



REVIEW

Progress, Challenges, and Prospects of Research on the Effect of Gene Polymorphisms on Adverse Reactions to Opioids

Jinsong Zhao · Shihong Cai · Long Zhang · Yuefeng Rao ·
Xianhui Kang · Zhiying Feng

Received: January 1, 2022 / Accepted: March 7, 2022 / Published online: April 16, 2022
© The Author(s) 2022

ABSTRACT

The abuse of opioids has become one of the most serious concerns in the world. Opioid use can cause serious adverse reactions, including respiratory depression, postoperative nausea and vomiting, itching, and even death. These adverse reactions are also important complications of clinical application of opioid drugs that may affect patient safety and recovery. Due to the fear of adverse reactions of opioids, clinicians often do not dare to use opioids in an adequate or appropriate amount, thus affecting the clinical medication strategy and the quality of treatment for patients. The prediction of

adverse reactions to opioids is one of the most concerned problems in clinical practice. At present, the correlation between gene polymorphism and the efficacy of opiates has been widely studied and preliminarily confirmed, but the research on the effect of gene polymorphism on the adverse reactions of opiates is relatively limited. Existing studies have made encouraging progress in predicting the incidence and severity of adverse opioid reactions and clinical management by using genetic testing, but most of these studies are single-center, small-sample clinical studies or animal experiments, which have strong limitations. When the same receptor or enzyme is studied by different experimental methods, different or even opposite conclusions can be drawn. These phenomena indicate that the correlation between gene polymorphism and adverse opioid reaction still needs further research and demonstration. At present, it is still too early to use genetic testing to predict opioid adverse reactions in clinic. In this paper, the correlation between gene polymorphism and adverse opioid reactions and a small number of clinical applications were reviewed in terms of pharmacokinetics and pharmacodynamics, in order to provide some suggestions for future research and clinical drug decision making.

J. Zhao · S. Cai · L. Zhang · Z. Feng (✉)
Department of Pain, The First Affiliated Hospital,
Zhejiang University School of Medicine, No. 79
Qingchun Road, Hangzhou 310003, Zhejiang,
China
e-mail: fzy1972@zju.edu.cn

J. Zhao · L. Zhang
Department of Anesthesiology, Ningbo No. 6
Hospital, Ningbo, China

Y. Rao
Department of Pharmacy, The First Affiliated
Hospital, Zhejiang University School of Medicine,
Hangzhou, Zhejiang, China

X. Kang
Department of Anesthesiology, The First Affiliated
Hospital, Zhejiang University School of Medicine,
Hangzhou, Zhejiang, China

Keywords: Single-nucleotide polymorphism; Opioid; Adverse reaction; Pharmacogenomics; Analgesics; Precision medicine

Key Summary Points

A possible uncertain correlation between single-nucleotide polymorphisms (SNPs) and opioid adverse reactions is being investigated.

A variety of genes, including those affecting the pharmacokinetics and pharmacodynamics of opioids, may promote or inhibit the occurrence of adverse reactions to opioids, but this possible role has not been effectively demonstrated.

At present, evidence-based approaches are lacking from most studies focused on the effects of SNPs on adverse reactions to opioids, and most are single-center studies. The results of studies on the same genotype can be contradictory.

Pharmacogenomics (PGx) can tailor the use of specific analgesics based on different genotypes, improving the efficacy of the analgesics and minimizing adverse reactions to opioids.

