.K. U24HG010135) and PharmGKB (R.H., T.E.K., K.S., U24HG010615). Additional NIH support includes R24 GM123930 (A.G.), U01 HG007269 (L.H.C.), UL1 TR001427 (L.H.C.), U01 HG010245 (T.C.S.), R01 DA042985 (E.D.K.), U01 HG8666 (C.A.P), R35 GM124939 (A.A.M.), and UL1 TR001082 (A.A.M.). Additional grant funding includes National Health and Medical Research Council of Australia project grant 1011251 (A.A.S.) and the Indiana University Grand Challenge Precision Health Initiative (T.C.S.). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Abstract (word count 250)

Opioids are mainly used to treat both acute and chronic pain. Several opioids are metabolized to some extent by CYP2D6 (codeine, tramadol, hydrocodone, oxycodone and methadone). Polymorphisms in *CYP2D6* have been studied for an association with the clinical effect and safety of these drugs. Other genes which have been studied for their association with opioid clinical effect or adverse events include *OPRM1* (mu receptor) and *COMT* (catechol-O-methyltransferase). This guideline updates and expands the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and codeine therapy and includes a summation of the evidence describing the impact of *CYP2D6*, *OPRM1* and *COMT* on opioid analgesia and adverse events. We provide therapeutic recommendations for the use of *CYP2D6* genotype results for prescribing codeine and tramadol and describe the limited and/or weak data for *CYP2D6* and hydrocodone, oxycodone and methadone and for *OPRM1* and *COMT* for clinical use.

INTRODUCTION

This document updates and expands the 2014 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6* genotype and codeine therapy (1). This document also contains new evidence reviews for other opioids and the *OPRM1* and *COMT* genes. We summarize literature supporting how *CYP2D6* genotype test results should be used to optimize therapy for codeine and tramadol and discuss the limited data for *CYP2D6* and hydrocodone, oxycodone and methadone and for *OPRM1* and *COMT* for clinical use. The primary outcome used to assess the effect of genetic polymorphisms on the drugs in this guideline was pain relief (analgesia), or occasionally adverse events. Genetic influences on drug metabolism, and drug-drug interaction effects on drug metabolism or analgesia, can provide mechanistic support for observed genetic effects on clinical outcomes, but do not alone serve as an evidence-base for the recommendations in this guideline. Although we recognize that opioids can be used for other indications, this guideline is focused only on pain control.

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *CYP2D6, OPRM1* and *COMT* genotypes and opioid use (alfentanil, alvimopan, buprenorphine, butorphanol, carfentanil, codeine, dezocine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, methylnaltrexone, morphine, nalbuphine, nalmefene, naloxone, naltrexone, opioids, oxycodone, oxymorphone, pentazocine, remifentanil, sufentanil, tapentadol, tilidine, tramadol) was conducted (see **Supplement** for more details). Evidence is summarized in **Tables S1 to S4**.

GENES: *CYP2D6, OPRM1,* AND *COMT*

Background

CYP2D6. *CYP2D6* is a highly polymorphic gene. Over 130 core alleles have been identified and named (www.PharmVar.org; ***CYP2D6* Allele Definition Table** (2, 3)). *CYP2D6* alleles have been extensively studied in multiple geographically-, ancestry-, and ethnically-diverse groups, and significant differences in allele frequencies have been observed (***CYP2D6* Allele Frequency Table** (2, 3)). The most commonly reported alleles are categorized into functional groups as follows: normal function (e.g., *CYP2D6*1*, **2* and **35*), decreased function (e.g., *CYP2D6*9*, **10*, **17, *29* and **41*), and no function (e.g., *CYP2D6*3-*6*) (4, 5). The *CYP2D6* locus and thus, allele function, are also influenced by deletions and gene duplications or multiplications. The *CYP2D6*5* allele represents a deletion of the gene from one allele, resulting in a no function allele. Gene duplications and multiplications are denoted by "xN" (e.g., *CYP2D6*1xN* with xN representing the number of *CYP2D6* gene copies in cis).

