Supplemental Material

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

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GUIDELINE UPDATES

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2D6, OPRM1,* and *COMT* genotype and select opioid therapy is published in full on the CPIC website (1). Relevant information will be reviewed periodically, and updated guidelines published online.

LITERATURE REVIEW

To update the existing CPIC guideline on codeine and *CYP2D6*, we searched the PubMed® database (September 2013 to July 2020) for keywords (codeine) AND (CYP2D6 OR (cytochrome P450 2D6)). For the remaining literature searches for other opioids and OPRM1 and COMT we searched the entirety of the PubMed® database (1966 to July 2020) using the keywords presented in the table below. Search results were filtered to show studies conducted in humans only.

Inclusion criteria included studies gathering primary data (i.e., no review articles or meta-analyses), studies in human subjects or cells and clear results pertaining to an association (or lack or) between genetic variants in *CYP2D6*, *OPRM1* and/or *COMT* and response to opioids. Following application of the inclusion criteria, 285 publications were reviewed and included in the evidence tables **S1-S4**. As some publications contained findings for more than one gene, they have been included in multiple evidence tables.

CYP2D6 searches	OPRM1 searches	COMT searches
Alfentanil AND (CYP2D6 OR (cytochrome P450 2D6))	Alfentanil AND (OPRM1 OR (mu opioid receptor))	Alfentanil AND (COMT OR (catechol-O-methyltransferase))
Alvimopan AND (CYP2D6 OR (cytochrome P450 2D6))	Alvimopan AND (OPRM1 OR (mu opioid receptor))	Alvimopan AND (COMT OR (catechol-O-methyltransferase))
Buprenorphine AND (CYP2D6 OR (cytochrome P450 2D6))	Buprenorphine AND (OPRM1 OR (mu opioid receptor))	Buprenorphine AND (COMT OR (catechol-O-methyltransferase))
Butorphanol AND (CYP2D6 OR (cytochrome P450 2D6))	Butorphanol AND (OPRM1 OR (mu opioid receptor))	Butorphanol AND (COMT OR (catechol-O-methyltransferase))
Carfentanil AND (CYP2D6 OR (cytochrome P450 2D6))	Carfentanil AND (OPRM1 OR (mu opioid receptor))	Carfentanil AND (COMT OR (catechol-O-methyltransferase))
Dezocine AND (CYP2D6 OR (cytochrome P450 2D6))	Codeine AND (OPRM1 OR (mu opioid receptor))	Codeine AND (COMT OR (catechol-O-methyltransferase))
Dihydrocodeine AND (CYP2D6 OR (cytochrome P450 2D6))	Dezocine AND (OPRM1 OR (mu opioid receptor))	Dezocine AND (COMT OR (catechol-O-methyltransferase))
Fentanyl AND (CYP2D6 OR (cytochrome P450 2D6))	Dihydrocodeine AND (OPRM1 OR (mu opioid receptor))	Dihydrocodeine AND (COMT OR (catechol-O-methyltransferase))

Hydrocodone AND (CYP2D6 OR (cytochrome P450 2D6))	Fentanyl AND (OPRM1 OR (mu opioid receptor))	Fentanyl AND (COMT OR (catechol-O-methyltransferase))
Hydromorphone AND (CYP2D6 OR (cytochrome P450 2D6))	Hydrocodone AND (OPRM1 OR (mu opioid receptor))	Hydrocodone AND (COMT OR (catechol-O-methyltransferase))
Levorphanol AND (CYP2D6 OR (cytochrome P450 2D6))	Hydromorphone AND (OPRM1 OR (mu opioid receptor))	Hydromorphone AND (COMT OR (catechol-O-methyltransferase))
Loperamide AND (CYP2D6 OR (cytochrome P450 2D6))	Levorphanol AND (OPRM1 OR (mu opioid receptor))	Levorphanol AND (COMT OR (catechol-O-methyltransferase))
Meperidine AND (CYP2D6 OR (cytochrome P450 2D6))	Loperamide AND (OPRM1 OR (mu opioid receptor))	Loperamide AND (COMT OR (catechol-O-methyltransferase))
Methadone AND (CYP2D6 OR (cytochrome P450 2D6))	Meperidine AND (OPRM1 OR (mu opioid receptor))	Meperidine AND (COMT OR (catechol-O-methyltransferase))
Methylnaltrexone AND (CYP2D6 OR (cytochrome P450 2D6))	Methadone AND (OPRM1 OR (mu opioid receptor))	Methadone AND (COMT OR (catechol-O-methyltransferase))
Morphine AND (CYP2D6 OR (cytochrome P450 2D6))	Methylnaltrexone AND (OPRM1 OR (mu opioid receptor))	Methylnaltrexone AND (COMT OR (catechol-O-methyltransferase))
Nalbuphine AND (CYP2D6 OR (cytochrome P450 2D6))	Morphine AND (OPRM1 OR (mu opioid receptor))	Morphine AND (COMT OR (catechol-O-methyltransferase))
Nalmefene AND (CYP2D6 OR (cytochrome P450 2D6))	Nalbuphine AND (OPRM1 OR (mu opioid receptor))	Nalbuphine AND (COMT OR (catechol-O-methyltransferase))
Naloxone AND (CYP2D6 OR (cytochrome P450 2D6))	Nalmefene AND (OPRM1 OR (mu opioid receptor))	Nalmefene AND (COMT OR (catechol-O-methyltransferase))
Naltrexone AND (CYP2D6 OR (cytochrome P450 2D6))	Naloxone AND (OPRM1 OR (mu opioid receptor))	Naloxone AND (COMT OR (catechol-O-methyltransferase))
Oxycodone AND (CYP2D6 OR (cytochrome P450 2D6))	Naltrexone AND (OPRM1 OR (mu opioid receptor))	Naltrexone AND (COMT OR (catechol-O-methyltransferase))
Oxymorphone AND (CYP2D6 OR (cytochrome P450 2D6))	Oxycodone AND (OPRM1 OR (mu opioid receptor))	Oxycodone AND (COMT OR (catechol-O-methyltransferase))
Pentazocine AND (CYP2D6 OR (cytochrome P450 2D6))	Oxymorphone AND (OPRM1 OR (mu opioid receptor))	Oxymorphone AND (COMT OR (catechol-O-methyltransferase))
Remifentanil AND (CYP2D6 OR (cytochrome P450 2D6))	Pentazocine AND (OPRM1 OR (mu opioid receptor))	Pentazocine AND (COMT OR (catechol-O-methyltransferase))
Sufentanil AND (CYP2D6 OR (cytochrome P450 2D6))	Remifentanil AND (OPRM1 OR (mu opioid receptor))	Remifentanil AND (COMT OR (catechol-O-methyltransferase))
Tapentadol AND (CYP2D6 OR (cytochrome P450 2D6))	Sufentanil AND (OPRM1 OR (mu opioid receptor))	Sufentanil AND (COMT OR (catechol-O-methyltransferase))
Tilidine AND (CYP2D6 OR (cytochrome P450 2D6))	Tapentadol AND (OPRM1 OR (mu opioid receptor))	Tapentadol AND (COMT OR (catechol-O-methyltransferase))
Tramadol AND (CYP2D6 OR (cytochrome P450 2D6))	Tilidine AND (OPRM1 OR (mu opioid receptor))	Tilidine AND (COMT OR (catechol-O-methyltransferase))
(opioid OR (opioids)) AND (CYP2D6 OR (cytochrome P450 2D6))	Tramadol AND (OPRM1 OR (mu opioid receptor))	Tramadol AND (COMT OR (catechol-O-methyltransferase))
"Opioid-Related Disorders"[Mesh] AND (CYP2D6 OR (cytochrome P450 2D6))	(opioid OR (opioids)) AND (OPRM1 OR (mu opioid receptor))	(opioid OR (opioids)) AND (COMT OR (catechol-O-methyltransferase))

	"Opioid-Related Disorders"[Mesh] AND (OPRM1 OR (mu opioid receptor))	"Opioid-Related Disorders"[Mesh] AND (COMT OR (catechol-O-methyltransferase))

GENE: *CYP2D6*

Genetic Test Interpretation

CYP2D6 genetic variants are typically reported as haplotypes, which are defined by a specific combination of single nucleotide polymorphisms (SNPs) and/or other sequence variants including insertions and deletions that are interrogated during genotyping analysis. *CYP2D6* haplotypes are assigned a star-allele (*) nomenclature to allow for the standardization of genetic polymorphism annotation (2, 3). A complete list of *CYP2D6* star allele nomenclature along with the genetic variants that define each star allele is available at https://www.pharmvar.org/. Information regarding *CYP2D6* haplotypes (star alleles) is also available at PharmGKB and PharmVar (***CYP2D6* Allele Definition Table (1, 4))**. Knowing which SNPs or other genetic variants a particular test interrogates is important as the inclusion or exclusion of certain genetic variants in a pharmacogenetic test could affect the reported star allele result (5, 6).

Reference laboratories usually report a diplotype, which is the summary of inherited maternal and paternal star alleles (e.g., *CYP2D6*1/*10*, where an individual inherited a **1* allele and a **10* allele). Commonly reported *CYP2D6* star alleles are categorized into clinical functional groups (i.e. normal function, decreased function, no function or increased function) based on the predicted activity of the encoded enzyme (***CYP2D6* Allele Definition Table (1, 4)**). The predicted phenotype (**Table 1, main manuscript**) is influenced by the expected function of each reported allele in the diplotype. A *CYP2D6* genotype to phenotype translation table has been developed by CPIC and is updated on an ongoing basis on the CPIC website (1).

Calculating CYP2D6 Activity Score. Gaedigk *et al*. developed a scoring system to provide a uniform approach for assigning a predicted CYP2D6 phenotype (7). The activity value of each allele reported in the diplotype is added together to calculate the CYP2D6 activity score. For example, to calculate the activity score of a *CYP2D6*1/*17* diplotype, the activity value of **1* (activity value = 1) and the activity value of **17* (activity value = 0.5) are totaled to provide the CYP2D6 activity score of 1.5. Note that a value of 0.5 indicates decreased activity and not that the activity conveyed by an allele is half of that encoded by a normal function allele. For this

guideline, an updated method to translate *CYP2D6* genotype into phenotype is utilized (8). CYP2D6 activity scores translate genotype into phenotype as follows: activity score of 0 = poor metabolizer, activity scores of $0 < x < 1.25$ = intermediate metabolizer, activity scores of $1.25 \leq x \leq 2.25$ = normal metabolizer, and activity scores greater than 2.25 = ultrarapid metabolizer. Therefore, a pharmacogenetic test result of *CYP2D6*1/*17* would result in a CYP2D6 activity score of 1.5 and a predicted phenotype of normal metabolizer.

CYP2D6 Structural and Gene Copy Number Variants. Because *CYP2D6* is subject to copy number variation (gene duplications, multiplications, or deletions), clinical laboratories may report gene copy number if directly tested. Most patients will have a normal copy number of 2, with one gene copy inherited maternally and one gene copy inherited paternally. When two *CYP2D6* gene copies are present, the diplotype may be reported as follows: *CYP2D6*1/*1* or *CYP2D6 (*1/*1)2N*, where "*2N*" represents the gene copy number. A copy number of "1" indicates the presence of a *CYP2D6* gene deletion (the patient possesses only one gene copy), and a copy number of "0" indicates both *CYP2D6* genes are deleted. *CYP2D6* gene deletions are indicated by the *CYP2D6*5* allele. A gene deletion that is present on one chromosome may be reported as follows: *CYP2D6*2/*5* or *CYP2D6 (*2/*2)1N*, where "*1N*" represents gene copy number and the *CYP2D6*5* allele is inferred. Typically, clinical laboratories will report a homozygous gene deletion as *CYP2D6*5/*5* or *CYP2D6 (*5/*5)0N*.

A copy number greater than two indicates the presence of a *CYP2D6* gene duplication or multiplication. When a *CYP2D6* gene duplication is present, the diplotype may be reported as *CYP2D6 (*1/*2)3N*, where "*3N*" represents gene copy number. A clinical laboratory may not report an exact copy number, but rather indicate that additional copies of the *CYP2D6* gene are present (e.g., *CYP2D6*1/*2* duplication or *CYP2D6 (*1/*2)xN*). In instances where a duplication/multiplication is present, and the exact copy number is not reported, most patients will likely have a *CYP2D6* gene copy number of 3. However, individuals carrying as many as 13 *CYP2D6* gene copies have been reported (9). Some clinical laboratories may not determine which allele is duplicated, therefore when calculating CYP2D6 activity score the duplication must be considered for each allele reported in the diplotype (10). For example, a genotype result of *CYP2D6 (*1/*4)3N* indicates a patient has three copies of the *CYP2D6* gene, with either two copies of the *CYP2D6*1* allele and one copy of the *CYP2D6*4* allele, or one copy of the *CYP2D6*1* allele and two copies of the *CYP2D6*4* allele. If the *CYP2D6*1* allele carries the

duplication, the CYP2D6 activity score of this diplotype will be 2 (normal metabolizer), whereas if the *CYP2D6*4* allele carries the duplication, the activity score will be 1 (intermediate metabolizer). Likewise, if the number of gene copies is not determined and it remains unknown which allele carries the duplication/multiplication, a *CYP2D6 (*1/*10)xN* genotype, for example, can be consistent with a NM (normal metabolizer) phenotype (*CYP2D6*1/*10x2*; activity score of 1.5 or *CYP2D6*1x2/*10,* activity score of 2.25) or UM (ultrarapid metabolizer) phenotype (or *CYP2D6*1x2/*10x2*; activity score of 2.5 or *CYP2D6*1x3/*10*; activity score of 3.25). As these examples illustrate, phenotype prediction will be more accurate if testing determines which allele carries the duplication/multiplication and the number of gene copies present. Consequences of *CYP2D6* copy number variation on pharmacotherapy has been reviewed by Jarvis *et al*. 2019 (11).

Note that a duplication may not be detected by copy number assays when paired with the *CYP2D6*5* allele (gene deletion). A *CYP2D6*2x2/*5* diplotype, for example, has a gene duplication on one allele and a gene deletion on the other for a total number of two gene copies. This diplotype may be reported as *CYP2D6*2/*2*.

Other structural variants include gene copies that consist of *CYP2D6* and *CYP2D7*-derived sequences (3, 12, 13). An overview of these variants can also be found in the "Structural Variation" document at https://www.pharmvar.org/gene/CYP2D6. The no function *CYP2D7-2D6* hybrid genes, collectively assigned as *CYP2D6*13* (14), may not be detected by a particular genotype test or gene copy number testing. In such cases the test may detect only the allele present on the second chromosome and report the diplotype as homozygous for that allele. For example, a test that does not detect *CYP2D6*13* will report a *CYP2D6*1/*13* diplotype as *CYP2D6*1/*1*. Hybrid genes can also occur in duplication configurations and cause positive gene duplication test results that may lead to an overestimation of activity and false-positive prediction of ultrarapid metabolism (13, 15). For example, a *CYP2D6*1/*13+*2* diplotype (activity score = 2 predicting normal metabolism) may be assigned as *CYP2D6*1/*2xN* (activity score ≥ 3 predicting ultrarapid metabolism).

Limitations of the Star (*) Nomenclature and Allele Assignments. The star (*) nomenclature has defined multiple suballeles (e.g., *CYP2D6*2.001, CYP2D6*4.002*), but these are not distinguished by current testing. This is of no consequence for *CYP2D6*4*, because all **4*

suballeles share 1847G>A causing aberrant splicing and absence of functional protein. For *CYP2D6*2*, however, it is unknown whether any of the sequence variations defining the suballeles convey a functional consequence. Also, there is no, or little, information regarding their frequencies because test laboratories do not discriminate between the suballeles. In addition, there are likely numerous known variants and suballeles that have not been designated by PharmVar at this time (investigators and clinical laboratories are encouraged to submit novel information to PharmVar).

The accuracy of a genotype test depends on the number of sequence variations/allelic variants tested. If no variation is found, a *CYP2D6*1* will be the 'default' assignment. Depending on which sequence variations are found, the allele assignment may vary. For example, if 2851C>T is present, but 1022C>T is not, the assignment is *CYP2D6*2*. In contrast, if 1022C>T is also present, the allele would be assigned as **17*. Additional examples are provided in the PharmVar *CYP2D6* GeneFocus paper (3). Also see 'CYP2D6 Other Considerations' below.

Note that the SNP positions provided above and below are according to the NG_008376.3 reference sequence. The M33388 "legacy" sequence contains errors causing certain SNP positions to shift by 1-base when mapped to the NG_008376.3 reference sequence. PharmVar uses NG_008376.3 as the 'gold standard' and strongly encourages the use and reporting of positions in respect to NG_008376.3 RefSeq. To facilitate SNP mapping, PharmVar cross-references positions between NG_008376.3 and M33388 (https://www.pharmvar.org/gene/CYP2D6).

Recent findings indicate that a SNP in a distal enhancer region impacts allele activity on the transcriptional level (16, 17). Specifically, it was reported that *CYP2D6*2* alleles lacking the enhancer SNP have decreased function. A study by a different found that the enhancer SNP did not lead to improved prediction of endoxifen levels in breast cancer patients (18). Furthermore, a recent study (19) found that this SNP (rs5758550) can also occur on many other star alleles and that the portion of an allele with and without rs5758550 may considerably vary among populations. Thus, it remains uncertain whether the effect of this SNP on CYP2D6 activity *in vivo* is of clinical significance. rs5758550 is not included in current test panels or allele definitions.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Desirable characteristics of pharmacogenetic tests, including naming of alleles and test report contents, have been extensively reviewed by an international group, including CPIC members (20). CPIC recommends that clinical laboratories adhere to these test reporting standards. CPIC gene-specific tables (see ***CYP2D6* Allele Definition Table**, ***CYP2D6* Allele Functionality Table** and ***CYP2D6* Allele Frequency Table** (https://cpicpgx.org/guidelines/guideline-for-codeine-and-cyp2d6/) adhere to these allele nomenclature standards (20). Moreover, the ***CYP2D6* Allele Definition Table**, ***CYP2D6* Allele Functionality Table**, and ***CYP2D6* Allele Frequency Table** may be used to assemble lists of known functional and actionable pharmacogenetic variants and their population frequencies, which may inform decisions as to whether tests are adequately comprehensive in interrogations of alleles. Furthermore, the Association for Molecular Pathology and College of American Pathologists (CAP) have published a joint recommendation for the key attributes of alleles recommended for clinical testing and a minimum set of variants that should be included in certain clinical genotyping assays (21) and are currently working on a similar paper for *CYP2D6*.

Clinical laboratories may analyze different sets of SNPs or other genetic variants, which are dependent on the genotyping platforms used and may affect the reported diplotype leading to discrepant results between methodologies. *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 phenotype can be assigned. Additionally, laboratories may differ in how *CYP2D6* copy number variants are reported, which can potentially affect phenotype prediction. Therefore, it is important to not only know the alleles interrogated by each laboratory, but also which sequence variants (e.g., SNPs, insertions, or deletions) are tested and how copy number variants are reported. Clinical laboratories commonly give an interpretation of the genotype result and provide a predicted phenotype. Phenotype assignment for this guideline is defined in the main manuscript and supplementary data but may differ from some clinical laboratory interpretations. Any *CYP2D6* genotyping results used to guide patient pharmacotherapy and/or deposited into patient medical records should be derived from validated

genotyping platforms in clinical laboratories that implement the appropriate regulatory standards and best practices (e.g., CAP, CLIA).

