


















Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2B6* Genotype and Methadone Therapy

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Methadone is a mu (μ) opioid receptor agonist used clinically in adults and children to manage opioid use disorder, neonatal abstinence syndrome, and acute and chronic pain. It is typically marketed as a racemic mixture of *R*- and *S*-enantiomers. *R*-methadone has 30-to 50-fold higher analgesic potency than *S*-methadone, and *S*-methadone has a greater adverse effect (prolongation) on the cardiac QTc interval. Methadone undergoes stereoselective metabolism. *CYP2B6* is the primary enzyme responsible for catalyzing the metabolism of both enantiomers to the inactive metabolites, *S*- and *R*-2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (*S*- and *R*-EDDP). Genetic variation in the *CYP2B6* gene has been investigated in the context of implications for methadone pharmacokinetics, dose, and clinical outcomes. Most *CYP2B6* variants result in diminished or loss of *CYP2B6* enzyme activity, which can lead to higher plasma methadone concentrations (affecting *S*- more than *R*-methadone). However, the data do not consistently indicate that *CYP2B6*-based metabolic variability has a clinically significant effect on methadone dose, efficacy, or QTc prolongation. Expert analysis of the published literature does not support a change from standard methadone prescribing based on *CYP2B6* genotype (updates at www.cpicpgx.org).

Methadone is a synthetic mu (μ) opioid receptor agonist indicated for the treatment of opioid use disorder, opioid withdrawal, and pain. Methadone has a long elimination half-life of ~1–3 days and undergoes extensive and stereospecific biotransformation to a primary and inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), catalyzed predominantly by cytochrome P450 2B6 (*CYP2B6*). The *CYP2B6* gene is highly polymorphic, with variants resulting in differing enzymatic activity, which can influence methadone metabolism and clearance. The purpose of this guideline is to provide clinicians with information that facilitates the interpretation of clinical *CYP2B6* genotyping test results and describe the evidence exploring the impact of *CYP2B6* genetic variation on methadone pharmacokinetics, dose, and clinical outcomes. Detailed guidelines for the use of methadone 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 was undertaken to evaluate a possible link between *CYP2B6* genotypes and methadone metabolism, exposure, clinical effects, and adverse effects (see **Supplement, Literature Review**). The evidence is summarized in **Table S1**.

GENE: *CYP2B6*

Background

The *CYP2B6* gene is highly polymorphic, with 49 star (*) allele haplotypes defined to date by the Pharmacogene Variation (PharmVar) Consortium (<https://www.pharmvar.org/gene/CYP2B6>; see ***CYP2B6* Allele Definition Table** online^{1–3}).

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Received March 15, 2024; accepted May 22, 2024. doi:10.1002/cpt.3338

The frequencies of these star (*) alleles differ across ancestrally diverse populations (see **CYP2B6 Allele Frequency Table** online^{1,2}). Alleles are categorized into functional groups as follows: normal function (e.g., *CYP2B6*1*), decreased function (e.g., *CYP2B6*6* and **9*), no function (e.g., *CYP2B6*18*), and increased function (e.g., *CYP2B6*4*). For some alleles, the function is uncertain (e.g., *CYP2B6*3*). Clinical allele function, as described in the **CYP2B6 Allele Functionality Table**, was determined based on reported *in vitro* and/or *in vivo* data when available.^{1,2} *CYP2B6*6* (c.516G>T, p.Q172H, splice defect, rs3745274 and c.785A>G, p.K262R, rs2279343) is the most frequent decreased function allele (15%–60% minor allele frequency depending on ancestry) and is the most extensively studied allele. Reduced protein expression due to aberrant splicing caused by the c.516G>T single-nucleotide variant (SNV) contributes to the reduced function of *CYP2B6*6* and other haplotypes containing this SNV.⁴ Thus, several studies genotype this SNV as a marker for reduced CYP2B6 activity. More broadly, however, *in vitro* and some *in vivo* studies suggest complex substrate-dependent catalytic effects for some *CYP2B6* variants (reviewed in⁵). Therefore, it is somewhat challenging to assign a uniform function to some *CYP2B6* alleles, as function may be substrate-specific.