The combination of *CYP2D6* alleles is used to determine a patient's diplotype. Each allele is assigned an activity value ranging from 0 to 1 (e.g., 0 for no function, 0.25 or 0.5 for decreased function, and 1 for normal function) (4, 5) (***CYP2D6* Allele Functionality Table**). If an allele contains multiple copies of a functional gene, the value is multiplied by the number of copies present. Thus, the *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0 to 3 but may exceed 3 in rare cases (4, 5). The CYP2D6 activity score can be translated into a standardized phenotype classification system (see **Table 1** and the ***CYP2D6* Diplotype to Phenotype Table** (2, 3)).

Relevant for this guideline is a recent CPIC-conducted modified-Delphi project to obtain consensus among a panel of international CYP2D6 experts for a uniform system for translating *CYP2D6* genotype/diplotype to phenotype (5). Modifications to CPIC's prior system include downgrading the activity value assigned to the *CYP2D6*10* allele from 0.5 to 0.25 and changing the phenotype assignment for an activity score of 1 from normal metabolizer to intermediate metabolizer. Reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes. Therefore, it is advisable to note a patient's *CYP2D6* diplotype and to calculate the activity score before making therapeutic decisions. See the ***CYP2D6*** **Diplotype to Phenotype Table** for a comprehensive translation of diplotype to phenotype (2, 3).

OPRM1. Opioid receptors are widely distributed in the central nervous system and in peripheral tissues. Three receptors of the class A G-protein coupled receptors are largely responsible for the opioid mechanisms of analgesia and adverse event profiles: the mu, kappa and delta receptors. The gene coding for the mu opioid receptor mu1, *OPRM1*, is highly polymorphic, with more than 200 known variant alleles. The most widely studied variant, rs1799971 (A118G) has been studied for its role in opioid response and alcohol and opioid use disorders (**Table S2**; (6)). The rs1799971 variant, which eliminates the N-glycosylation site, is associated with reduced expression *in vitro* and *in vivo*, although the mechanism of reduced receptor expression is unclear (7, 8).

COMT. Catechol-O-methyltransferase (COMT) is the enzyme responsible for the methyl conjugation of the catecholamines adrenaline, noradrenaline, and dopamine. COMT is a key regulator of catecholamine concentrations in the pain perception pathway and, as such, is a

regulator of pain perception and has been evaluated for its influence on opioid response. The most widely studied variant, rs4680 (p.Val158Met), produces an enzyme with 3-to-4-fold lower activity for methylation of dopamine versus the wild-type allele. For further information on *COMT*, see this reference (9).

Genetic Test Interpretation

CYP2D6. Clinical laboratories rarely sequence the *CYP2D6* gene or interrogate every known variant position. Instead, they typically test for variants that are used to determine common allele haplotypes using the star-allele (*) nomenclature system. Also, many laboratories test whether a gene duplication is present, but may not determine which allele is duplicated (e.g. discriminate *CYP2D6*2xN/*4* and **2/*4xN*) or quantitatively determine gene copy number (i.e. report xN indicating that the copy number is unknown or default to 'duplication'). Likewise, hybrid genes and other complex structural variants (see the PharmVar Structural Variation document at https://www.pharmvar.org/gene/CYP2D6 and (10) for details) may also not be detected by a test. Allele definitions are maintained by the Pharmacogene Variation Consortium (www.PharmVar.org). The ***CYP2D6* Allele Definition Table** and ***CYP2D6* Allele Functionality Table** found on the CPIC and PharmGKB websites contain a list of *CYP2D6* alleles (2, 3), the specific combination of variants that can be used to determine each allele, their functional status, and frequency across major ethnic populations as reported in the literature.

Genetic test results are reported as diplotypes, or the combination of the maternal and paternal alleles (e.g. *CYP2D6*1/*2*). Phenotypes are assigned based on the reported *CYP2D6* diplotype, as summarized in **Table 1** and in the ***CYP2D6* Allele Definition Table (2, 3)**. Also, *CYP2D6* is a gene that is subject to duplications and deletions in the germline, and thus any genetic test should

clearly indicate how copy number variants have been assessed and whether function can be assigned. The limitations of genetic testing as described here include: 1) rare and *de novo* impaired variants are not detected by most assays and thus, the samples may be reported as a functional default **1* allele; and 2) copy number assays do not normally discern which alleles have multiple copies. **Supplemental Data** (Genetic Test Interpretation Section) contains additional information regarding *CYP2D6* genetic test interpretation and phenotype assignment.

