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Codeine Therapy and *CYP2D6* Genotype

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Introduction

Codeine is used to relieve mild to moderately severe pain, and it belongs to the drug class of opioid analgesics.

The hepatic CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including codeine. CYP2D6 converts codeine in to its active metabolite, morphine, which provides its analgesic effect. However, pain relief may be inadequate in individuals who carry two inactive copies of *CYP2D6* ("poor metabolizers"), because of reduced morphine levels.

In contrast, individuals who carry more than two normal function copies of the *CYP2D6* gene ("ultrarapid metabolizers") are able to metabolize codeine to morphine more rapidly and more completely. As a result, even with normal doses of codeine, these individuals may experience the symptoms of morphine overdose, which include extreme sleepiness, confusion, and shallow breathing. Nursing mothers may also produce breast milk containing higher than expected levels of morphine that can lead to severe adverse events in their infants (1).

The FDA drug label for codeine states that even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose. The label also contains a boxed warning, which states that respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism (1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that for a patient identified as a CYP2D6 ultrarapid metabolizer, another analgesic should be used to avoid the risk of severe toxicity with a "normal" dose of codeine. CPIC also recommends avoiding codeine in patients identified as CYP2D6 poor metabolizers due to the possibility of lack of effect (see Table 1) (2).

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Table 1. 2014 Codeine therapy recommendations based on cytochrome P4502D6 (CYP2D6) phenotype, adapted from CPIC

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy[1]	Considerations for alternative opioids
Ultrarapid metabolizer (approximately 1–2% of patients)	Greater than 2.0	Increased enzyme activity. Increased formation of morphine following codeine administration, leading to higher risk of toxicity.	More than two copies of normal function alleles	**1/*1xN* **1/*2xN*	Avoid codeine use due to potential for toxicity.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.
Normal metabolizer (approximately 77–92% of patients)	1.0-2.0*	Normal enzyme activity. Normal morphine formation.	Two normal function alleles, or two decreased function alleles, or one normal function allele and one decreased or no function allele, or combinations of duplicated alleles that result in an activity score of 1.0 to 2.0	**1/*1* **1/*2* **2/*2* **1/*41* **1/*4* **2/*5* **1/*10*	Use label-recommended age- or weight-specific dosing.	
Intermediate metabolizer (approximately 2–11% of patients)	0.5*	Intermediate enzyme activity. Reduced morphine formation.	One decreased function allele and one no function allele	**4/*10* **5/*41*	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Monitor tramadol use for response.

Table 1. continued from previous page.

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy[1]	Considerations for alternative opioids
Poor metabolizer (approximately 5–10% of patients)	0	Low or absent enzyme activity. Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief.	Two no function alleles	**4/*4* **4/*5* **5/*5* **4/*6*	Avoid codeine use due to lack of efficacy.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.

* Activity scores are based on the formation of morphine from codeine. Other investigators may define normal metabolizers with a score of 1.5-2.0, and intermediate metabolizers with a score of 0.5-1.0.
[1] The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers. Table is adapted from Crews K.R. et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clinical pharmacology and therapeutics. 2014;95(4):376-82 (2). Please note, the nomenclature used in this table reflects the standardized nomenclature for pharmacogenetic terms proposed by CPIC in a 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" (3).

Drug: Codeine

Codeine is an opioid analgesic. It exerts its effects via the opioid receptors found throughout the body including the central nervous system and the gastrointestinal system. Codeine is a prodrug that only weakly binds the mu opioid receptor. Its analgesic properties depend upon its conversion to morphine that binds to the mu opioid receptor with 200-fold greater affinity than codeine.

Codeine is indicated for the relief of mild to moderately severe pain, where the use of an opioid analgesic is appropriate. Codeine is a Schedule II controlled substance, and there is a risk of misuse and abuse. As with any opioid drug, the dosing regimen should be adjusted for each individual patient. When the patient no longer requires codeine, the doses should be tapered gradually to prevent withdrawal symptoms in patients who have become physically dependent (1).

For codeine to exert its opioid activity, it must first undergo o-demethylation by CYP2D6 to morphine. Only about 5-10% of codeine is metabolized in this pathway, with about 80% of an administered dose of codeine being converted to inactive metabolites and excreted. However, the percentage of codeine converted to morphine can be much higher in individuals who have 3 or more active copies of *CYP2D6* ("ultrarapid metabolizers") (2). In contrast, individuals who lack active copies of *CYP2D6* ("poor metabolizers") have lower levels of morphine.

Morphine is further metabolized to morphine-6-glucuronide, which also has analgesic properties. Other metabolites are thought to be mostly inactive; they include codeine-6-glucuronide (~60%) and norcodeine (~5–10%), both of which share with codeine a similarly weak affinity for the mu opioid receptor (4).