CYP2D6 Other Considerations

There are several factors that cause potential uncertainty in *CYP2D6* genotyping results and phenotype predictions as follows: **1)** Laboratories providing genetic testing usually ignore the contribution of environmental variables such as taking CYP2D6 inhibitors when reporting CYP2D6 phenotypes. **2)** Because it is currently impractical to test for every variation in the *CYP2D6* gene, genotyping tests may not detect rare variants resulting in patients being assigned a default genotype. It also needs to be stressed that genotyping tests are not designed to detect unknown/*de novo* sequence variations. Depending on the sequence variations (or alleles present) in a given patient, the default genotype may be *CYP2D6*1/*1* (or wild-type) or another diplotype. If the rare or *de novo* variant adversely affects CYP2D6 enzyme function, then the patient's actual phenotype may differ from the predicted phenotype. **3)** Many star alleles have several suballeles. As an example, numerous suballeles have been identified for *CYP2D6*4* (i.e., *CYP2D6*4.001*, **4.002*, **4.003*, etc.) which may have additional SNPs which may or may not exert a functional change on their own. For *CYP2D6*4*, there is only a single core SNP, 1847G>A, that is shared among all suballeles and causes the splice defect rendering this allele nonfunctional. Thus, it is sufficient to test for 1847G>A to identify the *CYP2D6*4* allele. **4)** There are multiple gene units involved in duplication and other major rearrangements (3, 11); also see the Structural Variation document on the PharmVar *CYP2D6* page at https://www.pharmvar.org/gene/CYP2D6). Additionally, the pseudogenes *CYP2D7* and *CYP2D8* may be misinterpreted as functional duplications (22). If the specific gene units involved in the duplication or other rearrangements are not specifically tested for, the phenotype prediction may be inaccurate and CYP2D6 activity over-estimated. **5)** Some SNPs exist on multiple alleles. For example, *CYP2D6*69* carries the core SNPs for *CYP2D6*41* (2851C>T, 2989G>A, and 4181G>C) and the core SNPs for *CYP2D6*10* (100C>T and 4181G>C) in addition to multiple other SNPs (3). If a patient carries these genetic variants (in the absence of 1847G>A), a *CYP2D6*10/*41* diplotype is typically assigned, because this is the most likely result based on allele frequencies. However, a *CYP2D6*1/*69* genotype cannot be excluded with certainty. Testing for additional SNPs (e.g., 1061A>G, 3385A>C, and 3585G>A) would need to be performed to exclude *CYP2D6*1/*69* with certainty. Therefore, to unequivocally determine the presence of certain alleles, testing for multiple SNPs may be required. **6)** Allele frequencies may

vary considerably among individuals of different ancestral backgrounds. For instance, *CYP2D6*10* is common in Asian populations while *CYP2D6*17* is common in people of Sub-Saharan African ancestry. These alleles, however, have a considerably lower prevalence in other ethnic groups such as European ancestry. As another example, *CYP2D6*14* is present in Asian populations and therefore its core SNP (1759G>A) has been incorporated into Asian genotyping panels (23). Thus, the alleles that should be tested for a given population may vary. **7)** Certain alleles carry genes in tandem arrangements. One such example is *CYP2D6*36+*10* (one copy of the non-functional *CYP2D6*36* and one copy of the decreased function *CYP2D6*10*). This tandem can be found in Asians and is often reported as (i.e. defaulted to) *CYP2D6*10*. **8)** Phenotyping approaches might also be used to measure the combined effects of genetic and environmental factors and determine individual metabolic profiles *in vivo*. These usually involve the oral intake of a probe drug followed by the single measurement of the metabolite/probe (metabolic ratio) concentration in a plasma, capillary dried blood spot or urine sample (24, 25).

OTHER CONSIDERATIONS

Other genes affecting codeine metabolism and opioid response

Glucuronidation of codeine and morphine is mediated by the polymorphic UGT2B7 enzyme (26). Although the production of morphine-6-glucuronide is almost exclusively catalyzed by UGT2B7, several isoforms of the UGT1A subfamily are also involved in the formation of morphine-3-glucuronide. Conflicting evidence exists regarding the impact of the *UGT2B7*2* variant on the glucuronidation of codeine (27). The organic cation transporter OCT1 plays a role in hepatocellular uptake of morphine. Patients carrying *OCT1* polymorphisms resulting in reduced transporter function may be at higher risk of adverse effects after codeine administration, especially in patients who are also CYP2D6 ultrarapid metabolizers (28). Polymorphisms in the *ABCB1* transporter (*MDR1*) gene also appear to have a modest association with opioid dose requirements (29).

Effect of pregnancy on CYP2D6

Wadelius *et al*. demonstrated an increase in CYP2D6 activity by measuring dextromethorphan/dextrorphan metabolic ratio that was decreased by 53% in pregnancy, while Heikkinen *et al*. demonstrated that the norfluoxetine/fluoxetine metabolic ratio increased 2.4-fold (30, 31). The apparent oral clearance of metoprolol was shown to increase by 4 to 5-fold during

pregnancy (32). Although mean CYP2D6 activity appears to increase during pregnancy, the large interindividual variability in the increase and the limited number of subjects studied make it difficult to recommend how to adjust the activity scores of functional alleles during pregnancy. The CYP2D6 activity scores of nonfunctional alleles are not affected by pregnancy.

Ontogeny of CYP2D6

Functional CYP2D6 activity is not appreciably expressed in fetal liver, but increases rapidly after birth (33). These *in vitro* data together with *in vivo* data obtained from a longitudinal phenotyping study conducted in the first year of life (34) reveal considerable inter-individual variability in CYP2D6 activity within the first 2-4 weeks of life. In the neonatal setting, both ontogeny and genetic variation contribute to inter-individual variability in the disposition of CYP2D6 substrates and are consistent with functional CYP2D6 activity being acquired concurrently with the maturation of other systems, such as renal function (35). Overall, available data are consistent with genetic variation being more important than ontogeny as a determinant of variability in CYP2D6 activity beyond the first month of postnatal life. Therefore, *CYP2D6* genotype is expected to be equally reliable for inferring phenotype from genotype in children as in adults.

DRUG: OPIOIDS

Background

Codeine. Codeine is an opioid analgesic indicated for the relief of mild to moderate pain. The opioid active metabolites of codeine, morphine and morphine-6-glucuronide, are the primary contributors to codeine analgesia; codeine has a 200-fold lower affinity for μ-opioid receptors than does morphine (36, 37). Both codeine and morphine also have antitussive properties. *O*-demethylation of codeine into morphine by CYP2D6 represents a minor pathway in normal metabolizers, accounting for 5-10% of codeine clearance in such individuals but appears to be essential for its opioid activity. The percent of codeine converted to morphine can have about a 50% higher AUC in CYP2D6 ultrarapid metabolizers (38). Morphine is further glucuronidated to morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide has analgesic activity in humans, whereas morphine-3-glucuronide is generally not considered to possess analgesic properties but has neurotoxic effects. About 80% of an administered dose of codeine is converted to inactive metabolites by glucuronidation to codeine-6-glucuronide via UDP-glucuronosyltransferase (UGT) 2B7, and by *N*-demethylation to norcodeine via CYP3A4. The

analgesic activity of codeine-6-glucuronide in humans is unknown but likely to be low given its weak binding affinity, while norcodeine is thought to have no analgesic properties (37). Common adverse reactions to codeine include nausea, vomiting, drowsiness, lightheadedness, dizziness, sedation, shortness of breath, constipation, and itching. Serious adverse reactions include respiratory arrest and rare secondary hemodynamic consequences, and cardiac arrest.

Tramadol. Tramadol in its available racemic form is extensively metabolized via a number of pathways, including CYP2D6-mediated oxidation to *O*-desmethyltramadol (M1), which has a more than 200-fold higher affinity for μ-opioid receptors compared to the parent drug (36, 39). Thus, (+)-*O*-desmethyltramadol is principally responsible for opioid receptor-mediated analgesia, whereas (+)- and (-)-tramadol contribute to analgesia by inhibiting reuptake of the neurotransmitters serotonin and noradrenaline. Tramadol is used both in patients with nociceptive and neuropathic pain.

LEVELS OF EVIDENCE LINKING GENOTYPE TO PHENOTYPE

The evidence summarized in **Supplemental Tables S1-S4** is graded (40) on a scale of high, moderate, and weak, based upon the level of evidence:

> **High:** Evidence includes consistent results from well-designed, well-conducted studies.
>
> **Moderate:** Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.
>
> **Weak:** Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations (**Table 2**, **main manuscript**).

STRENGTH OF RECOMMENDATIONS

CPIC's therapeutic recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, *in*

vitro enzyme activity of tissues expressing wild-type or variant-containing CYP2D6, *in vitro* CYP2D6 enzyme activity from tissues isolated from individuals of known *CYP2D6* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies.

Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians. CPIC uses a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of antiretroviral agents (41):

Strong recommendation for the statement: "The evidence is high quality and the desirable effects clearly outweigh the undesirable effects."
Moderate recommendation for the statement: "There is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.
Optional recommendation for the statement: The desirable effects are closely balanced with undesirable effects, or the evidence is weak or based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.
No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

RESOURCES TO INCORPORATE PHARMACOGENETICS INTO AN ELECTRONIC HEALTH RECORD WITH CLINICAL DECISION SUPPORT

Clinical decision support (CDS) tools integrated within electronic health records (EHRs) can help guide clinical pharmacogenetics at the point of care (42-46). Resources to support the adoption of CPIC guidelines within an EHR are available on the CPIC website (1, 47). Based on the capabilities of various EHRs and local preferences, we recognize that approaches may vary across organizations. Our intent is to synthesize foundational knowledge that provides a common starting point for incorporating *CYP2D6* genotype results in an EHR to guide opioid use.

Effectively incorporating pharmacogenetic information into an EHR to optimize drug therapy should have some key attributes. Pharmacogenetic results, an interpreted phenotype, and a concise interpretation or summary of the result must be documented in the EHR (48). To incorporate a phenotype in the EHR in a standardized manner, genotype test results provided by the laboratory must be consistently translated into an interpreted phenotype (**Table 1, main**

manuscript; *CYP2D6* Diplotype to Phenotype Table (1, 4)). Because clinicians must be able to easily find the information, the interpreted phenotype may be documented as a problem list entry or in a patient summary section; these phenotypes are best stored in the EHR at the "person level" rather than at the date-centric "encounter level". Additionally, results should be entered as standardized and discrete terms to facilitate using them to provide point-of-care CDS (see **Codeine and Tramadol Pre- and Post-Test Alerts and Flow Chart** for example CDS alerts; (1, 4, 49, 50).

Because pharmacogenetic results have lifetime implications and clinical significance, results should be placed into a section of the EHR that is accessible independent of the test result date to allow clinicians to quickly find the result at any time after it is initially placed in the EHR. To facilitate this process, CPIC is providing gene-specific information figures and tables that include full diplotype to phenotype tables, diagram(s) that illustrate how *CYP2D6* pharmacogenetic test results could be entered into an EHR, example EHR consultation/genetic test interpretation language and widely used nomenclature systems (see (1, 46))**.** Point-of-care CDS should be designed to effectively notify clinicians of prescribing implications at any time after the test result is entered into the EHR. CPIC is also providing gene-drug specific tables that provide guidance to achieve these objectives with diagrams that illustrate how point-of-care CDS should be entered into the EHR, example pre- and post-test alert language, and widely used nomenclature systems for relevant drugs (1).

SUPPLEMENTAL TABLE S1. EVIDENCE LINKING CYP2D6 PHENOTYPE OR GENOTYPE WITH OPIOID METABOLISM OR RESPONSE.

Type of experimental model (*in vitro*, *in vivo* preclinical, or clinical)	**Major findings**	**References**	**Level of Evidence[a]**
Codeine			
In vitro	Decreased Vmax and higher apparent Km for codeine O-demethylation to morphine in human liver microsomes with PM phenotype by dextromethorphan metabolism versus NM phenotype	Dayer, *et al.* 1988 (51)	High
In vitro	Less morphine formation from codeine O-demethylation in human liver microsomes with PM phenotype by dextromethorphan versus NM phenotype	Mortimer, *et al.* 1990 (52)	High
In vitro	Higher apparent Km for codeine O-demethylation to morphine in microsomes prepared from yeast cells expressing human *CYP2D6*17* versus normal function.	Oscarson, *et al.* 1997 (53)	High
In vitro	Decreased Vmax for codeine O-demethylation to morphine in microsomes prepared from insect cells expressing human *CYP2D6* decreased-function alleles versus **1* alleles	Yu, *et al.* 2002 (54) Shen, *et al.* 2007 (55) Zhang, *et al.* 2009 (56)	High
Preclinical	No analgesia observed in rats deficient for CYP2D1, a homolog for CYP2D6 in humans, after codeine administration	Cleary, *et al.* 1994 (57)	High
Clinical	Reduced or no analgesia observed in CYP2D6 PM phenotype by drug metabolism assay	Sindrup, *et al.* 1990 (58) Desmeules, *et al.* 1991 (59) Poulsen, *et al.* 1996 (60) Eckhardt, *et al.* 1998	High
Clinical	Decreased analgesia from codeine observed in CYP2D6 PMs by genotype	Persson, *et al.* 1995 (61) Fagerlund, *et al.* 2001 (62) Foster, *et al.* 2007 (63)	Moderate

		VanderVaart, *et al.* 2011 (64) Shaw, *et al.* 2012 (65)	
Clinical	No statistical difference of analgesia between *CYP2D6* genotypes after codeine administration	Williams, *et al.* 2002 (66) Vree, *et al.* 2000 (67)	High
Clinical	*CYP2D6* decreased function alleles are more likely to be found in sickle cell disease patients who have failed codeine therapy compared to those who respond to codeine	Brosseau, *et al.* 2007 (68)	Moderate
Clinical	*CYP2D6*-guided prescribing of codeine results in improved analgesia and is beneficial to patients with IM (AS = 0.5) or PM (AS = 0) phenotypes as compared to standard prescribing	Smith, *et al.* 2019 (69)	Moderate
Clinical	*CYP2D6*-guided prescribing of codeine in patient with CYP2D6 NM (AS = 1.0-2.0) phenotypes does not result in a difference in analgesia as compared to standard prescribing	Smith, *et al.* 2019 (69)	High
Clinical	CYP2D6 PM and IM (AS 0.5) phenotypes are associated with lack of analgesic response to codeine	Radford, *et al*. 2019 (70)	Moderate
Clinical	No statistical difference of codeine dose requirements for postoperative pain between *CYP2D6* genotypes.	Baber, *et al.* 2015 (71)	Moderate
Clinical	The CYP2D6 PM phenotype is associated with reduced likelihood of developing opioid dependence	Tyndale, *et al.* 1997 (72)	Moderate
Clinical	CYP2D6 IM phenotype by drug metabolism assay associated with lower formation or excretion of morphine and related metabolites following codeine administration versus NM phenotype	Chen, *et al.* 1988 (73) Vevelstad, *et al.* 2009 (74)	High
Clinical	No significant difference in plasma concentration of morphine and related metabolites in IM (AS = 1.0) genotypes versus NM (AS = 2.0) genotype	Lotsch, *et al.* 2006 (75) Williams, *et al.* 2002 (66) Frost, *et al.* 2016 (76)	High
Clinical	*CYP2D6* PM genotype associated with reduced formation or excretion of morphine and related metabolites following codeine administration	Tseng, *et al.* 1996 (77) Eckhardt, *et al.* 1998 (78) Williams, *et al.* 2002 (66) Lotsch, *et al.* 2009 (29) Molanaei, *et al.* 2010 (79)	High

Clinical	CYP2D6 PM phenotype by drug metabolism assay associated with lower formation or excretion of morphine and related metabolites following codeine administration versus NM phenotype	Chen, *et al.* 1988 (73) Yue, *et al.* 1989 (80) Sindrup, *et al.* 1990 (58) Chen, *et al.* 1991 (81) Desmeules, *et al.* 1991 (59) Caraco, *et al.* 1996 (82) Poulsen, *et al.* 1996 (60) Caraco, *et al.* 1997 (83) Hasselstrom, *et al.* 1997 (84) Hedenmalm, *et al.* 1997 (85) Mikus, *et al.* 1997 (86) Poulsen, *et al.* 1998 (87) Eckhardt, *et al.* 1998 (78) Lötsch, *et al.* 2006 (75) Yue, *et al.* 1997 (88) Haffen, *et al.* 2000 (89) Frost, *et al.* 2016 (76)	High
Clinical	Low morphine formation following codeine administration in PM predicted by *CYP2D6* genotyping or dextromethorphan-based phenotyping	Lötsch, *et al.* 2009 (29)	High
Clinical	Higher plasma concentrations of morphine and related metabolites following codeine administration in healthy volunteers with *CYP2D6* gene duplication (> 2 functional alleles) than in carriers of 2 functional *CYP2D6* alleles	Kirschheiner, *et al.* 2007 (90)	High
Clinical	High morphine formation in UM predicted by dextromethorphan-based phenotyping and/or *CYP2D6* genotyping for allele multiplication	Lotsch, *et al.* 2009 (29) He, *et al.* 2008 (91) Yue, *et al.* 1997 (88)	High
Clinical	Rifampin induced codeine metabolism to morphine in NM but not PM phenotype by drug metabolism assay	Caraco, *et al.* 1997 (83)	High

Clinical	Patients with variant *CYP2D6* alleles *(*7, *29, *41*) had significantly lower excretion of morphine and related metabolites after codeine vs those without variant alleles	Shord, *et al.* 2009 (92) Chen, *et al.* 1991 (81)	High
Clinical	Heterozygous NMs (**1/*4*) associated with lower urinary excretion of morphine and related metabolites following codeine and paracetamol or levomepromazine with codeine and paracetamol administration versus homozygous NMs (**1/*1*)	Vevelstad, *et al.* 2009 (74)	High
Clinical	*CYP2D6*17* allele has higher activity in codeine metabolism compared to in metabolism of debrisoquine or dextromethorphan	Wennerholm, *et al.* 2002 (93)	Moderate
Clinical	Increased codeine metabolic ratio in *CYP2D6*29/*29* compared to *CYP2D6* genotypes comprised of the **1* and/or **2* alleles	Wennerholm, *et al.* 2002 (93)	Weak
Clinical	Cmax and AUC of morphine formed from codeine decreases as the number of *CYP2D6*10* alleles increases	Wu, *et al.* 2014 (94)	High
Clinical	Morphine/codeine concentration ratio increases as a patient's CYP2D6 activity score increases	Lam, *et al.* 2014 (95)	Weak
Clinical	CYP2D6 PM phenotype by drug metabolism assay associated with reduced opioid associated adverse effects following codeine administration versus NM phenotype	Caraco, *et al.* 1996 (82) Mikus, *et al.* 1997 (86)	High
Clinical	CYP2D6 PM phenotype by drug metabolism assay no difference in adverse effect profile in PM versus NM following codeine administration	Hasselstrom, *et al.* 1997 (84) Eckhardt, *et al.* 1998 (78)	High
Clinical	Greater incidence of sedation following codeine administration in healthy volunteers with an UM genotype versus those with a NM genotype	Kirchheiner, *et al.* 2007 (90)	High

Clinical	Increased opioid related adverse events, including fatal toxicity, observed in CYP2D6 UMs by genotype following normal doses of codeine	VanderVaart, *et al.* 2011 (64) Dalen, *et al.* 1997 (96) Gasche, *et al.* 2004 (38) Ciszkowski, *et al.* 2009 (97) Kelly, *et al.* 2012 (98)	Moderate
Clinical	Increased opioid-related adverse events, including fatal toxicity, in infants breastfed by a CYP2D6 UM mother	Koren, *et al.* 2006 (99) Madadi, *et al.* 2009 (100) Friedrichsdorf, *et al.* 2013 (101) Madadi, *et al.* 2007 (102) Sistonen, *et al.* 2012 (103)	Moderate
Clinical	Severe opioid related adverse events, including respiratory depression and hypoxia, observed in children with NM genotype after receiving codeine	Kelly, *et al.* 2012 (98) Friedrichsdorf, *et al.* 2013 (101) Voronov, *et al.* 2007 (104)	Weak
Clinical	*CYP2D6* genotype was not a predictor of changes in respiratory parameters in pediatric patients receiving codeine	Khetani, *et al.* 2012 (105)	Weak
Clinical	The *CYP2D6*4/*6* genotype is associated with codeine intolerance	Susce, *et al.* 2006 (106)	Weak
Clinical	No significant difference of risk of codeine-induced sedation between CYP2D6 phenotypes (PM = 0-0.5, IM = 1.0, NM = 1.5-2.0, UM ≥ 3)	Prows, *et al.* 2014 (107)	High
Clinical	The risk of codeine-induced adverse events increases as the number of normal function *CYP2D6* alleles in a patient increases	Prows, *et al.* 2014 (107)	High
Clinical	No significant difference in codeine-related side effects between *CYP2D6* genotypes.	Radfrod, *et al*. 2019 (70)	Moderate
Dihydrocodeine			

