

# Pain polymorphisms and opioids: An evidence based review

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**Abstract.** Despite the various different candidate genetic polymorphisms of potential clinical relevance, there is not enough understanding of the inter-individual variability in analgesic administration. The cytochrome P450 2D6 (CYP2D6) genotype is thought to be one of the most studied. The aim of the present evidence-based review was to determine if there is now sufficient evidence to make clinical recommendations based on a specific genomic profile. The data sources utilized were as follows: PubMed (NLM) database, Evidence Based Medicine Guidelines and Google. Research on clinical guidance standards, systematic reviews, meta-analyses and clinical trials, published prior to January 2018, were evaluated in English, using the MeSH terms ‘cancer pain’, ‘polymorphism’, ‘genetic’ and ‘gene polymorphism’. To assess the level of evidence, the Strength of Recommendation Taxonomy of the American Family Physician was applied. From the initial search, 12 systematic reviews and/or meta-analyses, 5 clinical trials and 10 guidelines were selected. The results indicated that genetic variation of  $\mu$ -opioid receptor 1 (OPRM1) may contribute to inter-individual differences in morphine consumption with recommendation grade A for OPRM1 A118G single nucleotide polymorphism (rs1799971). Polymorphisms associated with the metabolization process of morphine and other opioid drugs are very relevant in opioid titration and ethnic subgroup differences which have to be taken into account (particularly, for the recommendation grade A for the CYP2D6 polymorphism). In human studies, the catechol-O-methyl transferase (COMT)

genotype affects the efficacy of opioids in acute and chronic pain under different settings, with recommendation grade B to the COMT single nucleotide polymorphism rs4680 (Val/Met). Finally, polymorphisms of the ATP-binding cassette family of efflux transporters were highlighted. Consistent data on pain polymorphisms is now widely available; however, these results have had very little impact on clinical guidelines and daily oncologist practice. Persisting pain, side effects of grade 3 (NCI-CTCAE v4.0) and breakthrough pain with more than 4 episodes/day should be considered the criteria for pain multidisciplinary team discussions and for polymorphism screening.

## Introduction

Chronic pain inadequately treated is a major public health issue (1). This is particularly relevant, when we are talking of supportive care in cancer patients. Opioids are the most used analgesics for cancer pain, but the clinical benefits of opioid analgesics are dependent of substantial individual variations in the responses to opioids, insufficient drug dosing and/or a high rate of adverse events. The wide interindividual variability in sensitivity to opioids leads to unpredictable clinical responses to opioid treatment and adverse events, along with narrow therapeutic window and are still nowadays an important problem (1,2).

To date, only a limited number of studies have addressed the relationship between human genetic variations and sensitivity to opioids; however there is growing evidence that pharmacogenetic differences may impact in interindividual variability in opioid response. Human genetic variation may directly modulate opioids pharmacokinetic and pharmacodynamic effects; candidate genes are sought in polymorphisms of drug transporters, metabolizing enzymes or opioid receptors (1,2).

Cytochrome P450 (CYP) are enzymes located on the smooth endoplasmic reticulum membranes of liver hepatocytes and along the mucosal surface of the intestinal tract. The CYP system can inactivate or activate a given drug (type I reactions) and is responsible for glucuronidation and sulfation, connected with drug excretion (type II). Along with CYP iso-enzyme 3A4

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(CYP3A4), the most important enzyme is CYP 2D6 (CYP2D6). She is involved in the metabolism many drugs used in pain and palliative medicine (e.g., opioids, neuroleptics, antidepressants). More than 80 distinct allelic variants for CYP2D6 are known, which leads to a wide spectrum of metabolic capacity and phenotype diversity within populations for several drugs like tramadol, dihydrocodeine, codeine (3). Fentanyl is thought to be predominantly metabolized in the liver by CYP3A4-mediated N-dealkylation (less than 1% is metabolized by alkyl hydroxylation, N-dealkylation or amide hydrolysis) (4). Ketamine is mainly metabolized by CYP2B6 and CYP3A4 (5). Morphine is metabolized to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) via glucuronidation by phase II metabolism of UDP-glucuronosyl transferase 2B7 (UGT2B7). About 60% of morphine is converted to M3G and 6-10% is converted to M6G. Both metabolites are excreted in the urine. M6G is a very potent opioid analgesic, which activates  $\mu$ -opioid receptors, while M3G has no opioid properties and has been proposed to be responsible for neuroexcitatory effects, including allodynia, myoclonus and seizures. Two variants of the UGT2B7 gene have been described, with inconsistent results on their influence on morphine glucuronidation and pain relief (6).

The opioid pharmacogenetic studies in cancer patients have primarily focused on three genes:  $\mu$ -opioid receptor (OPRM), catechol-O-methyl transferase (COMT) and multidrug resistance 1 gene (MDR-1) (7).

Mu-opioid receptors (MOR) receptors are the main site of action of opioids. Recent genetic research shows that genetic variations in  $\mu$ -opioid receptor 1 (OPRM1) gene locus play an essential role in inter-individual responses. This may explain why some patients do need higher doses of opioid for pain relief, translating into decreased morphine potency in pupil constriction and experimental analgesia, or poor receptor signaling *in vitro* (8). Numerous single nucleotide polymorphisms (SNPs) in the mu opioid receptor have been identified, but the majority of genetic association studies have focused on the A118G polymorphism (A>G functional substitution at locus 118,) which codes for a non-synonymous change in OPRM1 exon 1 (9,10).

Another line of evidence indicates that the influence of COMT gene polymorphisms on pain has also been investigated. It has been shown that the Val158Met polymorphism, a common genetic variant in Caucasian populations, influences the activity of the COMT enzyme. This enzyme, which metabolizes dopamine, adrenaline and noradrenaline, is an important modulator of dopaminergic and noradrenergic neurotransmission, known to play a role in pain (11-13).