***OPRM1* and *COMT*.** Although clinical testing of *OPRM1* and *COMT* does exist, most platforms test only for *OPRM1* rs1799971 and *COMT* rs4680 and will therefore only reveal whether a patient is homozygous wild-type, heterozygous, or homozygous variant for those particular single nucleotide polymorphisms. To date, no standardized genotype to phenotype groupings have been proposed for *OPRM1* or *COMT*.

Available Genetic Test Options

See **Supplementary Material** and www.ncbi.nlm.nih.gov/gtr/ for more information on commercially available clinical testing options.

Incidental findings

Currently, there are no diseases or conditions which have been consistently linked to variation in the *CYP2D6, OPRM1,* or *COMT* genes independent of drug metabolism or drug response.

Other considerations

CYP2D6 is the primary enzyme responsible for the metabolism of many other commonly used medications. It is important to note that CPIC guidelines exist for other drugs metabolized by CYP2D6 (https://cpicpgx.org/guidelines/).

Modification of the predicted phenotype by drug-drug interactions. CYP2D6 metabolizer phenotype may be altered in a patient who is taking drugs that inhibit CYP2D6 activity (11, 12). A list of CYP2D6 inhibitors can be found at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. For this purpose, drugs are classified as strong, moderate, or weak inhibitors based on the U.S. Food and Drug Administration (FDA) guidance on drug interaction studies (13) (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit). For patients on strong CYP2D6 inhibitors, the CYP2D6 activity score is adjusted to 0 and the predicted phenotype is a poor metabolizer. For patients who are on moderate CYP2D6 inhibitors, the activity score is multiplied by 0.5 and then converted to the predicted phenotype (14, 15). There does not appear to be any clinically relevant induction of CYP2D6 activity by any medications; however, there are limited data showing that CYP2D6 enzyme activity increases during pregnancy (see **Supplement** for further discussion).

DRUG: OPIOIDS

Background

Opioids are mainly used to control acute and chronic pain. The analgesic effects and adverse event profiles of these agents exhibit large inter-individual variability. Excluding morphine, tapentadol and levorphanol, which are largely glucuronidated, multiple CYP pathways, predominantly CYP3A, CYP2B6, and CYP2D6, metabolize opioid agonists (**Figures S1-S4**). CYP3A is a major inactivating enzyme for some, such as N-dealkylation of synthetic phenylpiperidines (e.g. fentanyl, alfentanil) and semi-synthetic morphinan (e.g. hydrocodone, oxycodone) opioids. The opioids codeine and tramadol are O-demethylated by CYP2D6 to the more active metabolites morphine and O-desmethyltramadol, respectively (16, 17) (**Figures 1**

and 2). CYP2D6 converts hydrocodone and oxycodone into the active metabolites hydromorphone and oxymorphone, respectively, but both hydrocodone and oxycodone have clinical opioid activity (**Figures S3 and S4**). The main biotransformation of methadone is N-demethylation and this is predominantly by CYP2B6 (18). Active metabolites can mediate none, little or as much as all of the pharmacologic effect of an administered opioid, depending on metabolite concentration, and relative efficacy and potency compared to that of the parent drug. Other genes which have been studied for their association with opioid clinical effect or adverse events include *OPRM1* and *COMT*. For more drug background for codeine, tramadol, hydrocodone and oxycodone see **Supplement**.

Linking Genetic Variability to Variability in Drug-Related Phenotypes

CYP2D6

There is substantial evidence linking *CYP2D6* genotype to variability in codeine and tramadol clinical effect and toxicity (**Table S1**). Although **Table S1** contains summaries for all opioids, the recommendations for CYP2D6 focus on only drugs metabolized by CYP2D6 (i.e. codeine, tramadol, hydrocodone, oxycodone, and methadone).