Genetic test interpretation

The combination of inherited alleles determines a person's diplotype (also referred to as genotype). **Table 1** defines each predicted phenotype based on allele function combinations and provides example diplotypes. The phenotype categories for CYP2B6 include ultrarapid metabolizer (UM), rapid metabolizer (RM), normal metabolizer (NM), intermediate metabolizer (IM), and poor metabolizer (PM). The clinical significance of the CYP2B6 UM and RM categories remains to be established; these categories were created with the publication of the CPIC guideline for *CYP2B6*/

efavirenz to allow for the possibility of their utility for other CYP2B6 substrates.⁶ See the **CYP2B6 Diplotype-Phenotype Table** online for a complete list of possible diplotypes and phenotype assignments.^{1,2}

The assignment of *CYP2B6* genotypes can be complex. Many clinical laboratories report *CYP2B6* genotype results using star (*) allele nomenclature. The star (*) allele nomenclature for *CYP2B6* is found on the PharmVar website (<https://www.pharmvar.org/gene/CYP2B6>). Some laboratories test and report only on specific SNVs that have been most extensively studied, such as c.516G>T (rs3745274, p.Q172H/splice defect) and c.983T>C (rs28399499, p.I328T). These variants alone are the single-defining SNVs for *CYP2B6*9* and **18*, respectively. Of note, c.516G>T is found in combination with other variants in 16 other *CYP2B6* alleles (*6, *7, *13, *19, *20, *26, *29, *34, *36, *37, *38, *39, *40, *41, *42, *43). In cases where only c.516G>T is tested, it is not possible to distinguish between the various (*) alleles which contain this SNV alone or together with other variants. However, because c.516G>T not only causes an amino acid change but also aberrant splicing which decreases protein expression; it is considered a canonical decreased function allele and thus all alleles that carry c.516G>T are considered to be decreased or no-function alleles, depending on the presence of other variants. Of note, the *CYP2B6*6* allele consists of c.516G>T (*9) and c.785A>G (*4). However, at least 14 other alleles consist of c.516G>T (*9), c.785A>G (*4), and at least one additional variant (e.g., *CYP2B6*7*). If c.516G>T is detected, *CYP2B6*6* should only be assigned if the presence of c.785A>G is confirmed and the presence of the other variants found in the other alleles (e.g., c.1459C>T in the case of *CYP2B6*7*) are excluded (see **Figure S1**). Similarly, if c.785A>G is detected, *CYP2B6*6* should only be assigned if the presence of c.516G>T is confirmed and the presence of other variants is excluded. Furthermore, the defining core variant of the *CYP2B6*18* allele, c.983T>C, is also considered a canonical no-function allele. Tables on the CPIC website

Table 1 Assignment of predicted CYP2B6 phenotype based on genotype

Predicted phenotype	Genotypes	Examples of CYP2B6 diplotypes ^a
CYP2B6 ultrarapid metabolizer (UM)	An individual carrying two increased function alleles	*4/*4
CYP2B6 rapid metabolizer (RM)	An individual carrying one normal function allele and one increased function allele	*1/*4
CYP2B6 normal metabolizer (NM)	An individual carrying two normal function alleles	*1/*1, *1/*2, *2/*2
CYP2B6 intermediate metabolizer (IM)	An individual carrying one normal function allele and one decreased function allele OR one normal function allele and one no-function allele OR one increased function allele and one decreased function allele OR one increased function allele and one no-function allele ^b	*1/*6, *1/*18
CYP2B6 poor metabolizer (PM)	An individual carrying two decreased function alleles OR two no-function alleles OR one decreased function allele and one no-function allele	*6/*6, *18/*18, *6/*18
CYP2B6 indeterminate	An individual carrying one or two uncertain function alleles	*1/*3, *3/*3

^aPlease refer to the **CYP2B6 Diplotype-Phenotype Table** online for a complete list. For allele function and population-specific allele and phenotype frequencies, please refer to the **CYP2B6 Allele Functionality Table** and the **CYP2B6 Allele Frequency Table** online.^{1,2} ^bThere is a paucity of clinical data for diplotypes containing one increased function allele and one decreased/no-function allele, and the data varies based on substrate. For methadone, there is limited data that suggest that *4/*6 may have increased activity compared with CYP2B6 normal metabolizers.⁴³

contain a list of *CYP2B6* alleles, the combinations of variants that define each allele, CPIC clinical allele function, and reported allele frequencies across major ancestral populations.^{1,2}