In vitro	Decreased Vmax and increased Km for dihydrocodeine O-demethylation and increased Vmax and decreased Km for dihydrocodeine N-demethylation in human liver microsomes with the **4/*4* genotype compared to microsomes with a NM genotype or phenotype	Kirkwood, *et al.* 1997 (108)	Moderate
Clinical	No significant difference in dihydrocodeine Cmax, AUC, half-life or clearance between CYP2D6 NM and PM phenotypes as determined by drug metabolism assay.	Fromm, *et al.* 1995 (109)	Moderate
Clinical	CYP2D6 NM phenotype by drug metabolism assay significantly increased Cmax and AUC of dihydromorphine and increased metabolic clearance of dihydrocodeine to dihydromorphine compared to the PM phenotype.	Fromm, *et al.* 1995 (109)	Moderate
Clinical	*CYP2D6*1/*10-*36* genotype is not associated with dihydrocodeine toxicity	Shimizu, *et al.* 2018 (110)	Weak
Ethylmorphine			
In vitro	Low rate of O-deethylation of ethylmorphine in human liver microsomes with PM genotypes.	Liu, *et al.*1995 (111)	Moderate
Clinical	*CYP2D6 *1/*3* and **1/*5* genotypes are associated with low concentrations of excreted ethylmorphine metabolites	Aasmundstad, *et al.* 1995 (112)	Weak
Fentanyl			
Clinical	*CYP2D6 *10/*10* genotype associated with increased fentanyl consumption and reduced analgesia from fentanyl for postoperative pain compared to **1/*1*	Wu, *et al.* 2015 (113)	Moderate
Clinical	*CYP2D6 *1/*10* genotype is not associated with fentanyl consumption or analgesic effect fentanyl for postoperative pain compared to **1/*1*	Wu, *et al.* 2015 (113)	Moderate
Clinical	The CYP2D6 PM phenotype, identified by drug metabolism assay or genotyping, is associated with reduced likelihood of developing opioid dependence	Tyndale, *et al.* 1997 (72)	Weak

Clinical	*CYP2D6 *1/*9* and **1/*29* genotypes are associated with decreased clearance of fentanyl	Grimsrud, *et al.* 2019 (114)	Weak
Hydrocodone			
In vitro	Negligible rate of formation of hydromorphone from hydrocodone in human liver microsomes with *CYP2D6* PM genotypes as compared to microsome with NM genotypes.	Otton, *et al.* 1993 (115) Hutchinson, *et al.* 2004 (116)	Moderate
Clinical	The *CYP2D6 *5/*17* genotype is observed in patient with lack of response to hydrocodone in patients taking a concomitant CYP2D6 inhibitor	Tillman, *et al*. 2019 (117)	Weak
Clinical	Increased Cmax of hydromorphone and decreased excretion of unchanged hydrocodone in subjects with CYP2D6 NM compared to those with PM determined by drug metabolism assay.	Otton, *et al.* 1993 (115)	High
Clinical	CYP2D6 PM phenotype by drug metabolism assay is associated with reduced formation of hydromorphone from hydrocodone compared to NM phenotype	Kaplan, *et al.* 1997 (118)	Moderate
Clinical	*CYP2D6* PM genotypes are associated with reduced formation of hydromorphone from hydrocodone compared to NM genotypes.	Stauble, *et al.* 2014 (119)	High
Clinical	CYP2D6 PMs by genotyping are associated with increased norhydrocodone concentrations as compared to NMs and UMs	Stauble, *et al.* 2014 (119)	High
Clinical	Increase in 'good' subjective drug effects and reduced 'bad' effects from hydrocodone in subjects with NM compared to those with PM as determined by drug metabolism assay.	Otton, *et al.* 1993 (115)	Weak
Clinical	CYP2D6 phenotype by drug metabolism assay is not associated with effects of hydrocodone in healthy subjects	Kaplan, *et al.* 1997 (118)	Moderate
Clinical	Dysphoria observed in a patient with the **1/*2xN* genotype following administration of hydrocodone	de Leon, *et al.* 2003 (120)	Weak
Clinical	Hydrocodone is well tolerated by subjects with the **4/*4* or **4/*6* genotypes	Susce, *et al.* 2006 (106) Foster, *et al.* 2007 (63)	Weak

Clinical	*CYP2D6*2/*41* genotype is associated with fatal hydrocodone toxicity	Madadi, *et al.* 2010 (121)	Weak
Clinical	Adverse events, including nausea and vomiting, observed in a subject with the *CYP2D6*4/*4* genotype	Foster, *et al.* 2007 (63)	Moderate
Methadone			
Clinical	CYP2D6 UMs by genotype are more likely to require an increased dose of methadone in methadone maintenance therapy compared to PMs	Eap, *et al.* 2001 (122) Fonseca, *et al.* 2011 (123)	Weak
Clinical	*CYP2D6*4/*4* genotype is associated with increased methadone doses in methadone maintenance therapy	Levran, *et al.* 2013 (124)	Weak
Clinical	*CYP2D6*41/*41* genotype is associated with increased methadone doses in methadone maintenance therapy	Levran, *et al.* 2013 (124)	Weak
Clinical	No statistical differences of methadone maintenance dose in methadone maintenance therapy between *CYP2D6* copy number	Mouly, *et al.* 2015 (125)	Weak
Clinical	CYP2D6 PMs by genotype are more likely to adhere to methadone maintenance therapy as compared to UMs	Eap, *et al.* 2001 (122)	Weak
Clinical	No statistical difference in opioid cessation rates between *CYP2D6* genotypes in patients receiving methadone maintenance therapy	Victorri-Vigneau, *et al.* 2019 (126)	Weak
Clinical	No significant differences of levomethadone drug effects between *CYP2D6* genotypes (PM = 0, IM = if **41* allele is present and AS =0.5-1.0, UM = ≥3)	Lötsch, *et al.* 2006 (127)	Weak
Clinical	*CYP2D6* UM genotypes are associated with decreased satisfaction with methadone maintenance therapy	Perez de los Cobos, *et al.* 2007 (128)	Weak
Clinical	Increased methadone concentration:dose ratios in CYP2D6 PMs (AS = 0) by genotype compared to NMs (AS = 1.0-2.0)	Eap, *et al.* 2001 (122)	Weak
Clinical	Decreased methadone concentration:dose ratios in CYP2D6 UMs (AS ≥3) by genotype compared to NMs (AS = 1.0-2.0)	Eap, *et al.* 2001 (122)	Weak

Clinical	*CYP2D6* UM genotypes are associated with decreased trough concentrations of (S)- and (R)-methadone compared to NMs and IMs	Crettol, *et al.* 2006 (129)	Weak
Clinical	No effect of *CYP2D6* genotype (PM = 0, IM = if **41* allele is present and AS =0.5-1.0, NM = 1.0-2.0, UM = ≥3) on concentrations or clearance of methadone.	Lötsch, *et al.* 2006 (127) Crettol, *et al.* 2006 (129) Uehlinger, *et al.* 2007 (130) Coller, *et al.* 2007 (131) Shiran, *et al.* 2009 (132) Fonseca, *et al.* 2011 (123) Kringen, *et al.* 2017 (133) Victorri-Vigneau, *et al.* 2019 (126)	Moderate
Clinical	*CYP2D6* UM (AS ≥3 or presence of a promoter mutation) genotypes are associated with increased concentrations of both methadone enantiomers as compared to NMs (1.0-2.0)	Fonseca, *et al.* 2011 (123)	Weak
Morphine			
Clinical	CYP2D6 UMs by genotyping are associated with low morphine dose requirements	Candiotti, *et al.* 2009 (134)	Weak
Clinical	No statistical differences of morphine consumption between CYP2D6 NMs, IMs and PMs by genotyping	Candiotti, *et al.* 2009 (134)	Moderate
Clinical	Increased morphine-6-glucuronide concentrations as a result of morphine administration in PM subject by drug metabolism assay compared to NMs	Heiskanen, *et al.* 2000 (135)	Weak
Opioids			
Clinical	Adverse events, including nausea and vomiting, observed in a subject with the *CYP2D6*4/*4* genotype (hydrocodone, hydromorphone, morphine, oxycodone)	Foster, *et al.* 2007 (63)	Weak
Clinical	*CYP2D6* NMs and IMs by genotyping are associated with increased analgesia from opioids to treat postoperative pain (morphine, tramadol)	Seripa, *et al.* 2015 (136)	Weak

Clinical	PGx-guided prescription of opioids using a multi-gene panel results in improved analgesia and decreased dose requirements as compared to current standard of prescribing (unspecified opioids)	Senagore, *et al.* 2017 (137) Fulton, *et al.* 2019 (138)	Weak
Clinical	Opioid consumption increases as CYP2D6 activity score increases	Rocco, *et al.* 2019 (139)	Weak
Clinical	No statistical differences of opioid dose requirements between CYP2D6 PM and non-PM phenotypes (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, (R)-methadone, morphine, oxycodone, piritramide, tilidine, tramadol)	Lötsch, *et al.* 2009 (29)	Weak
Clinical	No statistical differences of severity of neonatal abstinence syndrome between *CYP2D6*6* alleles and *CYP2D6*1* (unspecified opioids)	Mactier, *et al.* 2017 (140)	Weak
Clinical	No statistical differences of severity of neonatal abstinence syndrome between the number of functional *CYP2D6* alleles (unspecified opioids)	Mactier, *et al.* 2017 (140)	Moderate
Clinical	No statistical differences of the risk of developing opioid dependence between *CYP2D6* rs1065852 carriers and non-carriers (unspecified opioids)	Christoffersen, *et al.* 2016 (141)	Weak
Clinical	No statistical differences of opioid-induced adverse events between CYP2D6 PM and non-PM phenotypes (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, (R)-methadone, morphine, oxycodone, piritramid, tilidine, tramadol)	Lötsch, *et al.* 2009 (29)	Moderate
Clinical	*CYP2D6 *2/*2* genotype is not associated with opioid-induced respiratory depression (fentanyl, hydromorphone, morphine)	Madadi, *et al.* 2013 (142)	Weak
Oxycodone			
Clinical	CYP2D6 PMs by drug metabolism assay have greater pain intensity and require more escape analgesia when treated with oxycodone than when treated with morphine	Heiskanen, *et al.* 2000 (135)	Weak

Clinical	Oxycodone has an analgesic effect in subjects with *CYP2D6* NM (AS = 1.0-2.0) or PM (AS = 0-1.0) genotypes or phenotypes by drug metabolism assay	Zwisler, *et al.* 2009 (143)	High
Clinical	CYP2D6 UM (AS = 1.5-≥3) phenotype by genotyping or drug metabolism assay is associated with increased analgesic effects of oxycodone as compared to NMs (AS = 1.0-2.0)	Samer, *et al.* 2010 (144)	Moderate
Clinical	*CYP2D6* PM (AS = 0-1.0) genotype is associated with decreased analgesic effects of oxycodone as compared to NMs (AS = 1.0-2.0)	Susce, *et al.* 2006 (106) Zwisler, *et al.* 2009 (143) Samer, *et al.* 2010 (144)	Moderate
Clinical	CYP2D6 PM (AS = 0-1.0) phenotype by genotyping is associated with decreased analgesic effects of oxycodone as compared to NMs (AS = 1.0-2.0)	Zwisler, *et al.* 2009 (143) Samer, *et al.* 2010 (144)	Moderate
Clinical	No statistical differences of opioid-induced adverse events between *CYP2D6* genotypes (PM = 0, NM = 1.0-2.0, UM ≥3)	Andreassen, *et al.* 2012 (145)	Moderate
Clinical	No statistical differences of oxycodone consumption in *CYP2D6* PM (AS = 0-1.0) genotypes as compared to NM (AS = 1.0-2.0) genotypes	Zwisler, 2010, *et al.* 2010 (146) Naito, *et al.* 2011 (147)	High
Clinical	*CYP2D6* PM (AS = 0) genotype is associated with increased oxycodone consumption to treat postoperative pain as compared to other phenotypes (IM = 0.5-1.0, NM = 1.5-2.0, UM ≥3)	Stamer, *et al.* 2013 (148)	Weak
Clinical	CYP2D6 PMs by genotyping or drug metabolism assay are associated with reduced likelihood of developing opioid dependence	Tyndale, *et al.* 1997 (72)	Moderate
Clinical	CYP2D6 PMs by drug metabolism assay are associated with increased exposure to oxycodone and noroxycodone as compared to NMs	Heiskanen, *et al.* 2000 (135) Samer, *et al.* 2010 (149)	Weak

Clinical	*CYP2D6* PM (AS = 0-1.0) genotypes are associated with decreased exposure to oxymorphone as compared to the NM phenotype (AS = 1.0-2.0)	Zwisler, *et al.* 2009 (143) Zwisler, *et al.* 2010 (146) Samer, *et al.* 2010 (149) Stamer, *et al.* 2013 (148) Andreassen, *et al.* 2012 (145) Balyan, *et al.* 2017 (150)	High
Clinical	*CYP2D6* PM (AS = 0) genotypes are associated with decreased exposure to noroxymorphone as compared to the NM (AS = 1.0-2.0) phenotype	Samer, *et al.* 2010 (149) Stamer, *et al.* 2013 (148) Andreassen, *et al.* 2012 (145)	High
Clinical	CYP2D6 PMs by drug metabolism assay are associated with decreased exposure to oxymorphone and noroxymorphone as compared to the NM phenotype	Zwisler, *et al.* 2009 (143) Samer, *et al.* 2010 (149)	High
Clinical	No statistical differences of oxycodone concentrations between *CYP2D6* genotypes (PM = 0-0.5, IM = 0.25-1.0, NM = 1.0-2.0, UM = ≥3)	Zwisler, *et al.* 2010 (146) Naito, *et al.* 2011 (147) Andreassen, *et al.* 2012 (145) Balyan, *et al.* 2017 (150)	High
Clinical	*CYP2D6* UM genotypes are associated with increased formation of oxymorphone from oxycodone	Gronlund, *et al.* 2010 (151) Liukas, *et al.* 2011 (152) Stamer, *et al.* 2013 (148)	Weak
Clinical	*CYP2D6* UM genotypes are associated with decreased AUC of oxycodone	Gronlund, *et al.* 2010 (151)	Weak
Clinical	*CYP2D6* UM genotypes are associated with decreased formation of noroxycodone from oxycodone	Gronlund, *et al.* 2010 (151) Samer, *et al.* 2010 (149)	Weak
Clinical	CYP2D6 UMs by drug metabolism assay are associated with decreased formation of noroxycodone from oxycodone	Samer, *et al.* 2010 (149)	Weak
Clinical	CYP2D6 UM (AS ≥3) phenotype by genotyping or drug metabolism assay is associated with an increase in Cmax of noroxymorphone and a decreased half-life of noroxymorphone as compared to the NM (AS = 1.0-2.0) phenotype	Samer, *et al.* 2010 (149)	Weak

Clinical	No statistical differences of noroxycodone concentrations between *CYP2D6* genotypes (PM = 0, IM = 0.5-1.0, NM = 1.0-2.0, UM ≥3).	Samer, *et al.* 2010 (149) Naito, *et al.* 2011 (147) Andreassen, *et al.* 2012 (145)	Moderate
Clinical	No statistical differences of noroxycodone concentrations between CYP2D6 phenotypes by drug metabolism assay.	Samer, *et al.* 2010 (149)	Moderate
Clinical	*CYP2D6* genotype is not associated with noroxymorphone concentrations	Stamer, *et al.* 2013 (148)	High
Clinical	*CYP2D6* IM (AS = 0.25-1.0) genotypes are associated with reduced formation of oxymorphone from oxycodone compared to NMs (AS = 1.0-2.0)	Naito, *et al.* 2011 (147) Balyan, *et al.* 2017 (150)	High
Clinical	Dysphoria in a patient with the *CYP2D6*1/*2xN* genotype following administration of oxycodone	de Leon, *et al.* 2003 (120)	Weak
Clinical	The *CYP2D6*4/*4* and **4/*6* genotypes are associated with nausea and vomiting following oxycodone administration	Susce, *et al.* 2006 (106) Foster, *et al.* 2007 (63)	Weak
Clinical	No statistical differences of incidence of adverse effects, including death, following oxycodone administration between *CYP2D6* genotypes (PM = 0-1.0 IM = 1.0, NM = 1.0-2.0).	Jannetto, *et al.* 2002 (153) Zwisler, *et al.* 2009 (143) Andreassen, *et al.* 2012 (145) Slanar, *et al.* 2012 (154)	Moderate
Clinical	No statistical differences of incidence of adverse effects, including death, following oxycodone administration between CYP2D6 NMs and PMs by drug metabolism assay.	Zwisler, *et al.* 2009 (143)	Moderate
Clinical	Increased CYP2D6 activity is associated with increased incidence of sedation, respiratory depression and psychomotor effects resulting from oxycodone administration	Samer, *et al.* 2010 (144)	Weak
Clinical	Maternal *CYP2D6* genotype is not associated with incidence of oxycodone-induced CNS depression in breastfed infants	Karthikeyan, *et al.* 2014 (155)	Weak
Tramadol			

In vitro	*CYP2D6*10* and **17* alleles are associated with decreased Vmax leading to a decreased intrinsic clearance of tramadol compared to **1*	Shen, *et al.* 2007 (55)	Moderate
Clinical	Decreased analgesia in CYP2D6 PMs by drug metabolism assay compared to IMs, NMs and UMs as a result of tramadol treatment	Poulsen, *et al.* 1996 (39) Enggaard, *et al.* 2006 (156)	Moderate
Clinical	Decreased analgesia in CYP2D6 PMs (AS = 0) by genotyping compared to IMs (AS = 0.5-2.0), NMs (AS = 2.0) and UMs (AS ≥3) as a result of tramadol treatment	Susce, *et al.* 2006 (106) Stamer, *et al.* 2007 (157)	Moderate
Clinical	*CYP2D6* PM (AS = 0) genotypes are more likely to require rescue analgesia for postoperative pain when treated with tramadol compared to IM (AS = 0.5-2.0), NM (AS = 2.0) and UM (AS ≥3) genotypes	Stamer, *et al.* 2003 (158) Stamer, *et al.* 2007 (157)	High
Clinical	No statistical differences of analgesia following tramadol treatment between CYP2D6 phenotypes by drug metabolism assay.	Wilder-Smith, *et al.* 2005 (159)	Weak
Clinical	No statistical differences of analgesia following tramadol treatment between CYP2D6 phenotypes by genotyping (PM = 0, NM = 1.0-2.0, UM = 2.0-≥3).	Kirchheiner, *et al.* 2008 (160)	Weak
Clinical	*CYP2D6* PM genotypes are associated with an increased analgesic effect of tramadol in treating postoperative pain as compared to other *CYP2D6* genotypes	Slanar, *et al.* 2012 (154)	Weak
Clinical	*CYP2D6* UM genotypes are associated with a decreased analgesic effect of tramadol in treating postoperative pain as compared to other *CYP2D6* genotypes	Slanar, *et al.* 2012 (154)	Weak
Clinical	*CYP2D6* genotype is not associated with the need for rescue analgesia in tramadol treatment of postoperative pain	Slanar, *et al.* 2012 (154)	Weak
Clinical	*CYP2D6*2* allele is not associated with response to tramadol	Nasare, *et al.* 2016 (161)	Weak
Clinical	Presence of the *CYP2D6*10* allele associated with lack of response to tramadol for postoperative pain	Zhao, *et al.* 2014 (162)	Weak