Codeine. The association of CYP2D6 metabolizer phenotype with the formation of morphine from codeine is well defined. Pharmacokinetic studies in healthy individuals receiving codeine show that poor metabolizers had a 96% lower mean serum morphine AUC and a 95% lower mean morphine Cmax compared to normal and intermediate metabolizers (19). Healthy subjects with the lowest morphine formation from codeine were identified by CYP2D6 genotype- or phenotype-based systems (19, 20). Using a cold pressor test in healthy volunteers, normal and intermediate metabolizers (by phenotyping) experienced analgesia with codeine administration,

while poor metabolizers showed no difference in analgesia with codeine administration compared to placebo (19). A decreased incidence of gastrointestinal side effects (i.e. constipation) was reported in poor versus normal metabolizers (21); whereas a later study by the same group of investigators found that central side effects (e.g., sedation, nausea, dry mouth) did not differ in healthy volunteers with poor versus normal or intermediate metabolizer status receiving codeine (19). Adverse drug reactions are more likely in children prescribed codeine post tonsillectomy if they had at least one normal function *CYP2D6* allele compared to those without any normal function alleles (22). The safety profile of codeine was evaluated by the FDA in 2013 and a Black Box warning was issued about the risk of codeine and codeine-containing products in post-operative pain management in children following tonsillectomy and/or adenoidectomy. The warning did not reference extremes of CYP2D6 function but recommendations hereby provided do (Table 2). Patients with severe sickle cell disease who failed codeine therapy for a pain crisis while taking hydroxyurea were found to be more likely to have a reduced function allele and an activity score of <1.5 as compared to those with mild disease (23).

In contrast to CYP2D6 poor metabolizers, pharmacokinetic studies show increased conversion of codeine to morphine in CYP2D6 ultrarapid versus normal metabolizers, which can result in toxic systemic concentrations of morphine even at low codeine doses. In healthy volunteers receiving codeine, ultrarapid metabolizers had a 45% higher median plasma morphine AUC and approximately 50% higher plasma concentrations of morphine and its glucuronides compared with normal metabolizers (24, 25). However, it should be noted that there is a large degree of variability within the patients genotyped as normal metabolizers (24), and it is possible that some

subjects may develop symptoms similar to patients genotyped as ultrarapid metabolizers (26). The genomic and/or environmental mechanisms causing considerable variation among individuals with the same diplotype are unknown. Case reports detail the occurrence of severe or life-threatening adverse events following standard doses of codeine in ultrarapid metabolizers (see **Table S1**).

Tramadol. CYP2D6 poor metabolizers have much lower median plasma concentrations of the tramadol active metabolite, (+)-O-desmethyltramadol, versus normal metabolizers. In patients receiving tramadol for postoperative analgesia, median plasma (+)-*O*-desmethyltramadol AUC was 0 (range 0-11) ng x h/ml in poor metabolizers compared to 67 (range 17-118) ng x h/ml in normal metabolizers (16). In addition, several prospective clinical trials have shown that, compared to CYP2D6 normal metabolizers, poor metabolizers more often fail to exhibit analgesia in response to tramadol (16, 27, 28). Pharmacokinetic studies in ultrarapid metabolizers showed higher peak plasma concentrations of (+)-*O*-desmethyltramadol after a dose of tramadol. In healthy volunteers receiving a single dose of tramadol, ultrarapid metabolizers had a 7% higher median (+)-*O*-desmethyltramadol AUC versus normal metabolizers, and also greater analgesia, increased miosis, and higher incidence of nausea versus normal metabolizers (29). Based on this evidence, tramadol has reduced clinical opioid efficacy in CYP2D6 poor metabolizers. Cases have been reported describing severe or life-threatening side effects following standard doses of tramadol in ultrarapid metabolizers (30, 31).

Hydrocodone. In CYP2D6 normal metabolizers, approximately 5% of a hydrocodone dose is O-demethylated by CYP2D6 to the minor metabolite hydromorphone (32), which has a 100-fold

higher affinity for μ-opioid receptors compared to the parent drug (33). The relationship between plasma hydromorphone or hydrocodone concentration and analgesia is unclear (34, 35). There is minimal evidence for altered pharmacokinetics and/or clinical effects of hydrocodone in CYP2D6 ultrarapid metabolizers (see **Table S1**). The evidence for the pharmacokinetic effects of CYP2D6 on hydrocodone in poor metabolizers is more established (**Table S1**). In healthy individuals receiving hydrocodone, the mean plasma hydromorphone Cmax was five-fold lower in CYP2D6 poor metabolizers compared to normal metabolizers (36); however, there are insufficient data on whether this translates into decreased analgesia or adverse events in poor metabolizers (see **Table S1**) (36, 37).