Furthermore, functional impairment of peripheral blood morphine transporters (multi-drug resistance protein, proteins 2 and 3; -MRP2 and MRP3 genes), and morphine transporters through the blood-brain barrier, like ATP-binding cassette (ABC) family of efflux transporters, may result in modification of brain's morphine concentration (14).

There are a growing number of candidate genes for genetic polymorphisms of potential clinical relevance (not all referred in this paper). The aim of this study is to determine if there is now enough evidence to make treatment recommendations based on specific genomic profile in cancer pain patients. In the future, a faster titration of opioid needs would be possible, with less episodes of irruptive pain or persistent

pain, fewer side effects and thus better quality of life. We would probably have a lower incidence of chronic pain. Identifying patients' subgroups more susceptible to refractory pain or adverse symptoms would give us the ability to anticipate cases of difficult pain control, with better pain control, fewer visits and hospitalizations for uncontrolled pain or adverse events and lower costs; pain control could increase cost-effectiveness.

## Materials and methods

A bibliographic survey was carried out in the following databases: PubMed (NLM), Evidence Based Medicine Guidelines and Google. Clinical guidelines, systematic reviews, meta-analyses and clinical trials, published until January 2018, were searched using MeSH terms 'cancer pain', polymorphism, genetic, gene polymorphism. Similar search strings were adapted for the others databases. In Google, search was also conducted by organization with particularly dedication to cancer pain issues. Only guidelines in English, which were published and downloadable from the web, were taken into consideration. Exclusion criteria in the selection of articles were: papers without any reference to polymorphism (or genetic variation) in the abstract, reporting drug use in non-cancer pain or being related to nursing practice or anti-cancer therapies or translational pain research (animal models).

The American Family Physician's (AFP) Strength of Recommendation Taxonomy (15) was applied to classify levels of evidence and recommending strengths. According to this taxonomy, the quality of the study is subdivided into three Levels of Evidence (Level of Evidence 1: Good quality studies, evidence-oriented decision; Level of Evidence 2: Limited quality studies, patient-oriented evidence; Level of Evidence 3: Other evidence) and the Strength of Recommendation in also divided in three levels-(Strength of Recommendation A: consistent, evidence patient-oriented; Strength of Recommendation B: Inconsistent or limited quality, evidence oriented for the patient; Strength of Recommendation C: consensus, evidence-oriented disease). The final text has been reviewed and approved by all authors.

## Results

The search for polymorphism (42 papers) or genetic (86 papers) or gene polymorphisms (34 papers) in patients with 'cancer pain' identified 35 systematic review and/or meta-analysis and 12 clinical trials. More than half of the articles were excluded because they did not concern systematic review and/or meta-analysis and clinical trials or they did not meet the inclusion/exclusion criteria (Fig. 1). For these analyses 12 systematic review and/or meta-analysis and 5 clinical trials were selected. The search for Clinical Guidance Standards found 10 guidelines with reference to pain polymorphism or genetics of pain (from a total of 38 found in our search).

*Clinical guidance standards.* We found at least 38 guidelines on supportive care and pain but reference to pain polymorphism, or the need to search for any particular polymorphism at the individual at level, was absent in the great majority; some have a generic reference to this subject.

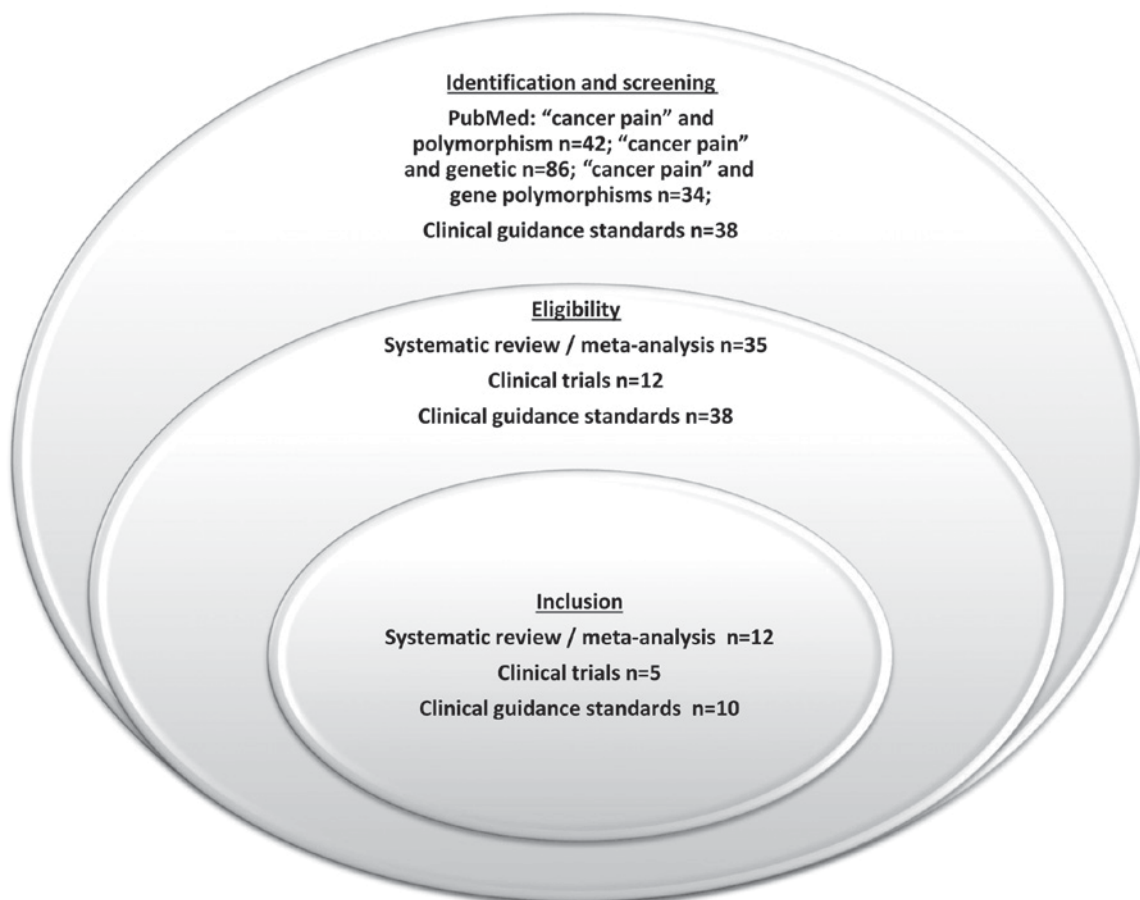


Figure 1. Flow diagram of the methods employed for the identification and selection of relevant articles included in the present evidence-based review.