Clinical	*CYP2D6*10/*10* genotype is associated with decreased analgesic effect of tramadol for postoperative pain as compared to **1/*1*	Dong, *et al.* 2015 (163)	Weak
Clinical	*CYP2D6*10/*10* genotype is not associated with analgesic effect of tramadol for postoperative pain	Dong, *et al.* 2015 (163)	Weak
Clinical	*CYP2D6*-guided prescribing of tramadol results in improved analgesia and is beneficial to CYP2D6 IMs (AS = 0.5) and PMs (AS = 0) by genotype plus use of CYP2D6 inhibitors as compared to standard prescribing	Smith, *et al.* 2019 (69)	Moderate
Clinical	*CYP2D6*-guided prescribing of tramadol in CYP2D6 NMs (AS = 1.0-2.0) by genotyping plus use of CYP2D6 inhibitors does not result in a difference in analgesia as compared to standard prescribing	Smith, *et al.* 2019 (69)	Moderate
Clinical	The *CYP2D6 *5/*17* genotype observed in patient with lack of response to tramadol in patients taking a concomitant CYP2D6 inhibitor	Tillman, *et al*. 2019 (117)	Weak
Clinical	*CYP2D6* PMs by genotyping require increased tramadol doses compared to NMs	Stamer, *et al.* 2003 (158)	Moderate
Clinical	CYP2D6 PM phenotypes by drug metabolism assay associated with decreased doses of tramadol compared to genotypes containing functional *CYP2D6* alleles	Wilder-Smith, *et al.* 2005 (159)	Weak
Clinical	No statistical difference in dose between CYP2D6 PM and non-PM phenotypes.	Lötsch, *et al.* 2009 (29)	Weak
Clinical	Tramadol consumption is significantly increased in postoperative patients with the **10/*10* genotype compared to **1/*1* and **1/*10*	Wang, *et al.* 2006 (164) Dong, *et al.* 2015 (163)	Moderate
Clinical	No statistical differences of analgesia and tramadol dose requirements following tramadol treatment between CYP2D6 phenotypes by drug metabolism assay	Halling, *et al.* 2008 (165)	Weak

Clinical	No statistical differences of tramadol dose requirements between *CYP2D6* genotypes.	Slanar, *et al.* 2012 (154)	Weak
Clinical	*CYP2D6*1/*10* genotype is not associated with consumption of tramadol for postoperative pain	Dong, *et al.* 2015 (163)	Moderate
Clinical	CYP2D6 IM and PM phenotypes by drug metabolism assay are associated with increased exposure to tramadol and decreased formation of O-desmethyltramadol from tramadol as compared to NMs	Poulsen, *et al.* 1996 (39) Paar, *et al.* 1997 (166) Abdel-Rahman, *et al* 2002 (167) Pedersen, *et al.* 2005 (168) Enggaard, *et al.* 2006 (156) Garcia-Quetglas, *et al.* 2007 (169) Halling, *et al.* 2008 (165)	Moderate
Clinical	CYP2D6 IM (AS = 1.0) and PM (AS = 0) phenotypes by genotyping are associated with increased exposure to tramadol and decreased formation of O-desmethyltramadol from tramadol as compared to NMs (AS = 1.0-2.0)	Paar, *et al.* 1997 (166) Abdel-Rahman, *et al.* 2002 (167) Levo, *et al.* 2003 (170) Borlak, *et al.* 2003 (171) Fliegert, *et al.* 2005 (172) Pedersen, *et al.* 2005 (168) Slanar, *et al.* 2007 (173) Pedersen, *et al.* 2006 (174) Stamer, *et al.* 2007 (157) Ojanpera, *et al.* 2007 (175) Kirchheiner, *et al.* 2008 (160) Allegaert, *et al.* 2008 (176) Halling, *et al.* 2008 (165) Bastami, *et al.* 2014 (177) Lane, *et al.* 2014 (178) Haage, *et al.* 2018 (179) Tanaka, *et al.* 2018 (180)	High
Clinical	Increased AUC and half-life and decreased clearance of tramadol in **10/*10* compared to other NMs	Gan, *et al.* 2002 (181) Yu, *et al.* 2018 (182)	Weak
Clinical	*CYP2D6* IM (AS = 0.25-1.0) and PM (AS = 0) genotypes are associated with increased formation of N-desmethyltramadol from tramadol compared to NMs (AS = 1.0-2.0)	Levo, *et al.* 2003 (170) Haage, *et al.* 2018 (179) Tanaka, *et al.* 2018 (180)	High

Clinical	Earlier Tmax of tramadol in NMs (AS = 1.0-2.0) by genotyping compared to PMs (AS = 0)	Filegert, *et al.* 2005 (172)	Moderate
Clinical	No statistical difference of tramadol concentrations between CYP2D6 phenotype by drug metabolism assay.	Enggaard, *et al.* 2006 (156)	Moderate
Clinical	No statistical difference of tramadol concentration between *CYP2D6* genotypes (PM = 0, IM = 0.5-1.0 , NM = (1.0-2.0), UM = 2.0-≥3)	Kirchheiner, *et al.* 2008 (160) Bastami, *et al.* 2014 (177) Tanaka, *et al.* 2018 (180)	Moderate
Clinical	Delayed Tmax of O-desmethyltramadol in CYP2D6 IMs by genotyping compared to NMs	Slanar, *et al.* 2007 (173)	Weak
Clinical	No statistical difference in clearance and concentrations of tramadol in *CYP2D6* UM genotypes (AS = 2.0-≥3)	Stamer, *et al.* 2007 (157) Kirchheiner, *et al.* 2008 (160) Saarikoski, *et al.* 2015 (183)	Weak
Clinical	No effect of *CYP2D6* UM (AS ≥3), NM (AS = 2.0) or IM (AS = 0.25-1.0) genotypes on concentrations of O-desmethyltramadol	Stamer, *et al.* 2007 (157) Bastami, *et al.* 2014 (177)	Weak
Clinical	No statistical difference in renal clearance of tramadol between *CYP2D6* genotype (PM = 0 , NM = 0.5-2.0, UM =2.0-≥3)	Kirchheiner, *et al.* 2008 (160)	Weak
Clinical	Increased formation of O-desmethyltramadol from tramadol in subjects with *CYP2D6* UM (AS = 2.0-≥3) genotypes compared to NM genotypes (AS = 0.5-2.0).	Kirchheiner, *et al.* 2008 (160) Saarikoski, *et al.* 2015 (183) Matic, *et al.* 2016 (184) Arafa, *et al.* 2018 (185)	High
Clinical	Increased (S)-O-desmethyltramadol/(R)-O-desmethyltramadol ratio in PMs by genotyping compared to NMs	Pedersen, *et al.* 2006 (174) Halling, *et al.* 2008 (165)	Moderate
Clinical	Increased (S)-O-desmethyltramadol/(R)-O-desmethyltramadol ratio in PMs by drug metabolism assay compared to NMs	Garcia-Quetglas, *et al.* 2007 (169) Halling, *et al.* 2008 (165)	Moderate
Clinical	The *CYP2D6*1/*10* and **10/*10* genotypes are associated with reduced clearance of tramadol as compared to **1/*1*	Li, *et al.* 2010 (186)	High
Clinical	*CYP2D6* UM genotypes are associated with increased (R)-O-desmethyltramadol concentrations as compared to other genotypes	Rauers, *et al.* 2010 (187)	High

Clinical	*CYP2D6* PM genotypes are associated with increased N-desmethyltramadol/O-desmethyltramadol concentration ratios compared to other *CYP2D6* genotypes	Fonseca, *et al.* 2016 (188)	High
Clinical	*CYP2D6*10/*10* genotype associated with increased formation of N-desmethyltramadol from tramadol as compared to **1/*1* or other genotypes comprised of the **1* and/or **2* alleles	Yu, *et al.* 2018 (182)	Moderate
Clinical	No statistical difference between *CYP2D6*10/*10* genotype in Cmax or AUC of O-desmethyltramadol, O-desmethyltramadol-glucuronide or N,O-desmethyltramadol-glucuronide as compared to normal metabolizers.	Yu, *et al.* 2018 (182)	Weak
Clinical	*CYP2D6*5/*5* genotype associated with increased formation of N-desmethyltramadol from tramadol as compared to **1/*1*, **10/*10* or other genotypes comprised of the **1* and/or **2* alleles	Yu, *et al.* 2018 (182)	Weak
Clinical	*CYP2D6*5/*5* and **10/*10* genotypes are associated with decreased O-desmethyltramadol and N,O-desmethyltramadol concentrations as compared to genotypes comprised of the **1* and/or **2* alleles	Yu, *et al.* 2018 (189)	Weak
Clinical	*CYP2D6*5/*5* and **10/*10* genotypes are associated with decreased O-desmethyltramadol/tramadol ratio and N,O-desmethyltramadol/N-desmethyltramadol ratio as compared to genotypes comprised of the **1* and/or **2* alleles	Yu, *et al.* 2018 (182) Yu, *et al.* 2018 (189)	High
Clinical	*CYP2D6*4* or **10* alleles are associated with decreased excretion of O-desmethyltramadol as compared to **1/*1*	Arafa, *et al.* 2018 (185)	High
Clinical	CYP2D6 PM phenotype by genotyping is associated with decreased AUC of N,O-desmethyltramadol enantiomers as compared to NMs and IMs	Haage, *et al.* 2018 (179)	Moderate
Clinical	No statistical differences of concentrations of N,O-desmethyltramadol between *CYP2D6* genotypes.	Tanaka, *et al.* 2018 (180)	Weak

Clinical	*CYP2D6* IM and PM genotypes are associated with decreased N,O-desmethyltramadol/N-desmethyltramadol ratio and increased N,O-desmethyltramadol/O-desmethyltramadol ratios compared to NMs	Tanaka, *et al.* 2018 (180)	High
Clinical	Increased frequency of tramadol-induced adverse events, including respiratory depression, in UMs and NMs by drug metabolism assay compared to IMs or PMs	Poulsen, *et al.* 1996 (39) Garcia-Quetglas, *et al.* 2007 (169) Gleason, *et al.* 1997 (190)	Weak
Clinical	Increased frequency of tramadol-induced adverse events, including respiratory depression, in UMs (AS = 2.0-≥3)and NMs (AS = 1.0-2.0) by genotyping compared to IMs (AS = 0.5-1.0) or PMs AS = 0)	Kirchheiner, *et al.* 2008 (160) Stamer, *et al.* 2008 (191) Kim, *et al.* 2010 (192) Elkalioubie, *et al.* 2011 (193) Orliaguet, *et al.* 2015 (194)	Moderate
Clinical	No statistical differences of tramadol-induced side effects between CYP2D6 phenotype by drug metabolism assay.	Wilder-Smith, *et al.* 2005 (159)	Weak
Clinical	No statistical differences of tramadol-induced side effects between *CYP2D6* genotypes.	Bastami, *et al.* 2014 (177)	Weak
Clinical	No significant association between *CYP2D6*10* and incidence of adverse events following tramadol consumption in postoperative patients	Wang, *et al.* 2006 (164)	Weak
Clinical	*CYP2D6*2* allele is not associated with incidence of tramadol-induced adverse events	Nasare, *et al.* 2016 (161)	Weak
Clinical	*CYP2D6*4* or **10* alleles are associated with decreased severity of tramadol-induced hepatotoxicity as compared to **1* and duplicated *CYP2D6* alleles	Arafa, *et al.* 2018 (185)	Moderate

[a]See Level of Evidence section for definitions.

SUPPLEMENTAL TABLE S2. EVIDENCE LINKING *OPRM1* GENOTYPE WITH OPIOID RESPONSE

Type of experimental model (*in vitro*, *in vivo* preclinical, or clinical)	Major findings	References	Level of Evidence[a]
In vitro	The rs17174801 G allele is associated with decreased expression and increased maximal activation of the mu opioid receptor compared to the WT receptor	Befort, *et al.* 2001 (195)	Weak
In vitro	The rs376950705 A allele is associated with decreased mu opioid receptor signaling compared to the WT receptor	Befort, *et al.* 2001 (195)	Weak
In vitro	The rs200811844 C allele is associated with decreased mu opioid receptor signaling compared to the WT receptor	Befort, *et al.* 2001 (195) Wang, *et al.* 2001 (196) Fortin, *et al.* 2010 (197)	Weak
In vitro	The rs1799971 G allele is associated with reduced expression of the mu opioid receptor compared to the WT receptor	Beyer, *et al.* 2004 (198)	Moderate
In vitro	The rs1799971 G allele does not significantly alter mu opioid receptor desensitization, internalization or resensitization	Beyer, *et al.* 2004 (198)	Moderate
In vitro	No significant difference in protein expression of the mu opioid receptor based on the presence of the rs1799971 G allele	Deb, *et al.* 2010 (199)	Moderate
In vitro	The rs1799971 G allele is associated with increased PKA activity and decreased pERK1/2 levels in opioid signaling	Deb, *et al.* 2010 (199)	Weak
In vitro	The rs17174822 T and rs376950705 A alleles are independently associated with decreased mu opioid receptor signaling	Fortin, *et al.* 2010 (197)	Weak

In vitro	DAMGO and other endogenous mu opioid receptor agonists have a reduced potency at receptors carrying the rs9282819 T, rs1799974 A, rs17174822 T, rs376950705 A or rs200811844 C alleles	Fortin, *et al.* 2010 (197)	Weak
In vitro	The rs34074916 A allele is associated with absence of DAMGO binding to the mu opioid receptor	Fortin, *et al.* 2010 (197)	Weak
Alfentanil			
Clinical	Subjects with the rs1799971 GG genotype show decreased cerebral processing of the sensory intensity or pain	Oertel, *et al.* 2008 (200)	Moderate
Clinical	Patients carrying the rs1799971 G allele require higher plasma concentrations of alfentanil to achieve a 50% increase in analgesia compared to patients with the AA genotype	Oertel, *et al.* 2006 (201)	Moderate
Clinical	Patients with the rs1799971 AG or GG genotypes have increased alfentanil dose requirements compared to patients with the AA genotype	Oertel, *et al.* 2006(201) Ginosar, *et al.* 2009 (202)	Moderate
Clinical	Patients with the rs1799971 GG genotype can tolerate higher alfentanil concentrations before they reach a 50% increase in respiratory depression compared to AA and AG subjects.	Oertel, *et al.* 2006 (201)	Moderate
Clinical	No significant difference in alfentanil-induced side effects based on rs1799971 genotype	Ginosar, *et al.* 2009 (202)	Weak
Buprenorphine			
In vitro	Opioid signaling from buprenorphine is reduced in mu opioid receptors with the rs1799971 G allele	Knapman, *et al.* 2014 (203)	Moderate
Clinical	No significant difference in analgesic response to buprenorphine based on rs1799971 genotype	Blanco, *et al.* 2016 (204)	Weak
Clinical	No significant difference in response to buprenorphine for the treatment of opioid dependence based on rs10485058, rs671531, rs558948 or rs645027 genotypes	Crist, *et al.* 2018 (205)	Moderate
Carfentanil			

Clinical	Subjects with the rs1799971 AG genotype show reduced global binding potential of carfentanil in PET images compared to subjects with the AA genotype	Weerts, *et al.* 2013 (206)	Moderate
Codeine			
Clinical	Patients with the rs1799971 AG genotype have reduced codeine dose requirements compared to patients with the AA genotype	Baber, *et al.* 2015 (71)	Moderate
Clinical	No significant difference in plasma concentrations of codeine, morphine or the morphine/codeine ratio based on rs1799971 genotype	Lam, *et al.* 2014 (95)	Weak
Clinical	No significant difference in incidence of codeine-induced CNS depression based on rs1799971 or rs563649 genotypes	Sistonen, *et al.* 2012 (103)	Weak
Fentanyl			
In vitro	rs1799971 does not alter the clinical effect of fentanyl at mu opioid receptors	Knapman, *et al.* 2014 (203)	Moderate
Clinical	Patients with the rs1799971 AA genotype have an increased ED50 for fentanyl compared to patients carrying the G allele	Landau, *et al.* 2008 (207)	High
Clinical	Patients carrying the rs1799971 G allele have a reduced analgesic response to fentanyl compared to patients with the AA genotype	Fukuda, *et al.* 2009 (208) Wong, *et al.* 2010 (209) Landau, *et al.* 2013 (210) Ginosar, *et al.* 2013 (211)	Weak
Clinical	No significant difference in analgesic response to fentanyl based on rs9384179 genotype	Fukuda, *et al.* 2009 (208)	Moderate
Clinical	Patients with the rs1799971 GG genotype have increased fentanyl dose requirements compared to patients with the AA or AG genotypes	Zhang, *et al.* 2010 (212) Zhang, *et al.* 2011 (213) Zhang, *et al.* 2018 (214)	Moderate

Clinical	Patients carrying the rs1799971 G allele have increased fentanyl dose requirements compared to patients with the AA genotype	Sugino, *et al.* 2014 (215) Fukuda, *et al.* 2009 (208) Wong, *et al.* 2010 (209) Mamie, *et al.* 2013 (216) Liao, *et al.* 2013 (217) Kim, *et al.* 2013 (218) Barratt, *et al.* 2015 (219)	Weak
Clinical	Patients carrying the rs9384179 G allele have decreased fentanyl dose requirements compared to patients with the AA genotype	Fukuda, *et al.* 2009 (208)	Moderate
Clinical	Patients with the rs1799971 AA genotype and who carry the rs9384179 G allele have decreased fentanyl dose requirements compared to other SNP combinations	Fukuda, *et al.* 2009 (208)	Moderate
Clinical	No significant difference in fentanyl dose requirements based on rs510769, rs4870266, rs3798683, rs1323042, rs609623, rs9397685 or rs644261 genotypes or the haplotypes GGGAACAC (H14), AGGGACAC (H15), GGGAACGC (H16) or AGAGACAC (H17)	Sugino, *et al.* 2014 (215)	Weak
Clinical	No significant difference in fentanyl-induced side effect based on rs1799971 genotype (including gastric motility, nausea and vomiting, sedation and dizziness)	Wallden, *et al.* 2008 (220) Zhang, *et al.* 2010 (212) Wong, *et al.* 2010 (209) Zhang, *et al.* 2011 (213) Pang, *et al.* 2012 (221) Liao, *et al.* 2013 (217) Zhang, *et al.* 2010 (212) Zhang, *et al.* 2018 (214) Liao, *et al.* 2013 (217)	Weak
Clinical	Patients carrying the rs1799971 G allele have a reduced incidence of fentanyl-induced pruritus compared to patients with the AA genotype	Wong, *et al.* 2010 (209) Ginosar, *et al.* 2013 (211) Wong, *et al.* 2010 (209)	Weak
Clinical	rs2075572 is not associated with the effects of fentanyl on gastric motility	Wallden, *et al* 2008 (220)	Weak
Clinical	The rs540825 AT genotype is associated with increased likelihood of fentanyl-induced emesis	Pang, *et al.* 2012 (221)	Moderate

Clinical	rs1799971 is not associated with the hypotensive effect of fentanyl	Saiz-Rodriguez, *et al.* 2019 (222)	Weak
Clinical	The G allele of rs1799971 is associated with an increased risk of somnolence following administration of fentanyl	Saiz-Rodriguez, *et al.* 2019 (222)	Weak
Clinical	No significant difference in incidence of fentanyl-induced emesis based on rs12210856, rs12190259, rs12205732, rs6912029, rs563649, rs9322446, rs675016, rs562859, rs606545, rs17181352, rs671531, rs583664, rs658156, rs9371776, rs558948, rs558025, rs645027, rs598160, rs644261 or rs11575856 genotypes	Pang, *et al.* 2012 (221)	Weak
Clinical	Patients with the rs9397685 AG genotype have reduced severity of postoperative nausea and vomiting linked to fentanyl	Sugino, *et al.* 2014 (215)	Weak
Clinical	No significant difference in incidence of postoperative nausea and vomiting linked to fentanyl based on the *OPRM1* haplotypes GGGAACAC (H14), AGGGACAC (H15) or AGAGACAC (H17)	Sugino, *et al.* 2014 (215)	Weak
Clinical	Patients carrying the *OPRM1* haplotype GGGAACGC (H16) have a reduced incidence of postoperative nausea and vomiting linked to fentanyl	Sugino, *et al.* 2014 (215)	Weak
Hydrocodone			
Clinical	Patients with the rs1799971 AA genotype exhibit an analgesic response which correlates to hydrocodone dose. This correlation is lost in patients with the AG or GG genotypes	Boswell, *et al.* 2013 (223)	Weak
Clinical	No significant difference in hydrocodone dosage requirements based on rs1799971 genotype	Boswell, *et al.* 2013 (223)	Weak
Clinical	No significant difference in plasma concentrations of hydrocodone or hydromorphone based on rs1799971 genotype	Boswell, *et al.* 2013 (223)	Weak
Clinical	Patients with the rs1799971 AG or GG genotypes have an increased incidence of hydrocodone-induced side effects compared to patients with the AA genotype	Boswell, *et al.* 2013 (223)	Weak