Oxycodone. In CYP2D6 normal metabolizers, approximately 11% of an oxycodone dose is O-demethylated by CYP2D6 to the minor metabolite oxymorphone, which has a 60-fold higher affinity for μ-opioid receptors compared to the parent drug (33). Although oxymorphone has a much higher μ-receptor affinity than the parent drug, data suggest the parent drug, oxycodone, may be the main contributor to pain relief (38).

CYP2D6 poor metabolizers generate lower peak concentrations of oxymorphone after a dose of oxycodone versus normal metabolizers. In patients receiving oxycodone for postoperative analgesia, no differences in oxycodone consumption were reported despite the median plasma oxymorphone Cmax was 67% lower in poor metabolizers compared to normal metabolizers (29). In cancer patients receiving oxycodone, serum concentrations of oxymorphone were not statistically significantly different between CYP2D6 ultrarapid metabolizers and normal metabolizers (39, 40). There are conflicting data on the association of CYP2D6 metabolizer

phenotype with the analgesic effect and toxicity of oxycodone in prospective clinical studies. Differential analgesic response to experimental pain was observed between normal metabolizers and poor metabolizers, as well as between ultrarapid metabolizers and normal and poor metabolizers in two studies in healthy volunteers (41, 42). However, clinical studies in postoperative patients and in cancer patients failed to demonstrate a significant difference in analgesia or adverse events to oxycodone by CYP2D6 phenotype (39, 40). Physiologic alterations (e.g., miosis) after dosing with oxycodone correlate better with exposure to the parent compound than with metabolites (17). Due to these conflicting data and small sample sizes particularly for ultrarapid metabolizers, it is difficult to conclude whether CYP2D6 metabolizer phenotype affects oxycodone analgesia or risk of toxicity (**Table S1**).

Methadone. Although methadone is metabolized to a minor extent by CYP2D6 to an inactive metabolite, CYP2D6 genotype does not appear to affect methadone adverse events, opioid dose requirements or analgesia (**Table S1**).

OPRM1 and COMT

Evidence review was also conducted for *OPRM1* and *COMT* genotypes and opioid use (**Table S2-S4**). *OPRM1* variants inconsistently have been shown to alter post-operative dose requirements for some opioids (**Table S2**). There is evidence for a small increase in post-operative morphine dose requirements (approximately 10%) in some clinical studies in patients carrying at least one copy of the *OPRM1* rs1799971 G allele, though the alteration in morphine dose is so modest as to not be clinically actionable (**Table S2**). There is also insufficient evidence at this time to conclude altered analgesic response to other opioids in relation to rs1799971, or other *OPRM1* variants.

For the most highly studied *COMT* variant, rs4680, there is no evidence to support an association of this variant with opioid adverse events, and there is mixed evidence for an association between *COMT* rs4680 genotype and analgesia or opioid dose requirements. For all other *COMT* variants, there is mixed evidence for an association between *COMT* genotype and analgesia, opioid dose requirements or adverse events (**Table S3**).

Therapeutic Recommendation

CYP2D6

Codeine and Tramadol. **Tables 2 and 3** summarize the therapeutic recommendations for codeine and tramadol based on CYP2D6 phenotype, respectively. For CYP2D6 normal metabolizers (i.e. CYP2D6 activity score 1.25 to 2.25), a label recommended age- or weight-specific starting dose of codeine or tramadol, as recommended in the product label, is warranted. A label recommended starting dosing is also recommended for intermediate metabolizers (i.e. activity score of 0.25 to 1); these patients should be monitored closely for less than optimal response and should be offered an alternative analgesic if warranted. For CYP2D6 poor metabolizers (i.e. activity score of 0), current evidence supports the avoidance of codeine and tramadol and the use of an alternative analgesics due to the likelihood of suboptimal or lack of effect. There is insufficient evidence in the literature to recommend a higher dose of codeine or tramadol in poor metabolizers, especially considering the evidence that some adverse events do not differ between poor and normal metabolizers (19). For CYP2D6 ultrarapid metabolizers (i.e. activity score of >2.25), codeine or tramadol should not be used, in order to avoid the risk of severe toxicity with label-recommended dosing. Non-opioid analgesics and if needed, other opioids that are not affected by CYP2D6 phenotype, are potential alternatives for use in

CYP2D6 poor and ultrarapid metabolizers based on the type, severity and chronicity of the pain being treated.