The genetics associated with pain arises, as in the position paper promoted by the European Pain Federation in January 2017 (2), as an explanation for the marked inter-individual variability in responsiveness to different opioids, both in terms of analgesic benefit and toxicity (2,16). This paper refers to genetic variability in  $\mu$ -opioid receptors (central and peripheral), with different binding affinities of the opioids, and additional  $\kappa$ - and  $\delta$ -opioid receptors to explain the need for individualization of pain treatment, both in terms of response to treatment and adverse events. However, authors cite, without further specification, that other molecular, pharmacological, genetic and phenotypic factors may explain the variation in observed clinical responses (2).

The National Comprehensive Cancer Network (NCCN) guidelines (January 2018) recognizes that different polymorphisms in CYP2D6, as in some ethnic group, may justify the existence of either slow or fast metabolizers of codeine (17). Codeine is a weak  $\mu$  and  $\delta$ -opioid receptor agonist with little direct analgesic effect. The action of the cytochrome P450 enzyme-CYP2D6-is necessary to convert the prodrug into active metabolites (codeine-6-glucuronide, norcodeine, morphine, morphine-3-glucuronide, morphine-6-glucuronide and normorphine). The poor/slow metabolizers (five to ten per cent of the population) will obtain reduced or no analgesic effects and the hyper-metabolisers metabolizers (five to ten percent) may experience more rapid morphine production with increased risk of toxicity. There is considerable inter-ethnic variability in gene encoding for CYP2D6 (17,18).

The European Palliative Care Research Collaborative opioid guidelines project endorsed by MASCC (Multinational Association of Supportive Care in Cancer, also refers that approximately 8% of the European population are poor metabolizers of codeine to morphine, with resulting diminished analgesic efficacy. Also genetic polymorphisms, with impact in O-demethylation (via CYP2D6) can lead to alterations in response to tramadol in a similar way to codeine. The active metabolite, O-desmethyltramadol, has a higher affinity to the  $\mu$ -opioid receptor, than the parent drug, however *in vivo*; production seems to be slow with minimal clinically relevant accumulation (19-21). Searching for this profile is not done routinely, despite the reference in the NCCN and WHO guidelines (17,22-24). In addition to the analgesic effect, codeine is probably used more often as antitussive than analgesic, in cancer patients (17,20-25). These authors suggest that the great interindividual variation in the amount and ratios of metabolite production may not be all accounted for by known polymorphisms. For instance the CNS adverse effects have been shown to occur even in the absence of significant CYP2D6 activity, suggesting a potential role for metabolites other than morphine in toxicity (17,20,21,25).

The World Health Organization (WHO) guideline explains that both codeine and tramadol may be less analgesic in poor metabolizers (22-24). Tramadol is also extensively metabolized in the liver by demethylation, oxidation and conjugation (2-4). The main active metabolite, O-demethyl-tramadol (M1), is the result of the catalytic action of CYP 2D6 and is two to

four times more potent than the parent compound. The poor metabolizers have 14-fold lower concentrations of the active metabolite and may have less analgesic efficacy (22-25). Schug *et al* (26) based on WHO guideline proposed in Expert opinion-Pain management of the cancer patient-that polymorphisms in CYP2D6 result in a range of metabolic patterns, from ultrarapid to ultra-slow metabolizers of codeine, with some patients showing no analgesic effect at all. This paper also refers that genetic variability in morphine metabolism may have a role in neurotoxic and hyperalgesic effects of M3G, but also with the influence of genetic variants of the OPRM1 gene, encoding the  $\mu$ -opioid receptor (26).

The Centers for Disease Control and Prevention (CDC) published the CDC Guideline for Prescribing Opioids for Chronic Pain clarifying that equianalgesic dose conversions are only estimates and do not account for individual variability in genetics and pharmacokinetics. This fact is particularly relevant to patients' members of racial and ethnic minority groups that can be at risk for inadequate pain treatment (27).

Also the Canadian or Scottish guidelines support that conversion ratios for opioids are subject to variations in kinetics governed by genetics and other drugs. Even with the same chronic pain syndrome, the underlying neurobiology will differ between individuals, influencing analgesic response and side effects (18,28). Studies into factors that contribute to the inter-individual variation in response to different treatments (clinical, genetic, pharmacokinetic, neurobiological) and clinical biomarkers for predicting response to treatments are still needed. Another factor that must be considered, when assessing opioid responses, is that several opioids including codeine, tramadol, oxycodone and hydrocodone are affected by variations in metabolism, mediated by cytochrome P450 enzyme CYP2D6, resulting in unpredictable effects in individuals (18,28).

Pharmacological Management of Cancer Pain in Adults-National Clinical Guideline No. 9 was promoted by Ireland experts and classified with level 5 of evidence (based on the Centre for Evidence Based Medicine method of Oxford University) the role of CYP2D6 enzyme inhibitors or genetic polymorphisms in morphine sulphate production with reduced analgesic response. This poor or absent analgesic effect of codeine can affect approximately 7% of Caucasian people, 3% of black people and 1% of Asian people (29). Wide inter-individual variability in opioid pharmacokinetics is influenced by genetic variation but also by age, ethnicity and the presence of renal or hepatic impairment (29,30). Further prospective research may allow prediction of inter-individual response to different opioids and better opioid prescribing (27).