INTRODUCTION

Opioids are used for acute pain (e.g., perioperative analgesia), moderate and severe cancer pain, and malignant chronic pain [1], and are the cornerstone of analgesic therapy. However, the abuse of opioids has become one of the most serious public health concerns in the world, especially in North America [2]. Due to the significant difference in the number and sensitivity of opioid receptors in the central distribution, individuals have great differences in drug dose and efficacy [3]. How to apply the minimum dose of opiates to obtain the maximum effect has been a research hotspot in

recent years. However, in clinical formulation of medication strategies, in addition to considering the efficacy of opioids, adverse reactions of opioids are an important factor limiting their use [4]. These include severe postoperative nausea and vomiting (PONV), respiratory depression (RD), lethargy, and constipation [5]. Some patients have experienced obvious adverse reactions without the expected analgesic effect of opioids, which seriously affect the quality of life of patients [6]. These adverse reactions can even lead to death due to severe respiratory depression [7], or it may force clinicians to lower or even stop opioid medication, resulting in further pain [8]. Therefore, the study of individual differences in adverse reactions to opioids is actually one of the most important factors for clinical use to ensure patient safety and formulate medication strategies. A large number of studies have used single-nucleotide polymorphism (SNP) as a tool and have found a significant correlation between the analgesic effect of opioids and SNP, with significant differences in the pharmacodynamics and pharmacokinetics of opioids in patients with different SNP [9, 10]. This indicates that the demand for opioid analgesia is different among individuals, which is likely to lead to huge differences in individual adverse reactions to opioids. In recent years, studies have increasingly begun to focus on the correlation between SNP and adverse reactions to opioids [11], expecting to find a new way to clinically predict the occurrence or severity of adverse reactions in patients. Most of these pioneering studies are animal experiments or single-center, small-sample clinical studies, and the results of these studies are sometimes ambiguous or even conflicting due to the excessive factors influencing the adverse reactions to opioids. However, these relatively limited research results may provide some hints for the future research direction of precision medicine and more rational opioid medication strategy. This paper is an objective review of the existing research content.

Methods

This is a review of the correlation between gene polymorphism and opioid adverse reactions, and the prospect of pharmacogenomics (PGx) application in precision medicine is discussed. We searched relevant articles within the PubMed, Scopus, and Cochrane databases, considering publications up to Jan 2022. All searches used the following research key words: (single nucleotide polymorphism OR SNP OR SNPs) AND (pain OR cancer pain OR chronic pain) AND (opioid OR opiates) AND (adverse reaction OR adverse reactions OR pharmaceutical side effect) AND (pharmacogenomics OR PGx) AND (analgesics OR analgesia) AND (precision medicine OR precision medicine initiative). Only full-length original articles were accepted, and the search was limited to English-language publications. Inclusion criteria were as follows: (1) articles involving acute pain (e.g., surgical or postoperative pain) or chronic severe and malignant pain requiring analgesic treatment with opioids; (2) the authors suggest a potential association between gene polymorphisms and opioid adverse reactions. It is important to note that this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Studies on the correlation between gene polymorphism and clinical efficacy of opiates are mainly carried out from two perspectives: pharmacokinetics and pharmacodynamics. Studies of the pharmacokinetics and SNP correlation of opioids have mainly investigated the differences in metabolism and clearance rates of opioids among different individuals from the perspective of drug transporters (including the ABC family and OCT1 family) and drug metabolic enzymes (such as the CYP family and UGT family). Studies on the correlation between opioid efficacy and SNP have focused on the differences in affinity between individual opioids and corresponding receptors, including OPRM1 and CHRM3. At present, most studies show that gene polymorphism has a significant effect on the pharmacodynamics and pharmacokinetics of opiates [12]. This effect may also

be one of the important factors leading to the different incidence and severity of adverse opioid reactions among individuals. Below, we will objectively explain the correlation between adverse reactions to opioids and SNP from the two perspectives of pharmacokinetics and pharmacodynamics, respectively, based on existing relevant studies.

POLYMORPHISMS AFFECTING PHARMACOKINETIC FACTORS

Drug Transporters

Two transporter superfamilies with the most common clinical concerns are the ATP-binding cassette (ABC) transporters and the solute carrier (SLC) transporters, as they play a crucial role in drug absorption, distribution, metabolism and elimination (ADME) [13]. Although a large number of studies have shown that ABCB1 gene polymorphism in the ABC family and OCT1 gene polymorphism in the SLC family have significant effects on opioid metabolism [14], there are some studies that disagree [15]. Therefore, we only review current studies that are based on the correlation between gene polymorphisms of the above two transporters and adverse opioid reactions, and do not suggest genetic testing of opioids for these two gene polymorphisms.