Hydrocodone. **Table 4** summarizes the CPIC recommendations for hydrocodone based on CYP2D6 phenotype. For CYP2D6 ultrarapid metabolizers, there is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time (no recommendation, CPIC level C). For CYP2D6 intermediate and poor metabolizers, there is some evidence to support decreased metabolism of hydrocodone to the more active metabolite hydromorphone, but there is insufficient evidence to determine if these effects on pharmacokinetics translate into decreased analgesia or adverse events. Because of this, the use of hydrocodone label recommended age- or weight-specific dosing is recommended. However, if there is no response to hydrocodone in a CYP2D6 intermediate or poor metabolizer, the use of an alternative analgesic (non-opioid or opioid not affected by CYP2D6 phenotype) should be considered (optional recommendation, CPIC level B). It is not known if increasing the dose of hydrocodone would affect analgesia response in intermediate or poor metabolizers.

Oxycodone and Methadone. There is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone or methadone based on *CYP2D6* genotype (**Tables S5 and S6**, no recommendation, CPIC level C).

OPRM1 and COMT

There are no therapeutic recommendations for dosing opioids based on either *OPRM1* or *COMT* genotype (**Tables S7- S10**, no recommendation, CPIC level C). Authors of this guideline

reviewed evidence for the following opioids (**Tables S2 and S3**): morphine, fentanyl, alfentanil, buprenorphine, codeine, hydrocodone, hydromorphone, levomethadone, methadone, naltrexone, oxycodone, remifentanil, sufentanil, and tramadol.

Other Considerations

Pediatrics

Several regulatory agencies worldwide advise against the use of codeine and tramadol in children younger than 12 years of age, and in children younger than 18 years of age after tonsillectomy and/or adenoidectomy (43-46). Due to these guidances, use of these drugs in children has decreased significantly in the US and some other countries, but continues in some clinical settings. Some advocate for careful genotype-guided use of codeine in specific pediatric patient populations (47-50).

Breastfed infants

The US FDA label includes a warning to mothers that breastfeeding is not recommended when taking codeine or tramadol (43, 44). Although evidence was cited for risk of excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in infant death due to maternal intake of codeine, the warning for tramadol was extrapolated from presence of tramadol and its active metabolite in breast milk and the evidence for adverse events in adults who are CYP2D6 ultrarapid metabolizers. Codeine and its metabolites, including morphine, are secreted into human breast milk. The amount is typically low and dose-dependent, but breastfeeding women with a CYP2D6 ultrarapid metabolizer phenotype may achieve high serum concentrations of morphine on standard codeine therapy (51). This may lead to high levels of

morphine in breast milk and dangerously high morphine exposure in their breastfed infants (52). A fatal opioid poisoning in a breastfed neonate from an ultrarapid metabolizer mother receiving codeine has been described (53); however a more recent review of this case calls into question the plausibility of neonatal opioid toxicity from breastfeeding (54). Our evidence review did not identify any published cases or studies related to adverse events due to infant exposure to tramadol in breast milk. The American College of Obstetrics and Gynecology provides clinical guidance for postpartum pain management as untreated or inadequately treated pain in lactating women also has adverse consequences for the postpartum mother and her breastfed infant (55).

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of *CYP2D6* genotype testing is that patients with genotypes that confer a higher risk of ineffective analgesia or of an adverse event may be identified and an alternative analgesic may be administered. *CYP2D6* genotyping is reliable when performed in qualified laboratories. However, as with any laboratory test, a possible risk to the patient is an error in genotyping that could have long-term adverse health implications for the patient.

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

Like all diagnostic tests, *CYP2D6* genotype is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient. Furthermore, there are several other factors that cause potential uncertainty in the genotyping results and phenotype predictions. These are discussed in detail in the **Supplementary Data** online.

Disclaimer

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Acknowledgements

We acknowledge the critical input of Dr. M. Relling, and members of the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the Pharmacogenomics Research Network (PGRN), funded by the National Institutes of Health (NIH). CPIC members are listed here: https://cpicpgx.org/members.