Summary, we can say that the guidelines are divided in 3 groups: One first group with reference to the route of metabolism of cytochrome P450 enzyme CYP2D6; a second group that presents a generic reference to the impact of the polymorphisms on pain treatment, without specifying any one; and a last group (not exhaustively referred to in this work) that does not present any reference to this matter.

*Systematic review and/or meta-analysis.* The search identified 35 systematic review and/or meta-analysis, but only 12 had direct reference to some specific polymorphism (Table I). Three reviews were excluded because they don't

have any reference to polymorphism (or genetic variation) in the abstract, five articles was only available in Japanese, Chinese or German language and three was reporting drug use in chronic non-cancer pain and the others was related with nursing practice or anti-cancer therapies or translational pain research (animal models). Data summarized in Table I.

These papers try to summarize and value the functional impact of several genotype groups/reference SNP identification. Principals polymorphism referred in this literature review and the strength of recommendation for pain polymorphisms are discussed below.

*Clinical trials.* The search identified 12 clinical trials, but only five had direct reference to some specific polymorphism in cancer patients (Table II). Clinical trials were related with polymorphisms in CYP2B6 (metabolism of ketamine), CYP2D6 (analgesia of tramadol) and UGT2B7 (morphine). One trial was related with single nucleotide polymorphism at nucleotide position 118 in the  $\mu$ -opioid receptor gene. Another reported pain outcomes and genetic variation was analyzed for 112 single nucleotide polymorphisms (SNPs) in 25 candidate genes relevant for opioid efficacy. The choice of the candidate SNPs was based on the expected clinical relevance of the variant alleles (allele frequency >0.10), previously described associations or putative functional effects related to pain and opioid pharmacology. The relevance of this papers and main findings are discussed below.

## Discussion

Revealing the relationship between genetic variations and individual differences in sensitivity to opioids will provide valuable information, for appropriate individualization of opioid doses required for adequate pain control. This evidence based review identifies the most promising polymorphism in the cancer pain treatment. However, application of this knowledge to clinical practice, creating easier to use diagnostic tools is more difficult to achieve (31).

Several candidate genes have been used to provide evidence for the genetic modulation of pain perception and response to analgesics. However due to the limited number of patients in prospective trials, the several number of genes and genetic variants investigated and the lack of clinical randomized trials, the level of evidence is in general low. Precision medicine and personalized analgesic treatments will require a more complete understanding of the effects of genetic variants and gene-gene interactions in response to analgesics (32).

According to our evaluation, three groups of polymorphism were highlighted in this research (Fig. 2; Table III). Firstly, the genetic variation of the  $\mu$ -opioid receptor may contribute to interindividual differences in morphine consumption. In the future, identifying single nucleotide polymorphisms of patients may provide information to modulate the analgesic dosage of opioid for faster achievement of satisfactory pain control (33,34). The mu opioid peptide receptor (MOP) is the principal site of pharmacologic actions for most clinically important opiate drugs, but there are more than 100 polymorphisms identified in the human  $\mu$  opioid peptide receptor (OPRM1) gene. These polymorphisms correlated with OPRM1 mRNA stability and opiate sensitivity, including

Table I. Systematic review and/or meta-analysis.

Author, year	Title	Major conclusions	Genotype groups/reference SNP identification	Evidence level	(Refs.)
Kuip <i>et al</i> , 2017	A review of factors explaining variability in fentanyl pharmacokinetics; focus on implications for cancer patients.	Patients with the CYP3A5*3 polymorphism (*3*3) had a ~2-fold higher fentanyl plasma concentration normalized by the measured absorption rate when compared with patients with the wild-type (*1*1) gene polymorphism and the patients with the heterozygous (*1*3) gene polymorphism (further research is needed).	Enzymes: CYP3A4*22; CYP3A5*3. Transporters: ABCB1 C1236T; SLCO1B1*a1 and SLCO1B*15.	1	(4)
Andersen <i>et al</i> , 2016	Personalizing supportive care in oncology patients using pharmacogenetic-driven treatment pathways.	CYP2D6 metabolizes codeine, tramadol, oxycodone and hydrocodone into their more potent metabolites. In case of new, worsening or persisting pain the CYP2D6 status should be determined. CYP2D6 ultra-rapid metabolizers and poor metabolizers should avoid tramadol, codeine, hydrocodone and oxycodone. Morphine dosing may require adjustment based on the COMT and OPRM1 genotype, as patients with GG genotypes are less sensitive to morphine's analgesic effect.	CYP2D6 genotype: Ultrarapid metabolizer *1/*1xN; *1/*2xN; *2/*2xN; Extensive metabolizer: *1/*1; *1/*2; *2/*2; *1/*9; *1/*10; *1/*41; *10/*10; *41/*41; *1/*3; *1/*4; *1/*5; *1/*6; Intermediate metabolizer: *4/*41; *5/*9; *4/*10; Poor metabolizer *3/*4; *4/*4; *5/*5; *5/*6. COMT (rs4680)-also identified as G472A, G586A, Val108Met and Val158Met. OPRM1 rs1799971.	2	(38)
Nielsen <i>et al</i> , 2015	Association Between Human Pain-Related Analgesia: An Updated Review.	Genetic variation can influence pharmacokinetics (such as drug transporters and drug-metabolizing enzymes) and/or pharmacodynamics (such as opioid receptor and catechol-O-methyltransferase enzymes). The methadone dose was increased in carriers of the 2 copies of the AGCGC (wild type) haplotype and of CGT, TTC, and TGT haplotypes composed of ABCB1 C1236T, G2677T/A, and C3435T. Methadone doses are affected by CYP2D6 phenotypes. Patients homozygous for the 118G allele (GG) required more morphine than patients homozygous for the 118Aallele (AA).	Morphine: ABCB1 C3435T; OPRM1 rs6912029, rs17999711 (A118G), rs589046, rs563649, rs9479757, rs2075572 rs533586; OPRD1 rs10504151, rs7836120, rs6473799, rs1365098, rs7016778, rs7824175, rs16918875, rs963549; OPRK1 rs1042114, rs533123, rs419335, rs2236857, rs2234918; COMT Val158Met, 11 SNPs. Tramadol/ acetaminophen OPRM1 A118G. Methadone: ABCB1 12 haplotypes; C3435T, 7 haplotypes; CYP2D6, CYP3A5, CYP2B6, CYP2C9, CYP2C19. Various: ABCB1 C3435T.	1	(31)
De Gregori <i>et al</i> , 2015	OPRM1 receptor as new biomarker to help the prediction of post mastectomy pain and recurrence in breast cancer.	OPRM1 may be used in near future to customize the opioid therapies, avoiding not only opioid side effects but also the disease progression.	OPRM1 SNP rs1799971 and rs563649.	3	(44)