Hydromorphone			
Clinical	Patients carrying the rs1799971 G allele have reduced satisfaction with their analgesia compared to patients with the AA genotype	Xia, *et al.* 2015 (224)	Weak
Clinical	rs1799971 is not associated with hydromorphone-induced side effects	Xia, *et al.* 2015 (224)	Weak
Levomethadone			
Preclinical	Levomethadone has a reduced potency (as measured by miotic effects) in subjects carrying the rs1799971 G allele than in subjects with the AA genotype.	Lötsch, *et al.* 2006 (127)	Moderate
Clinical	rs1799971 is not associated with incidence of levomethadone-induced vomiting	Lötsch, *et al.* 2006 (127)	Weak
Methadone			
In vitro	The clinical effect of methadone at mu opioid receptors is not significantly altered by the presence of the rs1799971 G allele	Knapman, *et al.* 2014 (203)	Weak
Clinical	rs1799971, in combination with variants in other genes, is associated with maximum dose of methadone	Hung, *et al.* 2011 (225)	Weak
Clinical	The rs1799971 G allele is associated with increased methadone dose requirements in methadone maintenance therapy	Wang, *et al.* 2012 (226) Moult, *et al.* 2015 (125)	Weak
Clinical	The rs2075572 C allele is associated with increased methadone dose requirements in methadone maintenance therapy	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in methadone dosage requirements in methadone maintenance therapy based rs499796, rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3378152, rs563649 or rs553202 genotypes	Wang, *et al.* 2012 (226)	Weak
Clinical	Patients with the rs558025 AG or GG genotypes have decreased methadone dose requirements in methadone maintenance therapy compared to patients with the AA genotype	Levran, *et al.* 2013 (227)	Weak

Clinical	Patients carrying the C allele of rs73568641 require a higher daily methadone dose for methadone maintenance treatment compared to patients with the TT genotype	Smith, *et al.* 2017 (228)	Moderate
Clinical	Patients carrying the rs10485058 G allele have a reduced response to methadone maintenance treatment for opioid dependence (measured by number of opioid-positive urine screens)	Crist, *et al.* 2018 (205)	Weak
Clinical	No significant difference in response to methadone maintenance treatment of opioid dependence based on rs671531, rs558948 or rs645027 genotype	Crist, *et al.* 2018 (205)	Weak
Clinical	rs1799971 is not associated with postmortem methadone plasma concentrations	Bunten, *et al.* 2010 (229)	Weak
Clinical	No significant difference in plasma concentrations of methadone or its metabolites based on rs1799971, rs2075572, rs499796, rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3378152, rs563649 or rs553202 genotypes	Wang, *et al.* 2012 (226)	Weak
Clinical	Patients carrying the rs1799971 G allele have a reduced incidence of methadone toxicity	Bunten, *et al.* 2011 (230)	Weak
Clinical	Patients carrying the rs499796 C allele have more severe changes in libido after commencing methadone maintenance treatment compared to patients with the TT genotype	Wang, *et al.* 2012 (226)	Weak
Clinical	rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3378152, rs563649 and rs2075572 are associated with changes in in libido after commencing methadone maintenance treatment	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in libido after commencing methadone maintenance treatment based on rs1799971 or rs553202 genotypes	Wang, *et al.* 2012 (226)	Weak
Clinical	rs499796 is not associated with onset of insomnia or severity of insomnia after commencing methadone maintenance treatment compared to patients with the TT genotype	Wang, *et al.* 2012 (226)	Weak

Clinical	rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3378152, rs563649 and rs2075572 are associated with onset of insomnia after commencing methadone maintenance treatment	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in onset of insomnia or severity of insomnia after commencing methadone maintenance treatment based on rs1799971 or rs553202 genotype	Wang, *et al.* 2012 (226)	Weak
Clinical	The rs1074287 AA, rs6912029 GG, rs12209447 CC, rs510769 GG, rs3798676 CC, rs7748401 TT, rs495491 TT, rs10457090 AA, rs589046 GG, rs3378152 AA or rs563649 GG genotypes are associated with increased severity of insomnia after commencing methadone maintenance treatment	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in severity of insomnia after commencing methadone maintenance treatment based on rs2075572 genotype	Wang, *et al.* 2012 (226)	Weak
Clinical	Patients with the rs1799971 AA genotype have increased fatigue after commencing methadone maintenance therapy compared to patients carrying the G allele	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in methadone-induced fatigue or withdrawal symptoms in methadone maintenance therapy based on rs2075572, rs499796, rs1074287, rs6912029, rs12209447, rs510769, rs3798676, rs7748401, rs495491, rs10457090, rs589046, rs3378152, rs563649 or rs553202 genotype	Wang, *et al.* 2012 (226)	Weak
Clinical	rs1799971 is not associated with withdrawal symptoms in methadone maintenance therapy	Wang, *et al.* 2012 (226)	Weak
Clinical	No significant difference in the number of suicide attempts made by patients undergoing methadone maintenance therapy based on rs1799971 genotype	Icick, *et al.* 2014 (231)	Weak
Clinical	No significant difference in the need to switch to alternative opioids due to inadequate analgesia or unacceptable side effects from morphine based on rs1799971 genotype	Ross, *et al.* 2005 (232)	Weak
Morphine			

In vitro	The rs1799974 A, rs376950705 A and rs200811844 C allele are independently associated with decreased maximal stimulation of the mu opioid receptor by morphine compared to the WT receptor	Wang, *et al.* 2001 (196)	Moderate
In vitro	The rs1799974 A allele does not alter mu opioid receptor desensitization following morphine pretreatment compared to the WT receptor	Wang, *et al.* 2001 (196)	Moderate
In vitro	The rs376950705 A and rs200811844 C alleles are independently associated with decreased desensitization of the mu opioid receptor following morphine pretreatment compared to the WT receptor	Wang, *et al.* 2001 (196)	Moderate
Preclinical	Morphine-6-glucuronide has a reduced potency in subjects carrying the rs1799971 G allele compared to subjects with the AA genotype (determined by changes in pupil size)	Lötsch, *et al.* 2002 (233) Skarke, *et al.* 2003 (234)	Weak
Preclinical	Morphine has a reduced potency in subjects carrying the rs1799971 G allele compared to subjects with the AA genotype (determined by changes in pupil size)	Lötsch, *et al.* 2002 (233) Skarke, *et al.* 2003 (234)	Weak
In vitro	No significant difference in the binding affinity of morphine or morphine-6-glucuronide to the mu opioid receptor based on the presence of the rs1799971 G allele.	Beyer, *et al.* 2004 (198)	Moderate
In vitro	No significant difference in the clinical effect of morphine at mu opioid receptors based on the presence of the rs1799971 G allele	Knapman, *et al.* 2014 (203)	Moderate
Clinical	Patients carrying the rs1799971 G allele have a reduced analgesic response to morphine (including an increased need for rescue analgesia) compared to patients with the AA genotype	Hirota, *et al.* 2003 (235) Campa, *et al.* 2008 (236) Matic, *et al.* 2014 (237) Lee, *et al.* 2016 (238) Skarke, *et al.* 2003 (234) Nielsen, *et al.* 2017 (239)	Weak
Clinical	No significant difference in the need to switch to alternative opioids due to inadequate analgesia or unacceptable side effects from morphine based on rs6912029, rs579316, rs589046, rs9479757, rs2075572 or rs583664 genotypes or the haplotypes TACCGGT (H1), TACCGCC (H2), TGCCGGT (H3), TATTACT (H4), TATTGGT (H5), GACTGCT (H6)	Ross, *et al.* 2005 (232)	Weak

Clinical	Patients carrying the rs9479757 A allele have reduced morphine analgesia to rectal thermal stimulation	Nielsen, *et al.* 2017 (239)	Moderate
Clinical	No significant difference in analgesic response to morphine based on rs9479757, rs589046, rs563649 or rs533586 genotypes	Nielsen, *et al.* 2017 (239)	Weak
Clinical	Patients with the rs1799971 GG genotype have increased morphine dose requirements compared to patients with the AA or AG genotypes	Klepstad, *et al.* 2004 (240) Chou, *et al.* 2006 (241) Sia, *et al.* 2013 (242) Somogyi, *et al.* 2016 (243) Chou, *et al.* 2006 (244) Bastami, *et al.* 2014 (245)	Moderate
Clinical	Patients carrying the rs1799971 G allele have increased morphine dose requirements compared to patients with the AA genotype	Coulbault, *et al.* 2006 (246) Sia, *et al.* 2008 (247) Tan, *et al.* 2009 (248) Oliveira, *et al.* 2014 (249) Matic, *et al.* 2014 (237) Hajj, *et al.* 2015 (250) De Gregori, *et al.* 2016 (251) Hajj, *et al.* 2017 (252) Li, *et al*. *2019 (253)*	Moderate
Clinical	Patients carrying the rs1799971 G allele have decreased morphine dose requirements compared to patients with the AA genotype	Kolesnikov, *et al.* 2011 (254)	Weak
Clinical	No significant difference in morphine dose requirements based on rs1799971 genotype	Chou, *et al.* 2006 (244) Huehne, *et al.* 2009 (255) Matsuoka, *et al.* 2012 (256) Mamie, *et al.* 2013 (216) De Gregori, *et al.* 2013 (257) Chidambaran, *et al.* 2015 (258)	Weak
Clinical	Patients with the rs6912029 TT genotype have increased morphine dose requirements	Tan, *et al.* 2009 (248)	Weak

Clinical	No significant difference in morphine dose requirements based on rs6912029, rs9479757 or rs2075572 genotypes	Klepstad, *et al.* 2004 (240)	Moderate
Clinical	No significant difference in morphine dose requirements based on rs7776341, rs563649, rs1319339, rs2075572, rs540825 or rs677830 genotypes	De Gregori, *et al.* 2016 (251)	Weak
Clinical	Patients carrying the rs73568641 C allele have increased morphine dose requirements compared to patients with the TT genotype	Smith, *et al.* 2017 (228)	Weak
Clinical	*OPRM1* haplotype TAGCCTG (H19) is associated with increased morphine dose requirements	De Gregori, *et al.* 2016 (251)	Moderate
Clinical	*OPRM1* haplotype CAACTAA (H22) is associated with decreased morphine dose requirements	De Gregori, *et al.* 2016 (251)	Moderate
Clinical	No significant difference in morphine dose requirements based on the haplotypes TAACCTG (H18), TAACTAA (H20) or TAACTTG (H21)	De Gregori, *et al.* 2016 (251)	Moderate
Clinical	No significant difference in plasma concentrations of morphine, morphine-6-glucuronide or morphine-3-glucuronide based on rs6912029, rs9479757 or rs2075572 genotypes	Klepstad, *et al.* 2004 (240)	Moderate
Clinical	Patients with the rs1799971 AG or GG genotype have increased plasma concentrations of morphine, morphine-6-glucuronide or morphine-3-glucuronide compared to patients with the AA genotype	Klepstad, *et al.* 2004 (240) Bastami, *et al.* 2014 (245)	Weak
Clinical	No significant difference in plasma concentrations of morphine based on rs1799971 genotype	Matsuoka, *et al.* 2012 (256)	Moderate
Clinical	Patients with the rs1799971 AA genotype are more likely to experience morphine-6-glucuronide toxicity following morphine treatment than patients with the GG genotype	Lötsch, *et al.* 2002 (259)	Weak

Clinical	No significant difference in the incidence of morphine-induced side effects based on rs1799971 genotype (including nausea and vomiting and pruritus)	Coulbault, *et al.* 2006 (246) Sia, *et al.* 2013 (242) Sia, *et al.* 2008 (247) Chou, *et al.* 2006 (241) Fujita, *et al.* 2010 (260) Jimenez, *et al.* 2012 (261) Sia, *et al.* 2008 (247) Tan, *et al.* 2009 (248) Sia, *et al.* 2013 (242)	Weak
Clinical	Patients with the rs1799971 AA genotype are more likely to experience morphine-induced nausea and/or vomiting than patients carrying the G allele	Sia, *et al.* 2008 (247) Tan, *et al.* 2009 (248) Kolesnikov, *et al.* 2011 (254) Somogyi, *et al.* 2016 (243)	Weak
Clinical	Patients with the rs1799971 GG genotype have a decreased severity of morphine-induced pruritus compared to patients with the AA or AG genotypes	Tsai, *et al.* 2010 (262)	Moderate
Clinical	Patients carrying the rs1799971 G allele have decreased severity of morphine-induced sedation compared to patients with the AA genotype	Kolesnikov, *et al.* 2011 (254)	Weak
Clinical	Patients with the rs1799971 AA genotype are at an increased risk of developing morphine-induced respiratory depression	Chidambaran, *et al.* 2015 (258)	Weak
Clinical	rs6912029 is not associated with morphine-induced nausea, vomiting or pruritus	Tan, *et al.* 2009 (248)	Moderate
Clinical	rs1799972 is not associated with incidence of morphine-induced side effects	Jimenez, *et al.* 2012 (261)	Weak
Clinical	Patients with the rs1799971 AG genotype and sleep apnea spend less time asleep with oxygen saturation <90% when treated with morphine compared to patients with the AA genotype	Rowsell, *et al.* 2019 (263)	Weak
Clinical	Patients with the rs1799971 AG genotype may have a reduced analgesic response to morphine-6-glucuronide	Romberg, *et al.* 2005 (264)	Weak

Clinical	No significant difference in severity of respiratory depression induced by morphine-6-glucuronide based on rs1799971 genotype	Romberg, *et al.* 2005 (264)	Weak
Naloxone			
In vitro	Cells which have been pretreated with morphine and that carry the rs1799971 G allele are unaffected by naloxone treatment. Morphine-pretreated cells with the AA genotype show decreased opioid signaling when treated with naloxone	Deb, *et al.* 2010 (199)	Weak
Preclinical	No significant difference in ACTH response to naloxone based on rs1799971 genotype	Hernandez-Avila, *et al.* 2003 (265) Chong, *et al.* 2006 (266) Hernandez-Avila, *et al.* 2007 (267)	Moderate
Preclinical	Subjects with the rs2075572 CC genotype have a reduced ACTH response to naloxone compared to subjects carrying the G allele.	Hernandez-Avila, *et al.* 2007 (267)	Weak
Preclinical	No significant difference in ACTH response to naloxone based on rs495491, rs3798683, rs609148 or rs648893 genotypes	Hernandez-Avila, *et al.* 2007 (267)	Weak
Preclinical	Subjects carrying the rs1799971 G allele have an increased and prolonged cortisol response to naloxone compared to subjects with the AA genotype	Chong, *et al.* 2006 (266) Hernandez-Avila, *et al.* 2003 (265)	Moderate
Preclinical	No significant difference in cortisol response to naloxone based on rs1799971, rs495491, rs2075572, rs3798683, rs609148 or rs648893 genotypes	Hernandez-Avila, *et al.* 2007 (267)	Weak
Naltrexone			
Preclinical	Subjects with the rs1799971 AG genotype show increased naltrexone occupancy of mu opioid receptors compared to subjects with the AA genotype	Weerts, *et al.* 2013 (206)	Weak
Clinical	Subjects carrying the rs1799971 G allele show reduced brain activation upon naltrexone treatment compared to patients with the AA genotype	Schacht, *et al.* 2013 (268)	Weak
Clinical	No significant difference in response to naltrexone in treating spasticity associated with multiple sclerosis based on rs1799971 genotype	Gironi, *et al.* 2008 (269)	Weak

Clinical	Patients carrying the rs1799971 G allele have an increased incidence of naltrexone-induced side effects	Setiawan, *et al.* 2011 (270) Coller, *et al.* 2011 (271)	Weak
Clinical	The rs1799971 genotype is not associated with degree of brain activation in response to alcohol taste cues in patients treated with naltrexone.	Lim, *et al*. 2019 (272)	Weak
Clinical	Patients carrying the rs1799971 G allele have an increased incidence of naltrexone-induced side effects	Setiawan, *et al.* (270) Coller, *et al.* (271)	Weak
Clinical	Patients carrying the rs1799971 G allele have increased sedation following naltrexone treatment compared to patients with the AA genotype	Ray, *et al.* 2012 (273)	Weak
Clinical	rs1799971, rs10485057, rs1294092, rs1381376, rs2075572, rs3823010, rs495491, rs511435, rs524731, rs548646, rs609148, rs648893, rs9322447 or rs9479757 genotypes are not associated with nicotine quit rate or secondary outcomes of smoking cessation	Roche, *et al.* 2019 (274)	Weak
Opioids			
In vitro	No significant difference in morphine or heroin binding to the mu opioid receptor compared to the WT receptor based on the presence of the rs1799971 G, rs17174801 G, rs376950705 A or rs200811844 C alleles.	Befort, *et al.* 2001 (195)	Weak
In vitro	No significant difference in mu opioid receptor internalization following stimulation with morphine based on the presence of the rs79220505 C allele	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	The rs76773039 A allele is associated with increased internalization of the mu opioid receptor following stimulation with morphine	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	No significant difference in morphine potency at the mu opioid receptor based on the presence of the rs76773039 A allele	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	The rs79910351 T allele is associated with an absence of mu opioid receptor internalization following stimulation with morphine or DAMGO	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	rs76773039 A allele is associated with decreased receptor tolerance and dependence on morphine	Ravindranathan, *et al.* 2009 (275)	Weak

In vitro	No significant difference in mu opioid receptor internalization based on the presence of the variants rs1799972, rs76546679, rs17174794 or rs62638690	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	*MOR1A* splice variant - the rs76546679 A and rs62638690 T alleles are independently associated with reduced morphine potency at the mu opioid receptor	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	*MOR1A* splice variant - no significant difference in the potency of morphine at the mu opioid receptor based on the presence of the variants rs1799972 or rs17174794	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	*MOR1A* splice variant - the rs17174794 G allele is associated with increased clinical effect of morphine at the mu opioid receptor compared to the WT allele	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	*MOR1A* splice variant - no significant difference in morphine clinical effect in receptors carrying the rs1799971, rs76546679 or rs17174794 variants compared to the WT receptor	Ravindranathan, *et al.* 2009 (275)	Weak
In vitro	Treatment of mu opioid receptors with the rs34074916 A allele with naltrexone, naloxone or buprenorphine is associated with an increase in receptor expression, while a corresponding increase is not seen with the WT receptor	Fortin, *et al.* 2010 (197)	Weak
Clinical	Patients carrying the rs1799971 G allele and with 'anger-out' characteristics have a reduced analgesic response to opioids compared to patients with the AA genotype and 'anger-out' characteristics	Bruehl, *et al.* 2006 (276)	Weak
Clinical	Patients with the rs79910351 CT genotype do not have an analgesic response to opioids (remifentanil, fentanyl, morphine, oxycodone, hydromorphone, methadone)	Skorpen, *et al.* 2016 (277)	Weak
Clinical	No significant difference in opioid dose requirements based on rs1799971 genotype (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, meperidine, (R)-methadone, morphine, oxycodone, piritramide, tilidine, tramadol and unspecified opioids)	Janicki, *et al.* 2006 (278) Lötsch, *et al.* 2009 (29) Naito, *et al.* 2011 (147) Klepstad, *et al.* 2011 (279) Henker, *et al.* 2013 (280) Thomazeau, *et al.* 2016 (281) Matic, *et al.* 2017 (282) Margarit, *et al.* 2019 (283)	Weak