The limitations of genetic testing as described here include: (i) alleles not tested for (which may be known or unknown) will not be reported by the genetic testing laboratory, and instead, the allele will be reported as *1 by default; (ii) if only the c.516G>T variant is genotyped, it will not be known if it exists alone or in combination with other variants, and the allele should be reported as *9 by default but, nevertheless, is sometimes reported as *6; (iii) similarly, due to limitations in the testing technology, the diplotype may be ambiguous for patients heterozygous for c.516G>T and c.785A>G (though the predicted phenotype would be IM in both cases); (iv) genotyping tests are not designed to detect unknown or *de novo* variants; and (v) *CYP2B6* structural variation including hybrid genes (rearranged gene structures formed from two separate genes) and duplications have been described, but little is known of their frequencies and clinical relevance.

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 inherited diseases or conditions have been consistently or strongly linked to germline genetic variants in *CYP2B6* independent of drug metabolism and response. *CYP2B6* genotype is clinically relevant for efavirenz dosing.⁶

Other considerations

CYP2B6 is inducible (e.g., by phenobarbital, rifampin, and chronic methadone itself), which can alter the relationship between *CYP2B6* genotype and phenotype.^{7,8}

DRUG: METHADONE

Background

Methadone was first synthesized in the 1930s and approved by the US Food and Drug Administration (FDA) in 1947 for analgesic and antitussive use.⁹ Subsequently, in the mid-1960s, it was shown to be effective in treating opiate addiction and approved for this use by the FDA in 1972. Methadone is currently used for the treatment of opioid use disorder, opioid withdrawal, neonatal abstinence syndrome, and acute and chronic pain. Methadone can be administered orally (approximately 85% bioavailable), rectally, and parenterally (intravenous, intramuscular, subcutaneous, intranasal). Methadone dosing varies based on indication, with lower doses typically used for the treatment of pain and higher doses typically used for the treatment of opioid use disorder.

Methadone pharmacology is complex due to chirality. In the United States, methadone is used as a racemic mixture of *R*- and *S*-methadone, although in other countries (e.g., Germany) *R*-methadone (levomethadone) alone is also used. Methadone is a μ opioid receptor agonist and effects are enantioselective. *R*-methadone exerts the majority of the opioid effects of the racemate because it has 30- to 50-fold higher binding affinity and analgesic

potency than *S*-methadone.^{10,11} *R*-methadone is also predominantly responsible for other μ opioid effects, including respiratory depression.^{10,12} *S*-methadone alone is in clinical trials for the treatment of depression.¹¹

While most other clinically relevant opioids are essentially pure μ agonists, methadone has several non-opioid targets. For example, methadone blocks N-methyl-D-aspartate (NMDA) receptors in laboratory studies.¹³ However, clinical methadone concentrations (often < 1 μ M) are lower than the IC₅₀ or Ki of methadone for the NMDA receptor (3–10 μ M).¹³ Thus, the clinical occurrence or significance of this non-opioid receptor effect remains unknown. Methadone also interacts with norepinephrine and serotonin reuptake transporters at concentrations which more closely resemble those achieved clinically.¹⁴ *R*-methadone appears more potent than *S*-methadone at these non-opioid receptors.¹⁴ Whether this influences methadone-induced analgesia is unknown.

In contrast to analgesia, some studies indicate that *S*-methadone is more potent than *R*-methadone at blocking the cardiac hERG channel, particularly at high (therapeutic or supratherapeutic) concentrations tested *in vitro*.^{15,16} hERG channel inhibition by methadone *in vitro* is concentration-dependent.^{15,16} There is concern that this blockade may lead to prolongation of the electrocardiogram QTc interval and in severe cases, torsade de pointes ventricular arrhythmia or sudden cardiac death.^{15–18} The definition of “long” QT interval is > 450 ms in males and > 460 ms in females,¹⁹ but generally more relevant is a drug effect which increases QTc by \geq 60 ms or QTc > 500 ms.²⁰ Clinically significant QTc prolongation (> 500 ms) and torsade de pointes have occurred, typically at high methadone doses (e.g., median 345 mg/day) and longer use,^{15,17,21–23} but torsade de pointes has occurred at daily doses as low as 30–40 mg.^{17,23} However, the relationship between dose and clinical QTc interval is weak (correlation coefficient, *r*, of ~0.2–0.3^{15,23–25}), the magnitude of methadone effect on QTc is small (i.e., ~10 ms per 100 mg dose^{26,27} and 15–30 ms per 1,000 ng/mL *S*-methadone^{15,24,25}), and the QTc rarely exceeds 500 msec.^{24,25,28} Multiple factors alone or in conjunction with methadone can affect QTc (e.g., genetic long-QTc interval, history of arrhythmia or prolonged QTc, electrolyte abnormalities, and concomitant medications).¹⁸ Clinical practice guidelines for methadone and electrocardiogram (ECG) monitoring are variable. Some recommend universal ECG prescreening^{29,30} and others recommend screening only in patients with significant risk factors^{18,31} and/or in patients receiving greater than 100–120 mg daily,^{18,30,31} and are beyond the scope of this guideline.