TABLE 1. ASSIGNMENT OF PREDICTED CYP2D6 PHENOTYPES BASED ON DIPLOTYPES

Phenotype[a]	**Activity score range**	**Activity score/genotypes[b]**	**Examples of *CYP2D6* diplotypes[b]**
CYP2D6 ultrarapid metabolizer	> 2.25	>2.25	**1/*1xN, *1/*2xN, *2/*2xN[c]*
CYP2D6 normal metabolizer	1.25≤x≤2.25	1.25 1.5 1.75 2.0 2.25	**1/*10* **1/*41, *1/*9* **10/*41x3* **1/*1, *1/*2* **2x2/*10*
CYP2D6 intermediate metabolizer	0<x<1.25	0.25 0.5 0.75	**4/*10* **4/*41, *10/*10* **10/*41*

		1	**41/*41, *1/*5*
CYP2D6 poor metabolizer	0	0	**3/*4, *4/*4, *5/*5, *5/*6*
CYP2D6 indeterminate	n/a	An individual carrying one or two uncertain function alleles	**1/*22, *1/*25, *22/*25*

[a]See the ***CYP2D6* Frequency Table** for race-specific allele and phenotype frequencies (2, 3).

[b]Assignment of allele function and allele activity values including citations for allele function can be found https://www.pharmgkb.org/page/cyp2d6RefMaterials (***CYP2D6* Allele Definition Table** and ***CYP2D6* Allele Functionality Table** (2, 3)). For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the ***CYP2D6* Genotype to Phenotype Table** (2, 3).

[c]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotypes into phenotypes.

TABLE 2. CODEINE THERAPY RECOMMENDATIONS BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	Implications	Recommendations	Classification of recommendation[a]
CYP2D6 ultrarapid metabolizer	> 2.25	Increased formation of morphine leading to higher risk of toxicity	Avoid codeine use because of potential for serious toxicity. If opioid use is warranted, consider a non-tramadol opioid.	Strong
CYP2D6 normal metabolizer	1.25≤x≤2.25	Expected morphine formation	Use codeine label recommended age- or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Reduced morphine formation	Use codeine label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider a non-tramadol opioid.	Moderate
CYP2D6 poor metabolizer	0	Greatly reduced morphine formation	Avoid codeine use because of possibility of diminished analgesia. If	Strong

		leading to diminished analgesia.	opioid use is warranted, consider a non-tramadol opioid.	
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

[a]Rating scheme described in the **Supplement**.

TABLE 3. TRAMADOL THERAPY RECOMMENDATIONS BASED ON CYP2D6 PHENOTYPE

Phenotype	**Activity score**	**Implications**	**Recommendations**	**Classification of recommendation[a]**
CYP2D6 ultrarapid metabolizer	> 2.25	Increased formation of O-desmethyltramadol (active metabolite) leading to higher risk of toxicity	Avoid tramadol use because of potential for toxicity. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 normal metabolizer	1.25≤x≤2.25	Expected O-desmethyltramadol (active metabolite) formation	Use tramadol label recommended age- or weight-specific dosing.	Strong

CYP2D6 intermediate metabolizer	0<x<1.25	Reduced O-desmethyltramadol (active metabolite) formation	Use tramadol label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine opioid.	Optional
CYP2D6 poor metabolizer	0	Greatly reduced O-desmethyltramadol (active metabolite) formation leading to diminished analgesia.	Avoid tramadol use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-codeine opioid.	Strong
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

[a]Rating scheme described in the **Supplement**.

TABLE 4. HYDROCODONE THERAPY RECOMMENDATIONS BASED ON CYP2D6 PHENOTYPE

Phenotype	**Activity score**	**Implications**	**Recommendations**	**Classification of recommendation[a]**
CYP2D6 ultrarapid metabolizer	> 2.25	Minimal evidence for pharmacokinetic or clinical effect.	No recommendation for hydrocodone therapy because of minimal evidence regarding adverse events or analgesia.	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Normal hydromorphone formation	Use hydrocodone label recommended age- or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	Minimal evidence for pharmacokinetic or clinical effect.	Use hydrocodone label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine or non-tramadol opioid.	Optional

CYP2D6 poor metabolizer	0	Decreased metabolism of hydrocodone to active metabolite, hydromorphone, but there is insufficient evidence to determine if these effects on pharmacokinetics translate into decreased analgesia or side effects.	Use hydrocodone label recommended age- or weight-specific dosing. If no response and opioid use is warranted, consider non-codeine and non-tramadol opioid.	Optional
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

[a]Rating scheme described in the **Supplement**.

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