Clinical	Patients with the rs1799971 AG or GG genotypes have increased opioid dose requirements compared to patients with the AA genotype (codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, tramadol)	Gong, *et al.* 2013 (284) Khalil, *et al.* 2017 (285)	Moderate
Clinical	Patients with the rs1799971 GG genotype have increased opioid dose requirements compared to patients with the AA or AG genotypes. (fentanyl, morphine)	Hayashida, *et al.* 2008 (286)	Moderate
Clinical	Patients with the rs1799971 AA genotype have increased opioid consumption compared to patients carrying the G allele (morphine and unspecified opioids)	Janicki, *et al.* 2006 (278)	Weak
Clinical	No significant difference in opioid dose requirements based on rs2075572, rs599548, rs9384179 or rs558025 genotypes (fentanyl, morphine)	Hayashida, *et al.* 2008 (286)	Weak
Clinical	No significant difference in opioid dose requirements based on rs540825, rs562859, rs548646, rs1323042, rs618207, rs639855, rs9479757 or rs497976 genotypes (unspecified opioids)	Klepstad, *et al.* 2011 (279)	Weak
Clinical	PGx-guided prescription of opioids, including *OPRM1* variants, results in a reduced requirement for opioids (unspecified opioids)	Senagore, *et al.* 2017 (137)	Weak
Clinical	*OPRM1* haplotypes AGAAA (H9) and AGGAA (H11) are independently associated with decreased opioid dose requirements compared to the GCGAA haplotype (H7) (fentanyl, morphine)	Hayashida, *et al.* 2008 (286)	Weak
Clinical	No significant difference in opioid dose requirements based on the *OPRM1* haplotypes ACGAA (H8), AGGGG (H10), ACGGA (H12) or AGGAG (H13) (fentanyl, morphine)	Hayashida, *et al.* 2008 (286)	Weak
Clinical	The rs79910351 TT genotype is associatedwith a lack of response to opioids	Olsen, *et al*. 2019 (287)	Weak
Clinical	Infants with the rs1799971 AG or GG genotypes have shorter hospital stays for treatment of neonatal abstinence syndrome compared to infants with the AA genotype (buprenorphine, methadone)	Wachman, *et al.* 2013 (288)	Moderate
Clinical	Mothers with the rs1799971 AG or GG genotype have infants who are less likely to require treatment for neonatal abstinence syndrome compared to mothers with the AA genotype (buprenorphine, methadone)	Wachman, *et al.* 2013 (288)	Weak

Clinical	An infant's rs1799971 genotype is not associated with the likelihood that they will require treatment for neonatal abstinence syndrome (methadone)	Mactier, *et al.* 2017 (140)	Weak
Clinical	The rs1799971 G allele is found at a higher frequency in opioid-dependent patients than in healthy controls (heroin, unspecified opioids)	Bond, *et al.* 1998 (289) Franke, *et al.* 2003 (290) Crowley, *et al.* 2003 (291) Carpentier, *et al.* 2013 (292) Beer, *et al.* 2013 (293) Ahmed, *et al.* 2018 (294)	Weak
Clinical	The rs1799971 G allele is associated with a decreased risk of developing opioid dependence	Zhou, *et al.* 2020 (295)	Moderate
Clinical	T allele of rs1799972 is associated with an increased likelihood of developing opioid dependence (unspecified opioids)	Bond, *et al.* 1998 (289)	Weak
Clinical	No significant difference in the likelihood of developing opioid dependence based on rs1799972, rs17180968, rs17180982 or rs17174629 genotypes (unspecified opioids)	Crowley, *et al.* 2003 (291)	Weak
Clinical	The rs9479757 AG genotype is found at a lower frequency in opioid-dependent patients compared to healthy controls (unspecified opioids)	Beer, *et al.* 2013 (293)	Weak
Clinical	The rs9479757 GG genotype is found at a higher frequency in opioid-dependent patients compared to healthy controls (unspecified opioids)	Beer, *et al.* 2013 (293)	Moderate
Clinical	No significant difference in likelihood of developing opioid dependence based on rs9479757 genotype (unspecified opioids)	Franke, *et al.* 2003 (290)	Weak
Clinical	rs3778151 and rs510769 do not differ in frequency between opioid-dependent patients and healthy controls (unspecified opioids)	Beer, *et al.* 2013 (293)	Weak
Clinical	The rs675026 CT and TT genotypes are found more frequently in patients with opioid dependence compared to healthy controls (unspecified opioids)	Christoffersen, *et al.* 2016 (141)	Weak
Clinical	rs540825 and rs563649 do not differ in frequency between opioid-dependent patients and healthy controls (unspecified opioids)	Christoffersen, *et al.* 2016 (141)	Weak

Clinical	The rs1799971 AA genotype is associated with increased adverse events in patients undergoing an opioid deprescription program	Muriel, *et al*. 2019 (296)	Weak
Clinical	No significant difference in the development of opioid tolerance based on rs1799971 genotype (oxycodone)	Naito, *et al.* 2011 (147)	Weak
Clinical	No significant difference in incidence of opioid-induced side effects based on rs1799971 genotype (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, (R)-methadone, morphine, oxycodone, piritramide, tilidine, tramadol and unspecified opioids)	Lötsch, *et al.* 2009 (29) Laugsand, *et al.* 2011 (297) Jones, *et al*. 2019 (298)	Weak
Clinical	Patients with the rs1799971 AA genotype had decreased opioid-induced sedation compared to patients with the AG or GG genotypes (fentanyl, hydromorphone, morphine, meperidine)	Henker, *et al.* 2013 (280)	Moderate
Clinical	No significant difference in incidence of opioid-induced nausea or vomiting based on rs540825, rs562859, rs548646, rs1323042, rs618207, rs639855, rs9479757 or rs497976 genotypes (fentanyl, hydromorphone, morphine or meperidine)	Laugsand, *et al.* 2011 (297)	Moderate
Clinical	The rs1799971 GG genotype is associated with a lower score of the 'sleep adequacy' subscale and higher scores of the SL6 and SL9 indices on the MOS-Sleep questionnaire in patients taking opioids for chronic pain	Margarit, *et al*. 2019 (299)	Weak
Oxycodone			
In vitro	No significant difference in the clinical effect of oxycodone at mu opioid receptors based on the presence of the rs1799971 G allele	Knapman, *et al.* 2014 (203)	Moderate
Clinical	The rs6848893 CT genotype is associated with a lower subjective "High Quality" score of oxycodone in healthy volunteers	Jones, *et al*. 2019 (298)	Weak
Clinical	rs1799971 is not associated with subjective effects of oxycodone in healthy volunteers	Jones, *et al*. 2019 (298)	Weak
Clinical	Patients with the rs1799971 AG genotype have a reduced analgesic response to oxycodone compared to patients with the AA genotype	Zwisler, *et al.* 2010 (300)	Weak
Clinical	Patients with the rs1799971 GG genotype require increased oxycodone doses to achieve analgesia compared to patients with the AA genotype	Cajanus, *et al.* 2014 (301)	High

Clinical	No significant difference in analgesic response to oxycodone based on rs1799971 genotype	Zwisler, *et al.* 2012 (302)	Weak
Clinical	The rs1799971 G and rs533586 T alleles are independently associated with a reduced oxycodone analgesic response to visceral pressure	Olesen, *et al.* 2015 (303)	Weak
Clinical	No significant difference in oxycodone analgesia to visceral heat or muscle pressure based on rs1799971 genotype	Olesen, *et al.* 2015 (303)	Weak
Clinical	The rs589046 C and rs9479757 G alleles are independently associated with a reduced oxycodone analgesic response to skin heat and visceral pressure	Olesen, *et al.* 2015 (303)	Moderate
Clinical	No significant difference in oxycodone analgesia to visceral heat or muscle pressure based on rs589046, rs9479757, rs533586, rs6912029 or rs563649 genotypes	Olesen, *et al.* 2015 (303)	Weak
Clinical	The rs563649 T allele is associated with a 'good' oxycodone analgesic response to skin heat	Olesen, *et al.* 2015 (303)	Weak
Clinical	No significant difference in oxycodone dose requirements based on rs1799971 genotype	Zwisler, *et al.* 2012 (302) Cajanus, *et al.* 2014 (301)	Moderate
Clinical	Patients with the rs1799971 AG genotype have a reduced ability to maintain mental focus following oxycodone treatment compared to patients with the AA genotype	Zwisler, *et al.* 2010 (300)	Weak
Clinical	No significant difference in incidence of oxycodone-induced side effects based on rs1799971 genotype	Zwisler, *et al.* 2010 (300) Zwisler, *et al.* 2012 (302)	Weak
Clinical	No significant difference in oxycodone-induced CNS depression in infants based on maternal rs1799971 genotype	Karthikeyan, *et al.* 2014 (155)	Weak
Pentazocine			
In vitro	No significant difference in the clinical effect of pentazocine at mu opioid receptors based on the presence of the rs1799971 G allele	Knapman, *et al.* 2014 (203)	Weak
Piritramide			

Clinical	Patients carrying the rs1799971 G allele have increased piritramide dose requirements compared to patients with the AA genotype	Barstosova, *et al.* 2015 (304)	Weak
Remifentanil			
Clinical	Remifentanil has a reduced effect on analgesic EEG results from patients carrying the rs1799971 G allele compared to patients with the AA genotype	Melia, *et al.* 2014 (305)	Weak
Clinical	Patients with the rs79910351 TT genotype do not respond to remifentanil	Skorpen, *et al.* 2016 (277)	Weak
Clinical	Patients carrying the rs1799971 G allele have an increased analgesic response to remifentanil compared to patients with the AA genotype	Rhodin, *et al.* 2013 (306)	Weak
Clinical	No significant difference in hemodynamic parameters or infant outcomes following cesarean section where remifentanil is used based on rs1799971 genotype	Bakhouche, *et al.* 2015 (307)	Weak
Clinical	Patients with the rs2075572 GG genotype have increased remifentanil dose requirements compared to patients carrying the C allele	Liu, *et al.* 2014 (308)	Weak
Clinical	Patients with the rs558025 GG genotype have increased remifentanil dose requirements compared to patients carrying the A allele	Liu, *et al.* 2014 (308)	Weak
Clinical	Patients with the rs1799971 AG genotype have increased remifentanil dose requirements compared to patients with the AA genotype	Al-Mustafa, *et al.* 2017 (309)	Moderate
Clinical	No significant difference in remifentanil dose requirements based on rs1799971, rsrs599548, rs6912029 or rs9479757 genotypes	Liu, *et al.* 2014 (308)	Weak
Clinical	No significant difference in remifentanil-induced side effects based on rs2075572, rs558025, rs599548, rs6912029 or rs9479757 genotypes	Liu, *et al.* 2014 (308)	Weak
Clinical	Patients with the rs1799971 GG genotype have reduced postoperative nausea and vomiting scores following anesthesia including remifentanil compared to patients with the AA or AG genotypes	Lee, *et al.* 2015 (310)	Moderate

Clinical	Patients with the rs1799971 AA or AG genotypes have improved postoperative nausea and vomiting outcomes when receiving remifentanil anesthesia by TIVA compared to inhalation while patients with the GG genotype show no difference between the two methods	Lee, *et al.* 2015 (310)	Weak
Clinical	No significant difference in remifentanil-induced side effects, including respiratory depression, based on rs1799971 genotype	Liu, *et al.* 2014 (308) Hannam, *et al.* 2016 (311)	Weak
Sufentanil			
Clinical	Patients with the rs1799971 AG genotype have a reduced analgesic response to sufentanil compared to patients with the AA genotype	De Capraris, *et al.* 2011 (312)	Weak
Clinical	Patients carrying the rs1799971 G allele have reduced sufentanil dose requirements compared to patients with the AA genotype	Camorcia, *et al.* 2012 (313) Xu, *et al.* 2015 (314) Hronova, *et al.* 2016 (315)	Weak
Clinical	Patients carrying the rs1799971 G allele have increased sufentanil dose requirements compared to patients with the AA genotype	Bartosova, *et al*. 2019 (316) Zhao, *et al*. 2019 (317) Wang, *et al*. 2019 (318)	Weak
Clinical	No significant difference in sufentanil-induced side effects, including nausea or pruritus, based on rs1799971 genotype	Xu, *et al.* 2015 (314) Zhao, *et al*. 2019 (317)	Weak
Clinical	No significant difference in the development of sufentanil withdrawal symptoms based on rs1799971 genotype	Hronova, *et al.* 2016 (315)	Weak
Tramadol			
Clinical	Patients carrying the rs1799971 G allele have a decreased analgesic response to tramadol/acetaminophen compared to patients with the AA genotype	Liu, *et al.* 2012 (319)	Moderate
Clinical	No significant difference in analgesic response to tramadol based on rs1799971 genotype	Zhao, *et al.* 2014 (162)	Weak
Clinical	Patients with the rs1799971 GG genotype have significantly increased tramadol dose requirements than patients with the AA or AG genotypes.	Wang, *et al*. 2019 (318)	Weak

Clinical	Patients with the rs1799971 GG genotype have a reduced likelihood of experiencing tramadol-induced nausea and vomiting compared to patients with the AA genotype	Kim, *et al.* 2010 (192)	Weak
Clinical	There is no notable difference in incidence of tramadol-induced nausea and vomiting between patients with the rs1799971 AA genotype and patients with the AG genotype	Kim, *et al.* 2010 (192)	Weak
Clinical	No significant difference in severity of tramadol-induced adverse events based on the presence of the rs1799971 AG genotype	Bastami, *et al.* 2014 (177)	Weak

[a]See Level of Evidence section for definitions.

SUPPLEMENTAL TABLE S3. EVIDENCE LINKING *COMT* GENOTYPE WITH OPIOID RESPONSE.

Type of experimental model (*in vitro*, *in vivo*, preclinical, or clinical)	Major findings	References	Level of Evidence[a]
Codeine			
Clinical	No significant difference in codeine dose requirements based on the *COMT* haplotypes CGG (H48), TCA (H29) or CCG (H30)	Baber, *et al.* 2015 (71)	Moderate
Clinical	No significant difference in plasma concentrations of codeine, plasma concentrations of morphine or morphine/codeine plasma concentration ratios following codeine administration based on the *COMT* haplotype CGG (H48), TCA (H29) or CCG (H30)	Lam, *et al.* 2014 (95)	Moderate
Clinical	No significant difference in codeine-induced CNS depression in infants based on rs4633, rs4818 or rs4680 genotype	Sistonen, *et al.* 2012 (103)	Moderate
Fentanyl			
Clinical	No significant difference in analgesic response to fentanyl based on rs4680 genotype	Landau, *et al.* 2013 (210)	Moderate
Clinical	No significant difference in fentanyl dose requirements based on rs4680 genotype	Mamie, *et al.* 2012 (216) Barratt, *et al.* 2015 (219) Zhang, *et al.* 2015 (320)	High
Clinical	No significant difference in fentanyl dose requirements based on rs6269, rs4633 or rs4818 genotype	Zhang, *et al.* 2015 (320)	High
Clinical	*COMT* haplotype ACCG (H23) is associated with increased fentanyl dose requirements compared to the GCGG (H21) and ATCA (H22) haplotypes	Zhang, *et al.* 2015 (320)	Moderate
Clinical	The rs4680 AA genotype is associated with occurrence of dystonia and parkinsonian symptoms following administration of fentanyl	Iselin-Chaves, *et al.* 2009 (321)	Weak
Clinical	rs4680 is not associated with the hypotensive effect of fentanyl	Saiz-Rodriguez, *et al*. 2019 (222)	Weak
Clinical	The rs4680 AG genotype is associated with an increased risk of somnolence following administration of fentanyl	Saiz-Rodriguez, *et al*. 2019 (222)	Weak

Clinical	No significant difference in fentanyl-induced side effects based on rs6269, rs4633, rs4818 or rs4680 genotypes or the *COMT* haplotypes GCGG (H21), ATCA (H22) or ACCG (H23)	Zhang, *et al.* 2015 (320)	High
Hydromorphone			
Clinical	No significant difference in analgesic response to hydromorphone based on rs4680 genotype	Xia, *et al.* 2015 (224)	Moderate
Clinical	No significant difference in hydromorphone-induced side effects based on rs4680 genotype	Xia, *et al.* 2015 (224)	Moderate
Methadone			
Clinical	No significant difference in methadone maintenance dose based on rs4680 genotype	Mouly, *et al.* 2015 (125)	Moderate
Morphine			
Clinical	Patients carrying the rs7290221 G, rs740603 A or rs5746849 A allele are more likely to stop morphine treatment due to inadequate analgesia	Ross, *et al.* 2008 (322)	Weak
Clinical	No significant difference in analgesic response to morphine based on rs2097603, rs737866, rs7287550, rs174680, rs174699, rs2239393 or rs165728 genotypes	Ross, *et al.* 2008 (322)	Moderate
Clinical	No significant difference in analgesic response to morphine based on rs165774 or rs174696 genotypes	De Gregori, *et al.* 2016 (251)	Moderate
Clinical	No significant difference in analgesic response to morphine based on rs6269, rs4818 or rs4633 genotypes	Ross, *et al.* 2008 (322) De Gregori, *et al.* 2016 (251)	High
Clinical	Patients carrying the rs6269 G, rs4633 C or rs4818 G alleles are more likely to need rescue analgesia following morphine treatment	Sadhasivam, *et al.* 2014 (323)	Moderate
Clinical	No significant difference in analgesic response to morphine based on rs4680 genotype	Ross, *et al.* 2008 (322) Lee, *et al.* 2016 (238) De Gregori, *et al.* 2016 (251) Nielsen, *et al.* 2017 (239)	Moderate
Clinical	Patients with the rs4680 AA genotype have a reduced analgesic response to morphine as compared to patients with the GG genotype	Ahlers, *et al.* 2013 (324)	Moderate
Clinical	Patients with the rs4680 AG or GG genotypes are less likely to have an analgesic response to opioids compared to patients with the AA genotype	Elens, *et al.* 2016 (325)	Moderate
Clinical	Analgesic response to morphine increases as the number of rs4680 A alleles increases	Cargnin, *et al.* 2013 (326)	Moderate
Clinical	Patients carrying the rs4680 G allele are more likely to need rescue analgesia following morphine treatment	Sadhasivam, *et al.* 2014 (323) Matic, *et al.* 2014 (237)	Moderate

Clinical	Patients with the rs4680 GG genotype take longer to achieve analgesia following morphine administration than patients with the AA or AG genotypes, while patients with the rs4680 AA genotype are quicker to achieve analgesia following morphine administration than patients with the AG or GG genotypes.	Elens, *et al.* 2016 (325)	Moderate
Clinical	Subjects carrying the rs4680 A allele have a reduced analgesic response to morphine and contact heat stimulation	Nielsen, *et al.* 2017 (239)	Moderate
Clinical	Patients carrying the rs4680 G allele have increased morphine dose requirements compared to the AA genotype	Rakvag, *et al.* 2005 (327) Matsuoka, *et al.* 2012 (256) Tan, *et al.* 2016 (328) De Gregori, *et al.* 2013 (257) Rakvag, *et al.* 2008 (329) Kolesnikov, *et al.* 2011 (254) Rakvag, *et al.* 2005 (327) Mamie, *et al.* 2013 (216) Somogyi, *et al.* 2016 (243) Khalil, *et al.* 2017 (285) Hajj, *et al.* 2017 (252) Matsuoka, *et al.* 2012 (256) Li, *et al.* 2019 (253)	Moderate
Clinical	Patients with the rs4680 AG genotype have increased morphine dose requirements compared to patients with the GG genotype	Oliveira, *et al.* 2014 (249)	Weak
Clinical	Patients with the rs4680 GG genotype have increased rescue morphine dose requirements compared to the AA or AG genotypes	Matic, *et al.* 2014 (237)	Weak
Clinical	Patients carrying the rs740603 A, rs6269 A or rs4818 C alleles require a lower dose of morphine	Rakvag, *et al.* 2008 (329) Li, *et al.* 2019 (253)	Weak
Clinical	Patients carrying the rs5746849 A or rs2239393 A alleles require lower doses of morphine	Rakvag, *et al.* 2008 (329)	Moderate
Clinical	Patients with the rs4818 CC have increased morphine requirements compared to patients with the CG or GG genotypes.	Tan, *et al.* 2016 (328) Sadhasivam, *et al.* 2014 (323)	Weak
Clinical	No significant difference in morphine dose requirements based on rs2075507, rs737866, rs7287550 or rs174699 genotypes	Rakvag, *et al.* 2008 (329)	Moderate
Clinical	Weight-adjusted morphine consumption increases as the number of rs4633 C alleles increases	Tan, *et al.* 2016 (328)	High
Clinical	rs4633 is not associated with morphine dose requirements	Li, *et al.* 2019 (253)	Weak