Methadone disposition has been studied for decades, and yet has been habitually misunderstood if not misrepresented, and only recently has a greater clarity been achieved regarding the data and mechanistic determinants of methadone metabolism and pharmacokinetics.^{32,33} Early reports suggested that the elimination half-life was variable (8–59 hours in adults); however, more recent studies clarify the long elimination half-life (~2–3 and ~1–2 days for *R*- and *S*-methadone, respectively).^{34,35} The major route of systemic clearance is hepatic *N*-demethylation to the inactive metabolite 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP). Methadone was initially identified as metabolized *in vitro* mainly by human liver microsomal and

cDNA-expressed CYP3A4, and human *in vivo* clearance was initially attributed predominantly to CYP3A4 based on extrapolated *in vitro* data.^{32,33} Subsequent investigations showed that CYP2B6 also efficiently metabolizes methadone *in vitro* and *in vivo*, and it is now unequivocally established that human *in vivo* methadone metabolism and clearance are mediated predominantly by CYP2B6 and minimally by CYP3A4.^{32,33,36} Recent pharmacokinetic modeling estimated the fraction metabolized via CYP2B6 at 74% and that via CYP3A4 as <5%.³⁷ CYP2B6 metabolizes *S*-methadone about 50% faster than *R*-methadone.³⁸ Methadone clearance appears to undergo autoinduction,^{7,39} attributed to upregulation of hepatic CYP2B6.⁸

Linking genetic variability to variability in drug-related phenotypes

There is limited literature exploring the impact of *CYP2B6* genetic variation on clinical outcomes during methadone treatment, including dose requirements, efficacy, and adverse events. Most studies instead focus on *CYP2B6* genotype effects on the pharmacokinetics of methadone. The clinical implications of changes in methadone disposition are less understood due to the titratability of methadone dose and the weak pharmacokinetic–pharmacodynamic relationship between methadone concentrations and QTc prolongation. More studies have evaluated oral administration rather than intravenous methadone, steady-state rather than single-dose, total rather than unbound concentrations, and patients (with potential confounders) rather than healthy subjects, and have focused predominantly on the impact of *CYP2B6*6* (and *c.516G>T* alone) and on pharmacokinetic data.

CYP2B6 variants and methadone plasma concentrations. The strongest data demonstrate higher plasma *S*-methadone concentrations in those with *CYP2B6* decreased and no-function alleles (**Table S1**). Steady-state trough *S*-methadone plasma concentrations are almost two times higher in *CYP2B6* PMs than in *CYP2B6* NMs.^{15,40,41} Few studies specifically compare *CYP2B6* IMs with NMs and PMs.⁴² Genotype effects on plasma *R*-methadone concentrations are less than for *S*-methadone.^{40,41} In most studies, decreased or no function *CYP2B6* alleles were not associated with significantly greater mean plasma *R*-methadone concentrations^{40,41} (**Table S1**).

CYP2B6 variants and methadone pharmacokinetics. *CYP2B6* decreased or no function alleles were associated with decreased clearance and/or increased area-under-the-curve (AUC) for *S*-methadone (**Table S1**). In one study, both *CYP2B6* PMs and IMs had lower *S*-methadone clearance compared with NMs.⁴³ Specifically, apparent oral clearance of *S*-methadone was 35 and 45% lower in *CYP2B6*1/*6* and *CYP2B6*6/*6* genotypes, and that of *R*-methadone was 25 and 35% lower, compared with *CYP2B6*1/*1* genotypes.⁴³ Only two studies included *CYP2B6* RMs. One study showed increased *R*- and *S*-methadone oral clearance in carriers of *CYP2B6*4* after a single dose.⁴³ The other study showed lower clearance in carriers of *CYP2B6*4*; however, *CYP2B6*4* and *CYP2B6*9* were analyzed separately without accounting for the *CYP2B6*6* haplotype.⁴⁴ There are no

studies with patients homozygous for *CYP2B6*4*. As with plasma methadone concentrations, the influence of *CYP2B6* genotype on methadone clearance is less with *R*- than *S*-methadone clearance (**Table S1**).⁴³ Furthermore, *CYP2B6* decreased function alleles are associated with decreased formation of *S*-EDDP and to a lesser degree *R*-EDDP.⁴³