To avoid treatment complications in patients who are either ultrarapid or poor metabolizers, opioids that are not metabolized by CYP2D6 may be used (e.g., morphine, oxymorphone, buprenorphine, fentanyl, methadone, hydromorphone), alongside non-opioids, depending upon the type of pain being treated (2, 5-7).

The most common adverse reactions to codeine include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating. One of the main serious adverse reactions associated with codeine is respiratory depression. The FDA-drug label for codeine now includes a boxed warning that states "Warning: Death related to ultra-rapid metabolism of codeine to morphine. Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism" (1, 8, 9).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are very polymorphic and can result in decreased, absent, or increased enzyme activity.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene is highly polymorphic, with more than 100 star (*) alleles described (10).

*CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the "normal metabolizer" phenotype. The *CYP2D6* alleles **2*, **33*, and **35* are also considered to have near-normal activity.

About 77–92% of individuals have at least one copy of a normal function allele (**1* or **2*), or two partially functioning alleles. These individuals are also "normal metabolizers" and are most likely to have a phenotypically normal response to codeine. However, there is a large amount of variability in codeine response within patients genotyped as normal metabolizers, and the causes of this variation, among individuals with the same diplotype, are unknown (2).

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (e.g., **3*, **4*, **5*, and **6*) (4, 11-13) or an enzyme with decreased activity (e.g., **10*, **17*, and **41*) (14-16) (see Table 2). There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians (17).

About 2–11% of patients are intermediate metabolizers—they carry either two decreased function alleles or one decreased function and one no function allele (18). These individuals may not respond as well to codeine because the metabolism of codeine to morphine is reduced.

In Asians and in individuals of Asian descent, only about 50% of *CYPD6* alleles are normal function, and the frequency of *CYP2D6* allele duplications is as high as 45% (19). Common no function variants are *CYP2D6*36* (the most commonly duplicated *CYP2D6* allele in the Asian population) and *CYP2D6*10*. Both these variants contain the SNP "100C>T" (see Nomenclature table) (17, 19-21). In Africans and African Americans, again, only about 50% of *CYPD6* alleles are normal function (11, 16, 17, 22).

About 5–10% of patients are poor metabolizers—they carry two no function alleles (18). In these individuals, codeine will provide little or no pain relief. Poor metabolizers are more commonly found in European Caucasians and their descendants. The majority allele in this population is the normal function *CYP2D6*1* (70%), but the remaining alleles include the no function *CYP2D6*4* and *CYP2D6*5* variants that largely account for the poor metabolizer phenotype in these populations (12, 15, 23).

Patients who are ultrarapid metabolizers carry at least 3 copies of the *CYP2D6* gene. The ultrarapid metabolizer phenotype has been estimated to be present in 1–2% of patients, but the prevalence varies widely in different

populations. It is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese (1, 18).

Each normal function *CYP2D6* allele increases the rate of codeine metabolism, increasing the risk of an initial morphine "overdose", with more side effects and a shorter duration of pain control (24). Even low codeine doses can result in toxic levels of morphine in patients with more than 2 normal function alleles (2). Several case reports have recorded the severe or life-threatening adverse effects that have occurred in patients who were ultrarapid metabolizers and were treated with standard doses of codeine (25, 26).

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient's result is reported as a diplotype, which includes one maternal and one paternal allele, e.g., *CYP2D6 *1/*2*. When patients have more than two copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", e.g., *CYP2D6*2x2*.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and calculating the CYP2D6 activity score. Each allele is assigned an activity value: 0 for no function, 0.5 for decreased function, and 1 for each copy of a normal function allele. The total CYP2D6 activity score is the sum of the values assigned to each allele—patients with a score of 1.0, 1.5, or 2.0 represent a range of normal metabolizers with normal enzyme activity. Poor metabolizers have an activity score of 0, patients with a score of 0.5 are intermediate metabolizers, and patients with a score of greater than 2.0 are ultrarapid metabolizers (see Table 1) (2).

Variants in other genes, such as *COMT*, *ABCB1*, *UGT2B7* and *OPRM1*, may also influence an individual's response to codeine. However, evidence is lacking on whether genetic testing for these variants will aid optimum codeine dosing (7, 27-29).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1,2] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA): Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.