Table I. Continued.

Author, year	Title	Major conclusions	Genotype groups/reference SNP identification	Evidence level	(Refs.)
Hwang <i>et al</i> , 2014	OPRM1 A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis.	The OPRM1 A118G polymorphism was associated with interindividual variability in postoperative responses to opioids. Carriers of the G-allele were observed to exhibit higher opioid analgesic requirements.	Genotypes AA AG GG (AA homozygotes and G-allele carriers).	1	(33)
Tammimäki <i>et al</i> , 2012	Catechol-O-methyltransferase gene polymorphism and chronic human pain: A systematic review and meta-analysis.	Low COMT activity has been associated with increased pain sensitivity in human pain studies and may enhance opioid analgesia and exacerbate adverse effects, at least in some cancer pains.	COMT single nucleotide polymorphism rs4680- Val158Met	1	(36)
Leppert <i>et al</i> , 2011	CYP2D6 in the metabolism of opioids for mild to moderate pain.	Experimental and clinical studies demonstrated that tramadol analgesia depends on CYP2D6 activity and is not recommend in patients with the ultra-rapid metabolizer genotype (duplication or multi-duplication of gene-mostly CYP2D6*1/CYP2D6*2 alleles) and renal impairment	>80 distinct allelic variants for CYP2D6 are known, including CYP2D6*4, CYP2D6*3, CYP2D6*6, CYP2D6*5, CYP2D6*1, CYP2D6*2, CYP2D6*10, CYP2D6*17.	3	(3)
Droney <i>et al</i> , 2011	Evolving knowledge of opioid genetics in cancer pain.	A number of different variations in the gene coding for CYP2D6 have been identified, with subsequent differential response to the codeine and morphine. The opioid pharmacogenetic studies in cancer patients that have shown some positive results have primarily focused attention on three genes; OPRM, COMT and multidrug resistance 1 gene (MDR-1).	OPRM rs1799971 (A118G), rs563649; COMT rs4680 (Val158Met), rs7290221, rs5746849; MDR-1 C3435T (rs1045642), GT2677A (rs2032582), C1236T (rs1128503); SNPs in gene coding $\beta$ -arrestin; SNPs in stat6 (MOR transcription); SNPs in UGT2B7.	2	(7)
Shi <i>et al</i> , 2010	Biological pathways and genetic variables involved in pain.	Four categories were identified for analgesic efficacy: Genes associated with receptor interaction, modulation of opioid effects, metabolism, and transport. Personalized analgesic treatment will require a more complete understanding of the effects of genetic variants and gene-gene interaction in response to pain and analgesics.	COMT: rs4680, haplotype of SNPs in intron 1, haplotype of 11 SNPs; OPRM1: rs17999711; IL-6 rs1800795; IL-8 rs4073; TNF- $\alpha$ rs1800629; ABCB1 rs1045642, rs2032582; CYP2B6 rs34830389, rs2279343; CYP2D6 rs35742686, rs3892097, rs5030655, rs5030867, rs1065852; UGT2B7 -840 G/A.	2	(32)
Andersen <i>et al</i> , 2009	Variation in the COMT gene: implications for pain perception and pain treatment.	A remarkable, complex relationship between COMT genotypes or haplotypes and pain phenotypes has been revealed. Met-allele (rs4680) was associated with a reduced need for morphine; rs740603 was associated with central side effects to morphine.	COMT gene: rs4680 (Val/ Met), rs2075507, rs737866, rs7287550, rs174680, rs7290221, rs5746849, rs740603, rs6269, rs6270A, rs4633, rs2239393, rs4680, rs165631, rs174699, rs165728.	2	(45)

Table I. Continued.

Author, year	Title	Major conclusions	Genotype groups/reference SNP identification	Evidence level	(Refs.)
Slatkin <i>et al</i> , 2009	Opioid switching and rotation in primary care: Implementation and clinical utility.	The pharmacogenetic factors influencing the opioid response and the mechanisms underlying incomplete cross-tolerance are not yet fully understood. Consequently, opioid switching and rotation remain largely trial-and-error procedures, both in terms of patient selection and with respect to implementation. There are >100 polymorphisms identified in the human MOP (OPRM1) gene. These polymorphisms may be associated with OPRM1 mRNA stability and opiate sensitivity, including opiate analgesia, tolerance, and dependence.	Opioid receptor heterogeneity (eg. OPRM1) and other genetic variations: COMT, CYP450 (CYP3A4, CYP3A5, CYP2D6), UGT, ABC1, solute carrier uptake transporters (1A2, IB3), melanocortin-1 (MIR) alleles, $\beta$ -arrestin-2 alleles.	3	(39)
Nagashima <i>et al</i> , 2007	Is there genetic polymorphism evidence for individual human sensitivity to opiates?		Referred to several reference SNP identification numbers of polymorphisms of the OPR1 gene.	2	(35)

opiate analgesia, tolerance and dependence. Particularly relevant is OPRM1 A118G polymorphism rs17999711 (33,34). In addition to the A118G polymorphism, another functional SNP (rs563649), which is located within an alternatively-spliced OPRM1 isoform (MOR-1K), has also has been the subject of several work (7,8). More precise studies are need to better understanding the relationship between gene polymorphisms and opiate sensitivity, that will allowed personalized pain treatment, by predicting opiate sensitivity and requirements for each patient (35).