CYP2B6 variants and methadone dose in opioid use disorder. *CYP2B6* genotype and methadone dose requirements have only been studied in the setting of opioid use disorder and not in the setting of pain (**Table S1**). In 321 Han Chinese patients, *CYP2B6*6* carriers were more likely to be stably maintained on a lower methadone maintenance dose (<55 mg vs >100 mg).⁴⁵ The mean methadone maintenance dose for *CYP2B6 c.516G>T* Israeli homozygotes (96 mg) was significantly lower than for *CYP2B6 c.516G>T* heterozygotes (129 mg) and noncarriers (150 mg),⁴⁶ and in 100 Taiwanese patients (44 mg vs. 52 mg vs. 68 mg, respectively).⁴⁷ However, the majority of studies fail to replicate these findings, with no significant association found between *CYP2B6* genotype and methadone dose in opioid use disorder (**Table S1**).

CYP2B6 variants and methadone treatment response in opioid use disorder. Studies have not found a significant effect of *CYP2B6* genetics on methadone response in the treatment of opioid use disorder (**Table S1**). The outcomes (response) measured are either self-reported cessation of opioids or a negative urine opioid screen. In a study of 208 patients, there was no difference in the allele frequency of *CYP2B6*6* in the responders vs. nonresponders.⁴¹ This was in contrast to lower trough plasma *R*- and *S*-methadone concentrations found in high-dose nonresponders compared with low-dose responders and high-dose responders.⁴¹ Similar results were found in a study of 105 patients with no difference in allele frequencies between responders and nonresponders.⁴⁸

CYP2B6 variants and methadone QTc interval. The main adverse effect studied in the context of *CYP2B6* genotype is QTc prolongation. However, there is only one study directly evaluating *CYP2B6* variants and the QTc interval.¹⁵ In that study of 179 patients, *CYP2B6* PMs had increased plasma *S*-methadone concentrations and had a mean QTc interval on methadone treatment 18 ms greater than other phenotype groups. *CYP2B6* PMs had a higher frequency of a long-QTc interval (i.e., >450 ms for males and >470 ms for females) than other phenotype groups. Although the *CYP2B6* PMs had decreased metabolism of *S*-methadone, the clinical importance of this genetic effect is unknown since no patient developed a QTc >500 ms during the study period, and there were no episodes of torsade de pointes during the study period.¹⁵

Therapeutic recommendations

The current evidence does not support changing standard prescribing for methadone (both acute and chronic dosing) based on *CYP2B6* genotype (**Table 2**). Most methadone-*CYP2B6* genetic evidence is for opioid use disorder. Oral methadone is generally titrated slowly in routine clinical care, and there is no

Table 2 Methadone dosing recommendations based on CYP2B6 phenotype

CYP2B6 phenotype	Implications for phenotypic measures	Therapeutic recommendation ^a	Classification of recommendation
CYP2B6 ultrarapid metabolizer	No data	No recommendation	No recommendation
CYP2B6 rapid metabolizer	Limited evidence for decreased R- and S-methadone plasma concentrations	Standard dosing, titration, and monitoring of methadone	Moderate
CYP2B6 normal metabolizer	Normal metabolism and plasma concentrations of R- and S-methadone	Standard dosing, titration, and monitoring of methadone	Strong
CYP2B6 intermediate metabolizer	Increased S-methadone plasma concentrations; unknown clinical implications No difference in steady-state R-methadone plasma concentrations	Standard dosing, titration, and monitoring of methadone	Moderate
CYP2B6 poor metabolizer	Increased S-methadone plasma concentrations; unknown clinical implications No difference in steady-state R-methadone plasma concentrations	Standard dosing, titration, and monitoring of methadone	Moderate
CYP2B6 indeterminate	n/a	No recommendation	No recommendation

^aClinical guidelines for ECG monitoring in the context of methadone therapy, including risk assessment of other clinical factors, should be followed.