Some individuals may be ultra-rapid metabolizers because of a specific *CYP2D6* genotype (gene duplications denoted as **1/*1xN* or **1/*2xN*). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

[2] Please note, the term "extensive metabolizer" has been replaced by the term "normal metabolizer" in the standardized nomenclature for pharmacogenetic terms proposed by CPIC in a 2016 paper, "Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC)" 3. Caudle, K.E., H.M. Dunnenberger, R.R. Freimuth, J.F. Peterson, et al., *Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC).* Genet Med, 2017. **19**(2): p. 215-223..

groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

Please review the complete therapeutic recommendations that are located here: (1)

2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): A standard starting dose of codeine, as recommended in the product label, is warranted in patients with an extensive metabolizer phenotype (i.e., a CYP2D6 activity score of 1.0–2.0). Likewise, a standard starting dose of codeine is warranted in patients with an intermediate metabolizer phenotype (i.e., activity score of 0.5); these patients should be monitored closely for less-than-optimal response and should be offered an alternative analgesic if warranted. If the CYP2D6 substrate tramadol is selected as alternative therapy in intermediate metabolizers, therapy should be monitored closely due to the possibility of poor response.

If clinical genotyping identifies a patient as a CYP2D6 poor metabolizer (i.e., activity score of 0), current evidence supports the avoidance of codeine and the use of an alternative analgesic due to the possibility of lack of effect. Use of an analgesic other than the CYP2D6 substrates tramadol, hydrocodone, or oxycodone in poor metabolizers may be preferable. There is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolizers, especially considering the evidence that select adverse effects do not differ between poor and extensive metabolizers. In a patient identified as a CYP2D6 ultrarapid metabolizer (i.e., activity score of >2.0), the choice of another analgesic should be made to avoid the risk of severe toxicity with a "normal" dose of codeine.

Please review the complete therapeutic recommendations that are located here: (2).

2013 Clinical practice Guideline from the "Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Recommendations Group: *CYP2D6* genotyping for safe and efficacious codeine therapy":

1. Who should be tested and when?
    - Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for CYP2D6 (Grade A – strong recommendation).
    - Children and adults who continue to have pain despite high doses of codeine should be tested for CYP2D6 (Grade B – moderate recommendation).
    - Genetic testing for CYP2D6 should be considered before administering codeine for the first time in all children and adults in order to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C – optional recommendation).
2. What gene variants should be tested?

Given the numerous polymorphisms in CYP2D6 and the diversity of the Canadian population, a full-scale analysis of both common and rare CYP2D6 variants is advised (Grade B- moderate recommendation)

- *CYP2D6* alleles with decreased or no function: *CYP2D6 *3- 12, 14-15, 17, 19-20, 29, 40-42, 44, 49, 50, 54-56, 59; *4XN, *10XN*
- *CYP2D6* alleles with normal or increased function: *CYP2D6 *2* (normal), **1XN* (increased), **2XN* (increased), **17XN*, **35XN* (increased), **41XN*, in addition to *CYP2D6* copy number determination.

Recommendations: Genotype-Specific Treatment Options

- Poor metabolizers of CYP2D6 should not receive codeine for pain relief (Grade A- strong recommendation).

- Ultrarapid metabolizers of CYP2D6 should avoid codeine for pain relief and receive alternative analgesics that do not have potent CYP2D6 metabolites (Grade B- moderate recommendation).
- Certain populations, especially opioid naïve breastfed neonates of mothers with functional *CYP2D6* gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of CYP2D6 should avoid codeine (Grade A – strong recommendation).
- In individuals with IM or EM *CYP2D6* genotypes, codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in *CYP2D6* EMs receiving codeine if they are receiving maximal therapeutic doses of codeine and have additional risk factors for toxicity.

Please review the complete therapeutic recommendations that are located here: (30)

Nomenclature

Nomenclature of selected *CYP2D6* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.5:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly CYP2D6T	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.5:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2850C>T[2] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
*CYP2D6*41*	2850C>T[2] (Cys296Arg)	NM_000106.5:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.5:c.985+39 G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2850C>T is also referred to as 2938C>T

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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References