Clinical	Patients carrying the *COMT* haplotype GACAAAACATT (H14) require lower doses of morphine	Rakvag, *et al.* 2008 (329)	Moderate
Clinical	The COMT haplotype ACCG (H23) is associated with decreased morphine requirements	Huehne, *et al.* 2009 (255) Li, *et al.* 2019 (253)	Moderate
Clinical	No significant difference in morphine dose requirements based on the *COMT* haplotypes GCGG (H21) or ATCA (H22)	Huehne, *et al.* 2009 (255)	Moderate
Clinical	Patients who are homozygous for the *COMT* haplotype ATCA (H22) have reduced morphine dose requirements compared to other diplotypes	De Gregori, *et al.* 2013 (257)	Moderate
Clinical	No significant difference in morphine dose requirements based on the *COMT* haplotypes AGAGGGGGGTT (H15), AATGGAACATT (H16), AATGGGGGGTT (H17), GACAAGGGGTT (H18), AATAAAACATT (H19) or GACGGGGGGTT (H20)	Rakvag, *et al.* 2008 (329)	Moderate
Clinical	Patients with the rs4680 GG genotype have increased serum concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide compared to patients with the AA or AG genotypes.	Rakvag, *et al.* 2005 (327)	Weak
Clinical	Patients carrying the rs7290221 G, rs5746849 A or rs740603 A alleles are more likely to stop morphine treatment due to side effects	Ross, *et al.* 2008 (322)	Moderate
Clinical	No significant difference in incidence of morphine-induced side effects based on rs7290221 or rs5746849 genotypes	Jimenez, *et al.* 2012 (261)	Weak
Clinical	Patients carrying the G allele of rs740603 are less likely to experience morphine-induced central side effects (drowsiness, confusion, hallucinations, nightmares)	Ross, *et al.* 2008 (322)	Moderate
Clinical	No significant difference in incidence of morphine-induced side effects, including postoperative nausea and vomiting, based on rs740603 genotype	Jimenez, *et al.* 2012 (261) Somogyi, *et al.* 2016 (243)	Moderate
Clinical	Patients carrying the T allele of rs174680 are less likely to experience morphine-induced central side effects (drowsiness, confusion, hallucinations, nightmares)	Ross, *et al.* 2008 (322)	Moderate
Clinical	The rs4680 AA genotype is associated with occurrence of dystonia and parkinsonian symptoms following administration of morphine	Iselin-Chaves, *et al.* 2009 (321)	Weak
Clinical	Patients carrying the rs4680 A allele have lower morphine-induced nausea scores compared to patients with the GG genotype.	Kolesnikov, *et al.* 2011 (254)	Moderate
Clinical	No significant difference in morphine-induced side effects based on rs4680 or rs7297550 genotypes	Ross, *et al.* 2008 (322) Jimenez, *et al.* 2012 (261)	Moderate

Clinical	No significant difference in morphine-induced side effects based on rs2097603, rs737866, rs6269, rs4633, rs2239393, rs174699, rs174680 or rs165728 genotypes	Ross, *et al.* 2008 (322) Jimenez, *et al.* 2012 (261)	Moderate
Clinical	Patients carrying the *COMT* haplotypes AATTGAAATAATT (H1) or (add sequence) H3 are less likely to experience morphine-induced central side effects (drowsiness, confusion, hallucinations, nightmares)	Ross, *et al.* 2008 (322)	Moderate
Clinical	No significant difference in morphine-induced central side effects (drowsiness, confusion, hallucinations, nightmares) based on the *COMT* haplotypes GACCCGGGCGGTT (H4), AATTGAAGCGGTT (H5), AATTCAAACAGTT (H6), AATTCGGACAGCC (H7), AATTCGGATAATT (H8), AGCCCGGATAATT (H9), GACCGAAGCGGTT (H10), AGCCGAAATAATT (H11), AATCGAAATAATT (H12) or AATTCGAGCGGTT (H13)	Ross, *et al.* 2008 (322)	Moderate
Naloxone			
Clinical	Patients with the rs4680 AA genotype have an increased ACTH peak, ACTH AUC and more rapid increases and decreases in ACTH response to naloxone than patients carrying the G allele.	Oswald, *et al.* 2004 (330)	Weak
Clinical	Patients with the rs4680 AA genotype have an increased cortisol AUC and a more rapid increase in cortisol response to naloxone than patients carrying the G allele.	Oswald, *et al.* 2004 (330)	Weak
Opioid			
Clinical	No significant difference in opioid dose requirements based on rs4680 genotype (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, meperidine, (R)-methadone, morphine, oxycodone, piritramide, tilidine, tramadol and unspecified opioids)	Lötsch, *et al.* 2009 (29) Klepstad, *et al.* 2011 (279) Henker, 2013 (280) Thomazeau, *et al.* 2016 (281) Wang, *et al*. 2019 (318) Margarit, *et al*. 2019 (283)	Moderate
Clinical	Patients with the rs4680 GG genotype have increased opioid dose requirements compared to patients with the AA or AG genotypes (buprenorphine, fentanyl, hydromorphone, morphine, oxycodone, unspecified opioids)	Candiotti, *et al.* 2014 (331) Wesmiller, *et al.* 2017 (332) Matic, *et al.* 2017 (282) Lucenteforte, *et al.* 2019 (333)	Moderate
Clinical	Patients with the rs4680 AA genotype have increased opioid dose requirements compared to patients with the AG genotype (hydromorphone, oxycodone, buprenorphine, fentanyl, morphine and unspecified opioids)	Wesmiller, *et al.* 2017 (332) Matic *et al.* 2017 (282)	Moderate

Clinical	The rs4680 AA and AG genotypes are associated with increased opioid consumption compared to the GG genotype	Hooten, *et al.* 2019 (334)	Moderate
Clinical	No significant difference in opioid dose requirements based on rs4633 genotype (hydromorphone, oxycodone, buprenorphine, fentanyl, meperidine, morphine and unspecified opioids)	Klepstad, *et al.* 2011 (279) Henker, *et al.* 2013 (280) Matic, *et al.* 2017 (282)	Moderate
Clinical	No significant difference in opioid dose requirements based on rs2020917, rs5993882, rs4646312 or rs165722 genotypes (unspecified opioids)	Klepstad, *et al.* (279)	Moderate
Clinical	Patients with the rs4818 GG genotype have reduced opioid dosing requirements compared to patients with the AA or AG genotypes (buprenorphine, fentanyl, hydromorphone, morphine, meperidine, oxycodone)	Henker, *et al.* 2013 (280) Candiotti, *et al.* 2014 (331) Matic, *et al.* 2017 (282)	Moderate
Clinical	No significant difference in opioid dose requirements based on rs6269 genotype (fentanyl, hydromorphone, morphine or meperidine)	Henker, *et al.* 2013 (280)	Weak
Clinical	PGx-guided prescription of opioids, including *COMT* variants, results in reduced requirement for opioids (unspecified opioids)	Senagore, *et al.* 2017 (137)	Weak
Clinical	No significant difference in opioid dose requirements based on the *COMT* haplotypes CGG (H48), TCA (H29) or CCG (H30) (hydromorphone, oxycodone, buprenorphine, fentanyl, morphine)	Matic, *et al.* 2017 (282)	Moderate
Clinical	Patients carrying one copy of the *COMT* haplotype GCGG (H21) have increased opioid requirements (fentanyl, hydromorphone, morphine or meperidine)	Henker, *et al.* 2013 (280)	Weak
Clinical	No significant difference in opioid dose requirements based on the *COMT* haplotypes ATCA (H22), ACCG (H23), ATCG (H24), GCGA (H25), ACCA (H26), GTGG (H27) or ACGA (H28) (fentanyl, hydromorphone, morphine or meperidine)	Henker, *et al.* 2013 (280)	Weak
Clinical	Infants with neonatal abstinence syndrome and the rs4680 AG or GG genotype have shorter hospital stays and are less likely to require treatment with two or more medications compared to infants with the AA genotype (hydromorphone, oxycodone, buprenorphine, fentanyl, morphine)	Matic, *et al.* 2017 (282)	Moderate
Clinical	No significant difference in length of hospital stay for treatment of neonatal abstinence syndrome or number of medications needed to treat neonatal abstinence syndrome based on maternal rs4680 genotype (buprenorphine, methadone)	Wachman, *et al.* 2013 (288)	Moderate

Clinical	Mothers carrying the rs4680 G or rs740603 A alleles are less likely to have infants who require two medications to treat neonatal abstinence syndrome (buprenorphine, methadone)	Wachman, *et al.* 2017 (335)	Moderate
Clinical	No significant difference in likelihood of requiring treatment for neonatal abstinence syndrome based on infant rs4633, rs4818, rs4680 or rs6269 genotype (methadone)	Mactier, *et al.* 2017 (140)	Weak
Clinical	A allele of rs4680 is more frequent in opioid-dependent patients than in non-dependent controls in family-based haplotype relative risk study. (unspecified opioids)	Horowitz, *et al.* 2000 (336)	Weak
Clinical	The rs4680 AA and AG genotypes are associated with increased likelihood of developing opioid dependence (unspecified opioids)	Oosterhuis, *et al.* 2008 (337)	Weak
Clinical	The A allele of rs4680 is associated with decreased likelihood of developing opioid dependence (heroin)	Levran, *et al.* 2015 (338)	Weak
Clinical	The rs4680 AA genotype is more frequent in living opioid-dependent patients than in deceased opioid-dependent patients (unspecified opioids)	Christoffersen, *et al.* 2016 (141)	Moderate
Clinical	No significant difference in likelihood of developing opioid dependence based on rs4680 genotype (heroin, unspecified opioids)	Horowitz, *et al.* 2000 (336) Demetrovics, *et al.* 2010 (339) Yang, *et al.* 2012 (340) Voisey, *et al.* 2011 (341) Vereczkei, *et al.* 2013 (342) Christoffersen, *et al.* 2016 (141)	Moderate
Clinical	No significant difference in likelihood of developing opioid dependence based on rs4818, rs8192488 or rs4633 genotypes (unspecified opioids)	Oosterhuis, *et al.* 2008 (337) Christoffersen, *et al.* 2016 (141)	Moderate
Clinical	No significant difference in likelihood of developing opioid dependence based on rs165774 genotype (unspecified opioids)	Voisey, *et al.* 2011 (341)	Weak
Clinical	The rs4680 AA and GG genotypes are associated with a higher incidence of adverse events, including vomiting and sexual dysfunction, in patients participating in an opioid deprescription program	Muriel, *et al*. 2019 (296)	Weak
Clinical	The rs165722 C, rs4633 T and rs4680 G alleles are associated with reduced intensity of opioid-induced nausea/vomiting (unspecified opioids)	Laugsand, *et al.* 2011 (297)	Weak
Clinical	rs4680 is not associated with opioid side effects, including sedation (buprenorphine, dihydrocodeine, fentanyl, hydromorphone, meperidine, (R)-methadone, morphine, oxycodone, piritramide, tilidine, tramadol)	Lötsch, *et al.* 2009 (29) Henker, *et al.* 2013 (280) Margarit, *et al.* 2019 (283)	Moderate

Clinical	No significant difference in the intensity of opioid-induced nausea/vomiting based on rs2020917, rs5993882 or rs4646312 genotypes (unspecified opioids)	Laugsand, *et al.* 2011 (297)	Moderate
Clinical	No significant difference in opioid-induced sedation based on rs4818, rs6269 or rs4633 genotypes (fentanyl, hydromorphone, morphine, meperidine)	Henker, *et al.* 2013 (280)	Weak
Clinical	*COMT* haplotypes TCA (H29) and CCG (H30) are independently associated with increased opioid sensitivity, as measured by opioid-induced respiratory depression (fentanyl, hydromorphone, morphine)	Madadi, *et al.* 2013 (142)	Weak
Oxycodone			
Clinical	The rs4680 AA and AG genotypes are associated with an increased subjective "Stimulated" response to oxycodone in healthy volunteers compared to the GG genotype	Jones, *et al*. 2019 (298)	Weak
Clinical	rs165599 and rs737865 are not associated with subjective responses to oxycodone in healthy volunteers	Jones, *et al*. 2019 (298)	Weak
Clinical	The rs4818 GG and rs6269 GG genotypes are associated with an adequate analgesic response to oxycodone	Lee, *et al.* 2011 (343)	Weak
Clinical	No significant difference in oxycodone dose requirements based on rs6518591, rs737866, rs887200, rs737865, rs1544325, rs8185002, rs174675, rs5993882, rs740603, rs4646312, rs4633, rs2239393, rs4818, rs4680, rs4646316, rs165774, rs174696, rs9306235, rs9332377, rs165599, rs887199 or rs2518824 genotypes or the *COMT* haplotypes AATATCT (H31), AGCGGCT (H32), GATGTTG (H33), AATGTTG (H34), AATGTTT (H35), TTACACA (H36), CCGGGCG (H37), TTACACG (H38), CCGGGTG (H39), TTACATG (H40), TCACGCG (H41), CGAGC (H42), CGATC (H43), TGGGT (H44), CGATT (H45), TGGTT (H46) or CAGTT (H47)	Kambur, *et al.* 2013 (344)	Moderate
Remifentanil			
Clinical	No significant difference in analgesic effect of remifentanil based on rs4680 genotype	Jensen, *et al.* 2009 (345)	Weak
Sufentanil			
Clinical	Patients with the rs4680 GG genotype have increased sufentanil dosing requirements compared to patients with the AA genotype	Hronova, *et al.* 2016 (315)	Weak
Clinical	No significant difference in sufentanil dosing requirements based on rs4633 or rs4818 genotypes	Hronova, *et al.* 2016 (315)	Weak

Clinical	No significant difference in sufentanil-induced withdrawal syndrome based on rs4680, rs4633 or rs4818 genotypes	Hronova, *et al.* 2016 (315)	Weak
Tramadol			
Clinical	No significant difference in analgesic response to tramadol based on rs4680 genotype	Zhao, *et al.* 2014 (162)	Moderate

[a]See Level of Evidence section for definitions.

SUPPLEMENTAL TABLE S4. EVIDENCE LINKING *COMT* AND *OPRM1* GENOTYPE WITH OPIOID RESPONSE.

Type of experimental model (*in vitro*, in vivo preclinical, or clinical)	Major findings	References	Level of Evidence
Clinical	Patients with the *OPRM1* rs1799971 AA genotype and the *COMT* rs4680 AA genotype have a lower analgesic response to fentanyl as compared to other genotype combination groups	Landau, *et al*. 2013 (210)	Weak
Clinical	Patients with the *OPRM1* rs1799971 AA genotype and the *COMT* rs4680 AA genotype require decreased morphine doses compared to other genotype combination groups	Reyes-Gibby, *et al*. 2007 (346) DeGregori, *et al*. 2013 (257)	Moderate
Clinical	Patients with the *OPRM1* rs1799971 AG genotype and the *COMT* rs4680 AG genotype require decreased morphine doses compared to patients with the rs1799971 AA genotype	Kolesnikov, *et al*. (254)	Weak
Clinical	Patients with the *OPRM1* rs1799971 AG genotype and the *COMT* rs4680 AG genotype have lower morphine-induced nausea scores compared to patients with the rs1799971 genotype	Kolesnikov, *et al*. (254)	Weak
Clinical	Combined *OPRM1* rs1799971 and *COMT* rs4680 genotype is not associated with length of hospital stay for treatment of neonatal abstinence syndrome	Wachman, *et al*. 2013 (288)	Weak
Clinical	Combined *OPRM1* rs1799971 and *COMT* rs4680 genotype is not associated with number of medications used in treatment of neonatal abstinence syndrome	Wachman, *et al*. 2013 (288)	Weak
Clinical	Patients carrying the *OPRM1* rs1799971 G allele and the *COMT* rs4680 GG genotype are more likely to require rescue morphine compared to other genotypes	Matic, *et al*. 2014 (237)	Moderate

Clinical	Combined *OPRM1* rs1799971 and *COMT* rs4680 genotype is not associated with rescue morphine dose requirements	Matic, *et al*. 2014 (237)	Weak
Clinical	Combined *OPRM1* rs1799971 and *COMT* rs4633, rs4818 and rs4680 genotypes are not associated with morphine consumption	Tan, *et al*. 2016 (328)	Weak
Clinical	Patients with the combined *OPRM1* rs1799971 G allele and *COMT* rs4680 AA genotype have increased opioid dose requirements compared to other genotype combinations	Khalil, *et al*. 2017 (285)	Weak
Clinical	Patients with the combined *OPRM1* rs1799971 G allele and *COMT* rs4633 TT genotype have increased opioid dose requirements compared to other genotype combinations	Khalil, *et al*. 2017 (285)	Weak
Clinical	Combined *OPRM1* rs1799971 and *COMT* rs6269 genotype is not associated with opioid dose requirements	Khalil, *et al*. 2017 (285)	Weak
Clinical	Combined *OPRM1* rs1799971 and *COMT* rs4818 genotype is not associated with opioid dose requirements	Khalil, *et al*. 2017 (285)	Weak
Clinical	Patients carrying the *OPRM1* rs1799971 G allele and the *COMT* rs4680 GG genotype have increased opioid dose requirements compared to patients with the *OPRM1* rs1799971 AA genotype and carrying the *COMT* rs4680 A allele	Matic, *et al*. 2017 (282)	Moderate

SUPPLEMENTAL TABLE S5. OXYCODONE THERAPY RECOMMENDATIONS BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	Implications	Recommendations	Classification of recommendation[a]	Considerations
CYP2D6 ultrarapid metabolizer	> 2.25	Increased metabolism to active metabolite, oxymorphone, but this does not appear to translate into increased analgesia or side effects.	No recommendation for oxycodone therapy because of weak evidence regarding adverse events or analgesia.	No recommendation	CPIC defines "weak" evidence as insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information. Further research may change the magnitude and/or direction of the net effect.
CYP2D6 normal metabolizer	1.25≤x≤2.25	Expected oxymorphone formation	Use oxycodone label recommended age- or weight-specific dosing.	Strong	

CYP2D6 intermediate metabolizer	0<x<1.25	Decreased metabolism of oxycodone to active metabolite oxymorphone, but this does not appear to translate into decreased analgesia or side effects.	No recommendation for oxycodone therapy because of weak evidence regarding adverse events or analgesia.	No recommendation	CPIC defines "weak" evidence as insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information. Further research may change the magnitude and/or direction of the net effect.
CYP2D6 poor metabolizer	0	Decreased metabolism of oxycodone to active metabolite oxymorphone, but this does not appear to translate into decreased analgesia or side effects.	No recommendation for oxycodone therapy because of inconsistent evidence regarding adverse events or analgesia.	No recommendation	Inconsistent evidence indicates both supporting and non-supporting evidence for an association between oxycodone use and adverse events, or analgesia.
CYP2D6 Indeterminate	n/a	n/a	No recommendation	No recommendation	n/a

[a]Rating scheme described in the Strength of Recommendations section.