evidence to support an even slower titration in PMs. Only one study directly compared the QTc interval across CYP2B6 metabolizer groups.¹⁵ The results do not support using CYP2B6 genotype to guide dosing. Because the relationship between methadone concentrations and QTc is weak with a low magnitude of effect, the relationship between CYP2B6 genotype and methadone pharmacokinetics cannot be extrapolated to CYP2B6 genotype and risk of QTc prolongation and thus cannot support using CYP2B6 genotype to guide dosing. Clinical guidelines for ECG monitoring in the context of methadone therapy, including risk assessment of other clinical factors, should be followed. None of the pharmacogenetic information in this guideline should be interpreted to influence the use of ECG monitoring guidelines.

Pediatrics. Methadone is also used in the pediatric setting for the treatment of neonatal abstinence syndrome, iatrogenic opioid withdrawal, chronic pain, and perioperative pain. With regard to CYP2B6 ontogeny, CYP2B6 mRNA expression levels reach adult levels by 1 year of age.⁴⁹ The impact of CYP2B6 phenotypes on the pharmacokinetics of methadone is similar in children and adolescents as compared with adults.^{50,51} A population pharmacokinetic model extrapolated adult pharmacokinetic parameters to a pediatric population and predicted increased exposure to methadone in CYP2B6 PMs.⁵² Clinical outcome data associated with CYP2B6 phenotypes in pediatrics are limited to one study in which infants exposed to methadone *in utero* were less likely to require treatment for neonatal abstinence syndrome if they carried a CYP2B6 decreased function allele⁵³ and to one fatal case report of an infant who was a CYP2B6 PM and breastfeeding from a mother receiving methadone.⁵⁴ Therefore, there is not enough data to support changes in prescribing based on CYP2B6 phenotype

in children at this time, which is consistent with our adult recommendations.

Recommendations for incidental findings

Not applicable.

Other considerations

Although methadone is metabolized to a minor extent by CYP2D6, the CPIC guideline for opioids concludes that CYP2D6 genotype does not appear to affect methadone adverse events, dose requirements, or analgesia (CPIC Level C – no recommendation).⁵⁵

Implementation of this guideline. Not applicable.

POTENTIAL BENEFITS AND RISKS FOR PATIENTS

While CYP2B6 genotype is associated with the pharmacokinetics of methadone, specifically S-methadone more than R-methadone, this has not been associated with clinically significant implications for therapeutic or adverse effects. Thus, there is insufficient evidence to change the prescribing practices of methadone based on CYP2B6 genetics. There is also insufficient evidence to change currently recommended ECG monitoring practices based on CYP2B6 genetics and an absence of evidence to recommend a slower methadone dose titration schedule based on CYP2B6 genetics.

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

There are some important limitations to CYP2B6 genetic tests, as previously described in the Genetic Test Interpretation section. Based on clinical consequences for methadone of known variant alleles, this might not be clinically relevant for methadone.

Therefore, it is important that clinical providers appreciate the limitations of targeted genotyping tests and understand which *CYP2B6* variant alleles were and were not genotyped by a testing laboratory when interpreting results. In addition to altered activity of genetic variants, *CYP2B6* is highly susceptible to induction and inhibition, thus clinical activity (including that of allelic variants)⁵⁶ will reflect the influence of genetics and environment (drug interactions).⁵⁷

SUPPORTING INFORMATION

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

ACKNOWLEDGMENTS

We acknowledge the critical input of members of the Clinical Pharmacogenetics Implementation Consortium (CPIC), funded by the National Institutes of Health. CPIC members are listed here: <https://cpicpgx.org/members/>.

FUNDING

This work was funded by the National Institutes of Health (NIH) for CPIC (U24HG010135 and U24HG013077) and PharmGKB (U24HG010615). PharmVar is supported by the Children's Mercy Research Institute (CMRI). P.Z. is financed by Universidad Autónoma de Madrid, Margarita Salas contract, grants for the requalification of the Spanish university system. R.T. was funded in part by the Canada Research Chairs program (Chair in Pharmacogenomics) and R01 DA043526. Z.D. is funded by NIH/NIGMS grant R35GM145383. EDK is supported by NIH R01DA042985. AAS is supported by ANZCA grant RC21/009.

CONFLICTS OF INTEREST

The authors declared no competing interests in this work.

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