1. Codeine sulfate tablets for oral use [package insert]. Columbus, OH: Roxane Laboratories; 2010. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=fa3ed180-298a-4f9d-9d05-15182d7218bf
2. Crews K.R., Gaedigk A., Dunnenberger H.M., Leeder J.S., et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. 2014;95(4):376–82. PubMed PMID: 24458010.
3. Caudle K.E., Dunnenberger H.M., Freimuth R.R., Peterson J.F., et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19(2):215–223. PubMed PMID: 27441996.
4. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Codeine and Morphine Pathway, Pharmacokinetics [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/pathway/PA146123006
5. Nicholson W.T., Formea C.M. Clinical perspective on the Clinical Pharmacogenetics Implementation Consortium Updated 2014 guidelines for CYP2D6 and codeine. Clin Chem. 2015;61(2):319–21. PubMed PMID: 25301855.
6. Crews K.R., Caudle K.E., Dunnenberger H.M., Sadhasivam S., et al. Considerations for the Utility of the CPIC Guideline for CYP2D6 Genotype and Codeine Therapy. Clin Chem. 2015;61(5):775–6. PubMed PMID: 25770140.
7. Bell G.C., Donovan K.A., McLeod H.L. Clinical Implications of Opioid Pharmacogenomics in Patients With Cancer. Cancer Control. 2015;22(4):426–32. PubMed PMID: 26678969.
8. Boyle K.L., Rosenbaum C.D. Oxycodone overdose in the pediatric population: case files of the University of Massachusetts Medical Toxicology Fellowship. J Med Toxicol. 2014;10(3):280–5. PubMed PMID: 24610706.
9. Racoosin J.A., Roberson D.W., Pacanowski M.A., Nielsen D.R. New evidence about an old drug--risk with codeine after adenotonsillectomy. N Engl J Med. 2013;368(23):2155–7. PubMed PMID: 23614474.
10. Reny J.L., Fontana P. Antiplatelet drugs and platelet reactivity: is it time to halt clinical research on tailored strategies? Expert Opin Pharmacother. 2015;16(4):449–52. PubMed PMID: 25495963.
11. Yokota H., Tamura S., Furuya H., Kimura S., et al. Evidence for a new variant CYP2D6 allele CYP2D6J in a Japanese population associated with lower in vivo rates of sparteine metabolism. Pharmacogenetics. 1993;3(5):256–63. PubMed PMID: 8287064.
12. Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): clinical consequences, evolutionary aspects and functional diversity. The pharmacogenomics journal. 2005;5(1):6–13. PubMed PMID: 15492763.
13. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*1 [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/haplotype/PA165816576
14. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*4 [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/haplotype/PA165816579
15. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*6 [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/haplotype/PA165816581
16. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Haplotype CYP2D6*10 [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/haplotype/PA165816582

17. Bradford L.D. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. Pharmacogenomics. 2002;3(2):229–43. PubMed PMID: 11972444.
18. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Drug/Small Molecule: Codeine [Cited 2012 July 24]. Available from: http://www.pharmgkb.org/drug/PA449088
19. Ramamoorthy A., Flockhart D.A., Hosono N., Kubo M., et al. Differential quantification of CYP2D6 gene copy number by four different quantitative real-time PCR assays. Pharmacogenet Genomics. 2010;20(7):451–4. PubMed PMID: 20421845.
20. Wu X., Yuan L., Zuo J., Lv J., et al. The impact of CYP2D6 polymorphisms on the pharmacokinetics of codeine and its metabolites in Mongolian Chinese subjects. Eur J Clin Pharmacol. 2014;70(1):57–63. PubMed PMID: 24077935.
21. Hosono N., Kato M., Kiyotani K., Mushiroda T., et al. CYP2D6 genotyping for functional-gene dosage analysis by allele copy number detection. Clin Chem. 2009;55(8):1546–54. PubMed PMID: 19541866.
22. Sistonen J., Sajantila A., Lao O., Corander J., et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenetics and genomics. 2007;17(2):93–101. PubMed PMID: 17301689.
23. Ingelman-Sundberg M., Sim S.C., Gomez A., Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. Pharmacology & therapeutics. 2007;116(3):496–526. PubMed PMID: 18001838.
24. Weinshilboum R. Inheritance and drug response. The New England journal of medicine. 2003;348(6):529–37. PubMed PMID: 12571261.
25. Gasche Y., Daali Y., Fathi M., Chiappe A., et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med. 2004;351(27):2827–31. PubMed PMID: 15625333.
26. Ciszkowski C., Madadi P., Phillips M.S., Lauwers A.E., et al. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med. 2009;361(8):827–8. PubMed PMID: 19692698.
27. Somogyi A.A., Coller J.K., Barratt D.T. Pharmacogenetics of opioid response. Clin Pharmacol Ther. 2015;97(2):125–7. PubMed PMID: 25670515.
28. Baber M., Chaudhry S., Kelly L., Ross C., et al. The pharmacogenetics of codeine pain relief in the postpartum period. Pharmacogenomics J. 2015;15(5):430–5. PubMed PMID: 25752520.
29. Cascorbi I., Bruhn O., Werk A.N. Challenges in pharmacogenetics. Eur J Clin Pharmacol. 2013;69 Suppl 1:17–23. PubMed PMID: 23640184.
30. Madadi P., Amstutz U., Rieder M., Ito S., et al. Clinical practice guideline: CYP2D6 genotyping for safe and efficacious codeine therapy. J Popul Ther Clin Pharmacol. 2013;20(3):e369–96. PubMed PMID: 24214521.

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