Secondly, polymorphism associated to the metabolism process of morphine and other opioid drugs, mainly polymorphism of CYP enzymes, are nowadays very relevant in opioid titration and rotation. Also referenced in the literature are genetic polymorphisms in genes of uridine diphosphate glucuronosyltransferase (UGT) enzymes. Ethnic and population subgroups differences have to be taken in account. Prospective trials of cancer patients and healthy controls are need, at a national or regional level, to identify these subgroups (31). Catechol-O-methyltransferase (COMT) is one of several enzymes that metabolize catecholamines. In human studies, COMT genotype affects the efficacy of opioids in acute and chronic pain in different settings (e.g. migraines, fibromyalgia, musculoskeletal pain and cancer pain). Low COMT activity increases opioid receptors and enhances opioid analgesia and adverse effects in cancer pains. Pain animal models had elucidated the mechanism behind these findings: COMT inhibitors are pronociceptive, except for neuropathic pain. The complex network between adrenergic and dopaminergic activity in different parts of the nociceptive system may have a role in the action of low COMT activity (36).

Finally, ATP-binding cassette (ABC) family of efflux transporters consists of around 50 human members. However ABCB1 (MDR1) is the most well characterized, coding for the P-glycoprotein (P-gp) efflux transporter (31).

Among all, only two of them satisfied the proposed criteria as A level of recommendation: OPRM1 polymorphism A118G (rs1799971) and polymorphisms in cytochrome P450 enzyme-CYP2D6 (Table III). These polymorphisms were studied in randomized trials and are extensively referred in the systematic reviews and meta-analyzes. An algorithm of management of pain and polymorphism screening is proposed in the Fig. 3 (17,19,37). Actual guidelines make some appointments about these genetic variations, as responsively for interindividual differences in the response to opioids, yet almost all without, without proposed a real clinical setting to use them (17,38,39).

It is important to remind, that a combined effect of SNPs in multiple genes is possible and its investigation, at the same time, should remain a concern for prospective studies in this field. And also take in consideration, the role of environmental factor in interpatient variability in responses to opioids. Information on type of SNPs (intronic, exonic, or intergenic) was not present in the majority of these papers. Only two papers referred to intronic SNPs in COMT (rs7290221, rs5746849, rs4646312, rs6269 and rs740603). Usually intronic SNPs are not drivers, but could be functional by changing the conformation of RNA and DNA neighboring the SNPs (7,40-42).

Table II. Clinical trials.

Author, year	Type of study and the population	Intervention (reference SNP identification)	Results	Evidence level	(Refs.)
Li <i>et al</i> , 2015	Prospective cohort study. n=49 chronic pain patients.	Impact of the CYP2B6*6 allele (c.516G>T, rs3745274 and c.785A>G) on ketamine plasma clearance and on adverse effects.	CYP2B6*6 allele is associated with a substantial decrease in steady-state ketamine plasma clearance with higher plasma concentrations and incidence of adverse effects.	2	(5)
Fladvad <i>et al</i> , 2012	Prospective study, case-control (patients randomly divided). n=2201 cancer pain patients.	Pain outcomes and genetic variation was analyzed for 112 single nucleotide polymorphisms (SNPs) in 25 candidate genes relevant for opioid efficacy. HTR3A rs2276302; HTR3C rs6807670; HTR3E rs7627615; HTR3C rs6807362; HTR3D rs939334; COMT rs4646312; HTR4 rs4264931; ABCB1 rs1045642; TACR1 rs12713837; ARRB2 rs2036657; ARRB2 rs3786047; ARRB2 rs7208257; HINT1 rs3852209; STAT6 rs167769; HTR3D rs6443930; HRH1 rs346076; HTR3C rs6766410; HRH1 rs2606731; ADRA2A rs1800545; OPRM1 rs9479757; ADRA2A rs11195419; DRD3 rs963468; DRD3 rs3773679; DRD3 rs3732790; STAT6 rs3024971; GNAZ rs3788339; HTR3B rs1176744; HTR3A rs1062613; DRD2 rs1125394.	None of the examined SNPs exceeded P-values corrected for multiple testing for any of the outcomes in the EPOS study, as previously shown for opioid dose. A consensus is required if the information on genetic variation is to be used in clinical decision making, for example, as has been done previously for estimating warfarin dose, which is based on clinical and genetic data.	1	(46)
Wang <i>et al</i> , 2006	Prospective cohort study. n=70 gastric cancer Chinese patients.	Impact of CYP2D6*10 C188T polymorphism/CYP2D6*10 (100C>T) genotype on postoperative analgesic effect of tramadol.	CYP2D6*10 allele had a significant impact on analgesia with tramadol in the immediate postoperative period of gastrectomy.	2	(47)
Chou <i>et al</i> , 2006	Prospective cohort study. n=80 female patients (hysterectomy).	Contributes to the variability of morphine efficacy of the polymorphism (single nucleotide polymorphism at nucleotide position 118 in the $\mu$ -opioid receptor gene).	Cancer patients homozygous for the 118G allele require higher doses of morphine to relieve pain in postoperative period (no statistically significant difference).	2	(34)
Holthe <i>et al</i> , 2002	Prospective cohort study. n=70 cancer patients.	Investigated whether the UGT2B7 H268Y and UGT1A1*28 polymorphisms contributed to the variability in morphine glucuronide-to-morphine plasma ratios among cancer patients undergoing analgesic therapy with morphine.	UGT2B7 H268Y polymorphism cannot account for the considerable variation in glucuronide-to-morphine ratios. Contribution of UGT1A1 to the formation of M3G appears to be of minor biological significance	2	(48)



Table III. Strength of recommendation for pain polymorphisms.