SUPPLEMENTAL TABLE S6. METHADONE THERAPY RECOMMENDATIONS BASED ON CYP2D6 PHENOTYPE

Phenotype	Activity Score	Implications	Recommendations	Classification of recommendation[a]
CYP2D6 ultrarapid metabolizer	> 2.25	No effect or insufficient evidence for methadone adverse events, opioid dose requirements, or analgesia.	No recommendation	No recommendation
CYP2D6 normal metabolizer	1.25≤x≤2.25	Expected metabolism	Use methadone label recommended age- or weight-specific dosing.	Strong
CYP2D6 intermediate metabolizer	0<x<1.25	No effect or insufficient evidence for methadone adverse events, opioid dose requirements, or analgesia.	No recommendation	No recommendation
CYP2D6 poor metabolizer	0	No effect or insufficient evidence for methadone adverse events, opioid dose requirements, or analgesia.	No recommendation	No recommendation
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

SUPPLEMENTAL TABLE S7. MORPHINE THERAPY RECOMMENDATIONS BASED ON *OPRM1* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs1799971 G	The rs1799971 G allele is associated with small but statistically significant decreases in analgesia and/or increases in morphine requirements in some studies. However, this does not appear to translate into clinically actionable dose alterations.	No recommendation	No recommendation	Most publications focus on morphine for postoperative pain. Many factors contribute to variability in postoperative morphine response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use. Due to the marginal difference in dose between genotypes and numerous other factors affecting this outcome, the safest recommendation is to "start low and go slow."
Other variants	No effect or insufficient evidence for morphine adverse events, opioid dose requirements, or analgesia.	No recommendation	No recommendation	

[a]Rating scheme described in the Strength of Recommendations section.

SUPPLEMENTAL TABLE S8. FENTANYL THERAPY RECOMMENDATIONS BASED ON *OPRM1* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs1799971 G	No effect for fentanyl adverse events and analgesia. Mixed evidence for an association between OPRM1 rs1799971 and fentanyl dose requirements.	No recommendation	No recommendation	Many factors contribute to variability in fentanyl response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use.
Other variants	No effect or insufficient evidence for fentanyl adverse events, opioid dose requirements, or analgesia.	No recommendation	No recommendation	Many factors contribute to variability in fentanyl response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use.

[a]Rating scheme described in the Strength of Recommendations section.

SUPPLEMENTAL TABLE S9. OTHER OPIOIDS (ALFENTANIL, BUPRENORPHINE, CODEINE, HYDROCODONE, HYDROMORPHONE, LEVOMETHADONE, METHADONE, NALTREXONE, OXYCODONE, REMIFENTANIL, SUFENTANIL, AND TRAMADOL) THERAPY RECOMMENDATIONS BASED ON *OPRM1* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs1799971 G	No effect or insufficient evidence for adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy.	No recommendation	No recommendation	Many factors contribute to variability in postoperative opioid response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use.
Other variants	No effect or insufficient evidence for opioid adverse events, opioid dose requirements, analgesia, or change in opioid dependence/withdrawal therapy.	No recommendation	No recommendation	Many factors contribute to variability in postoperative opioid response including age, psychological status, tolerance, surgery type and duration, genetics and presurgical pain and opioid use.

[a]Rating scheme described in the Strength of Recommendations section.

SUPPLEMENTAL TABLE S10. OPIOID THERAPY RECOMMENDATIONS BASED ON *COMT* GENOTYPE

Genotype	Implications	Recommendations	Classification of recommendation[a]	Considerations
rs4680 A	No effect for opioid adverse events. Insufficient evidence for an association between *COMT* rs4680 genotype, analgesia and opioid dose requirements.	No recommendation	No recommendation	Many factors contribute to variability in opioid response including other gene variants, age, psychological status, indication and duration of opioid use. Mixed evidence indicates both supporting and non-supporting evidence for an association with neither direction dominating.
Other variants	Insufficient evidence for an association between *COMT* genotype, analgesia, opioid dose requirements and adverse events.	No recommendation	No recommendation	Many other factors contribute to variability in opioid response including other gene variants, age, psychological status, indication and duration of opioid use.

[a]Rating scheme described in the Strength of Recommendations section.

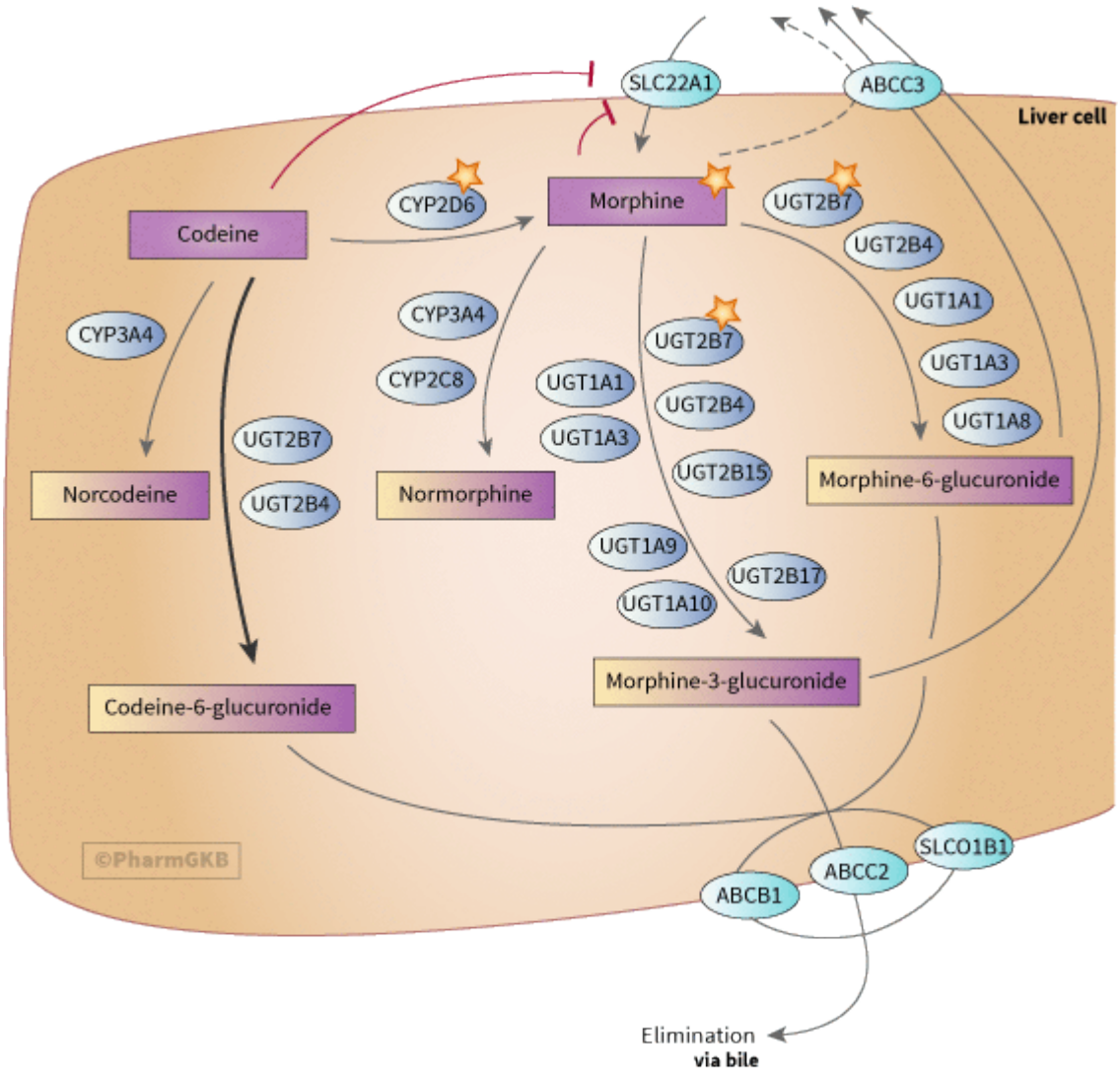

FIGURE S1. CODEINE METABOLISM. Permission has been given by PharmGKB and Stanford to use figure (https://www.pharmgkb.org/pathway/PA146123006) (37). Pathway images and data are available under a Creative Commons BY-SA 4.0 license.

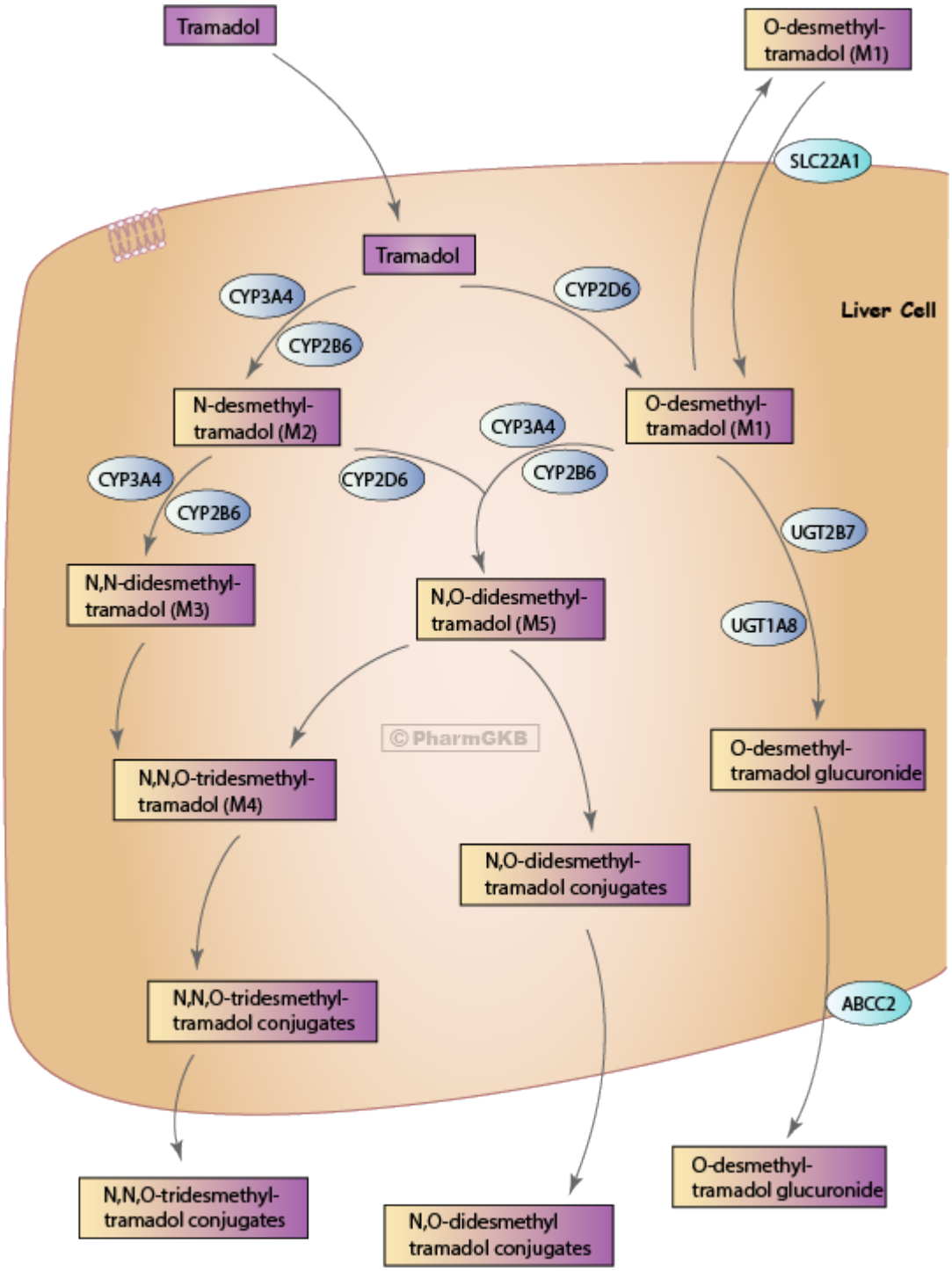

FIGURE S2. TRAMADOL METABOLISM. Permission has been given by PharmGKB and Stanford to use figure (https://www.pharmgkb.org/pathway/PA165946349) (347). Pathway images and data are available under a Creative Commons BY-SA 4.0 license.

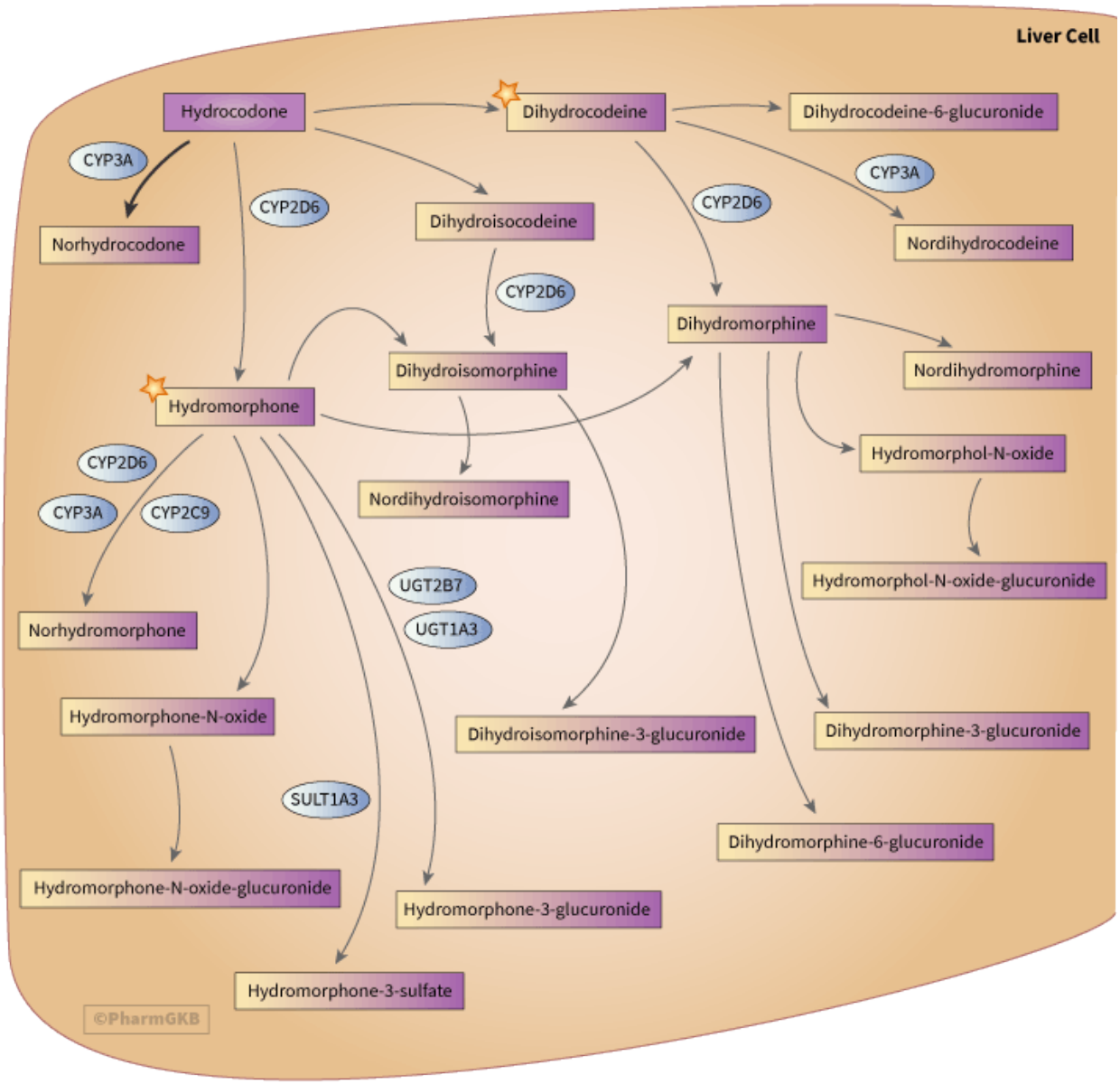

FIGURE S3. HYDROCODONE METABOLISM. Permission has been given by PharmGKB and Stanford to use figure (https://www.pharmgkb.org/pathway/PA166221421) (348). Pathway images and data are available under a Creative Commons BY-SA 4.0 license.

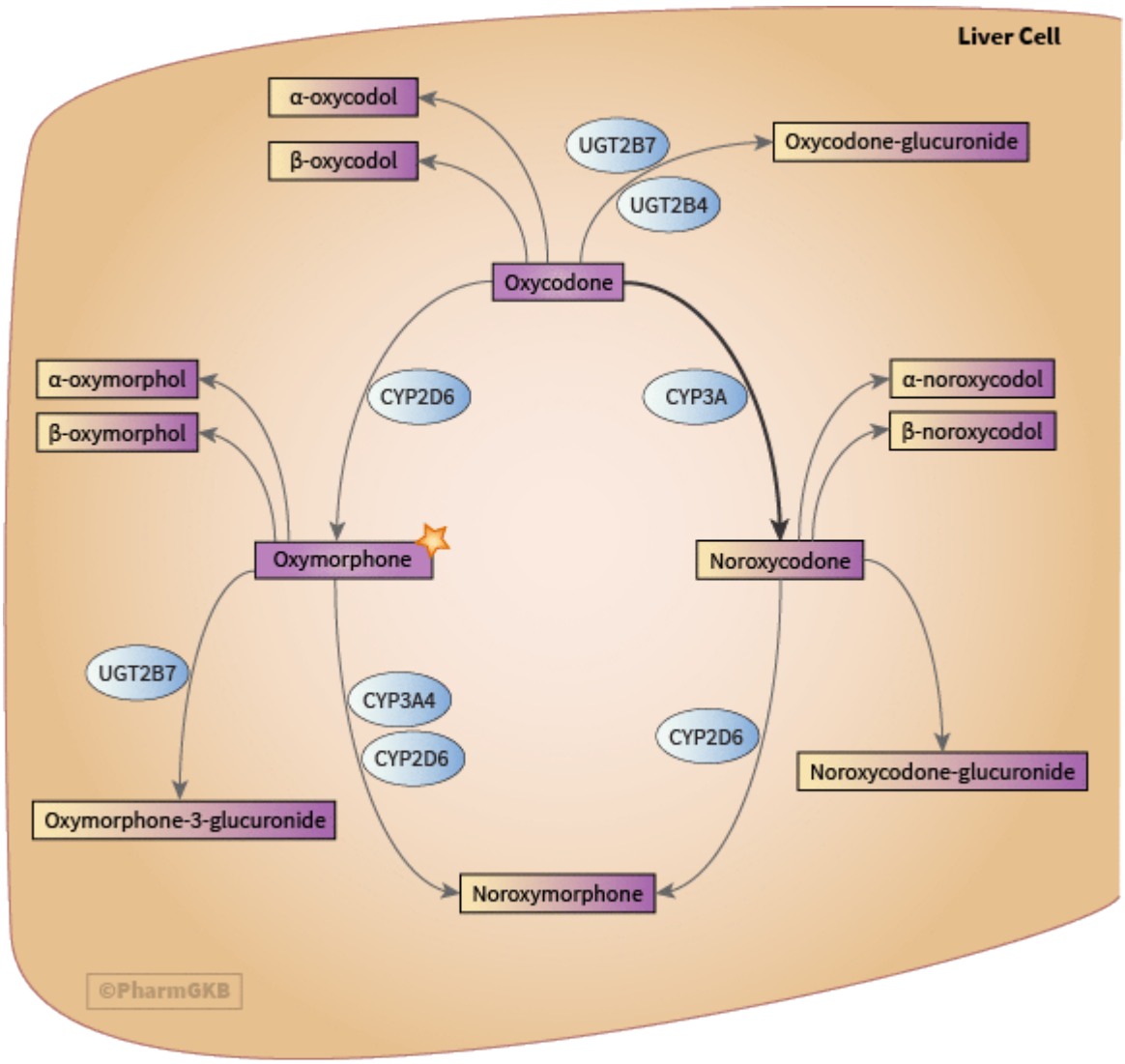

FIGURE S4. OXYCODONE METABOLISM. Permission has been given by PharmGKB and Stanford to use figure (https://www.pharmgkb.org/pathway/PA166170927) (349). Pathway images and data are available under a Creative Commons BY-SA 4.0 license.

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