Polymorphism	Impact	Recommendation level
$\mu$ -opioid receptors (central and peripheral): OPRM1 polymorphism A118G (rs1799971)	Individualization of pain treatment in terms of response to treatment and adverse events. If OPRM1 G/G genotype consider initiating morphine at a higher dose and/or more aggressive dose titration. May also influence tramadol/acetaminophen analgesic response.	A
Polymorphism in cytochrome P450 enzyme: CYP2D6 genotype (particularly CYP2D6*10 allele/C188T)	Several opioids metabolisms are affected (codeine, tramadol, oxycodone, hydrocodone, methadone). Poor metabolizers may be at risk of treatment failure due to the inability to convert the parent drug into its more active metabolite. Ultra-rapid metabolizers may be at risk of treatment-related toxicities to supratherapeutic concentrations of the more active metabolites.	A
Polymorphism in catechol-O-methyltransferase (COMT) enzyme: Single nucleotide polymorphism rs4680 (Val158Met)	Low COMT activity (Val158Met) can increase opioid receptors and enhance opioid analgesia and adverse effects. If COMT G/G genotype, consider initiating morphine at a higher dose and/or more aggressive dose titration.	B
Polymorphism in cytochrome P450 enzyme: CYP2B6*6 allele (c.516G>T, rs3745274 and c.785A>G)	Variations in metabolism of ketamine.	C
Polymorphism in cytochrome P450 enzyme: CYP3A5*3 gene single nucleotide polymorphism	May influence fentanyl pharmacokinetics.	C
Polymorphism in ABCB1 (MDR1): C1236T, G2677T/A and C3435T	Methadone doses are subject to ABCB1 genetic modulations. C3435T polymorphism (variant T allele) may influence dose requirements for others opioids (e.g. morphine).	C

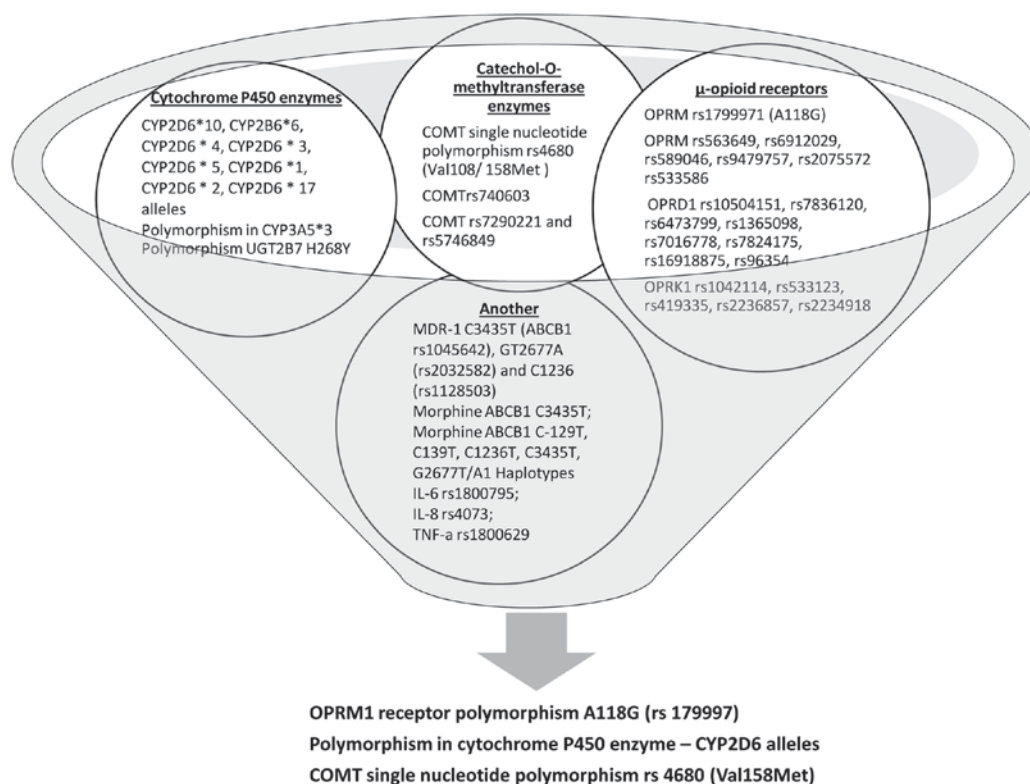


Figure 2. Principals polymorphisms referred to in the present literature review.

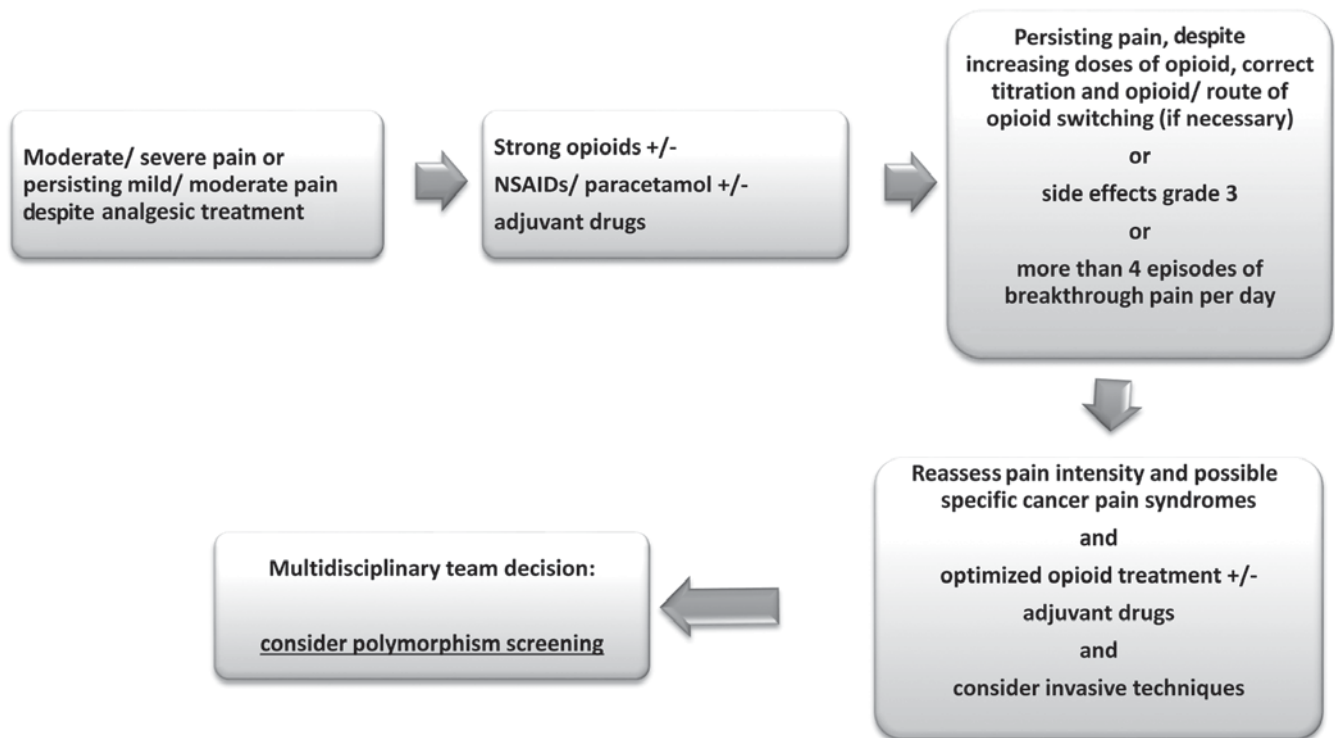


Figure 3. Proposed algorithm for the management of pain and polymorphism screening. NSAIDs, non-steroidal anti-inflammatory drugs.

The clinical utilization in daily practice is also much dependent of the cost of time and laboratory resources of these analyses (38). Pain is an oncology emergence and pain drugs titration may be incompatible with delayed laboratory tests and very expensive polymorphism determinations. Frequently the allocation of technical and economic resources to anti-cancer treatment limits the evolution of these strategies for better individualized supportive and palliative care treatment. Resources are currently limited and a global balance is needed for fairer and more equitable treatment worldwide. The identification of population or ethnic subgroups more prone to poor pain control may lead to a strategy of lowering the costs of the treatments. However, an investment in the development of laboratory tests for the rapid identification of these polymorphisms and an exhaustive training for health professionals is still an unmet need.

One limitation of this work is the criteria for the literature search, particularly the limitation to clinical guidelines, systematic reviews, meta-analyses and randomized clinical trials in English. This evidence-based review is not a systematic review, in the strict sense of the term, because they do not include reviews and systematic reviews and they need a different frame of search terms and analyses. Furthermore our goal was to apply the levels of evidence and recommending strengths of The American Family Physician's (AFP) Strength of Recommendation Taxonomy (15).

There is considerable inter-ethnic variability in gene encoding for CYP2D6. The differences between countries and the ethnic variations may result in loss of data not published in English or published in some national journals. Data from retrospective series or no randomized trials can have some importance in this field and should be addressed in a future paper. A statistical meta-analysis, with the strength of the

associations of the SNPs with pain score, is also a future project. Other aspect to take in account, is the bias frequent found on this kind of research. The papers summarized in the systems reviews and meta-analyses try to highlight differences in pain prevalence and treatment conditioned by the polymorphism or other genetic alterations, however it's difficult to eliminated the effect of numerous others factors, with influence on human pain, and specially cancer pain.

An algorithm of management of pain and polymorphism screening is proposed and three groups of polymorphism are considered of relevance for present utilization on clinical practice. Genetic variation of the  $\mu$ -opioid receptor may contribute to interindividual differences in morphine consumption (with recommendation grade A for OPRM A118G rs1799971) but there are more than 100 polymorphisms identified in the human  $\mu$  opioid peptide receptor (OPRM1) gene. Polymorphism associated to the metabolism process of morphine and other opioid drugs are nowadays very relevant in opioid titration and rotation. Ethnic and population subgroups difference have to be taken in account. A recommendation grade A was awarded for polymorphism in cytochrome P450 enzyme-CYP2D6). In human studies, COMT genotype affects the efficacy of opioids in acute and chronic pain in different settings, with recommendation grade B to COMT single nucleotide polymorphism rs4680 (Val158Met).

Consistent data on pain polymorphism is nowadays available, however with very little impact on clinical guidelines and daily oncologist practice. Persisting pain, side effects grade 3 (NCI-CTCAE version 4.0) and breakthrough pain more than 4 episodes/day are point as criteria's to pain multidisciplinary team discussion and consider polymorphism screening (43). Resources are currently limited and a global

balance is needed for fairer and more equitable treatment worldwide. An investment in the development of laboratory tests for the rapid identification of these polymorphisms is still an unmet need.

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### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

CV obtained and assessed the data for this review, proposed the levels of evidence and recommended strengths. RF, DP and RM interpreted the results of the study, the levels of evidence and the recommended strengths, and wrote the article. The final manuscript was reviewed and approved by all authors.

### Ethics approval and consent to participate

Not applicable.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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