ABCB1

The target of opioids is mainly in the central nervous system (CNS), so the transport of opiates across the blood–brain barrier (BBB) is one of the key factors affecting the efficacy and clearance of opiates. Opioids enter the CNS via the BBB mainly through passive transport, while removal is mainly through an efflux transporter at the BBB [16]. These efflux transporters are essential for the prevention and treatment of adverse reactions caused by opioid abuse and overdose. ABCB1-coded P-glycoprotein (P-gp) is an efflux transporter that limits intracellular drug accumulation by pumping compounds out of cells [17]. A study in mice showed that P-gp is one of the main

components of the blood–cerebrospinal fluid (CSF) barrier. As an outward drug transporter for ATP energy supply, P-gp plays an important role in regulating the clearance of opioids from the CNS [18]. ABCB1 and C. 3435C>T polymorphisms are associated with adult morphine BBB transporter activity, and the homozygous TT genotype is associated with a higher maximum morphine concentration in the CSF than that observed in those with other genotypes [19]. This correlation can lead to an increase in the incidence of opioid-related respiratory depression after surgery [20]. Recent research has revealed that mutations in ABC family genes in the morphine response pathway affect the clinical outcome of morphine administration, including RD, in children [21]. Chidambaran et al. [22] first confirmed that ABCC3 variation has a significant effect on the pharmacokinetics of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G). A further study selected 42 ABCC3 gene polymorphisms for comparative analysis of the incidence of RD and the incidence of prolonged anesthesia recovery time caused by RD. The results revealed that although there was no significant statistical association between ABCC3 polymorphism and RD, seven ABCC3 polymorphisms located in the 48731392-48744612 bp chromosome 17 region, especially two adjacent polymorphisms, rs739923 and rs4148412, resulted in a significant association with prolonged recovery time in the postanesthesia care unit (PACU).

Compared with mean duration to achieve PACU discharge readiness (duration of PACU stay), children with these high-risk genotypes for prolonged RD stayed in the PACU about 50 min longer [21]. This finding suggests that polymorphisms found in specific regions of the ABCC3 gene (CHR17: 48731392-48744612) are associated with severe RD.

OCT1

Opioids are mainly metabolized in hepatocytes [23], so the rate of uptake of opioids by hepatocytes is one of the important factors determining the rate of opioid metabolism. OCT1 (alternative name SLC22A1) is a transporter in the liver that transports morphine from the

bloodstream to hepatocytes. The downregulation of OCT1 protein expression due to the gene polymorphisms and decreased OCT1 transporter activity results in a decrease in intrahepatic morphine uptake, a decrease in the morphine clearance rate, and an increase in systemic morphine levels. The higher the plasma morphine level, the higher the incidence of morphine-induced PONV and RD will be. An in vitro study by Tzvetkov et al. [24] showed that overexpression of OCT1 by HEK293 cells is associated with a fourfold increase in morphine uptake. OCT1 genotypic variation can affect morphine clearance, characterized by decreased morphine clearance in children with OCT1 genotypic deficiency [25]. This genotype may affect the incidence of morphine-related adverse reactions. In a prospective study of 311 children who underwent tonsillectomy, Balyan et al. [26] found an association between non-synonymous polymorphisms in the OCT1 gene and morphine-induced adverse postoperative outcomes. There was a significant correlation between OCT1 SNP rs12208357 and refractory PONV, and another SNP, rs72552763, was associated with RD. Previous studies have suggested that both SNP rs12208357 and SNP rs72552763 are associated with reduced liver intake of morphine in European Americans [27]. However, their expression was not observed in the Asian population [28]. This finding suggests that race is an important factor in adverse reactions to opioids (Table 1).

Drug-Metabolizing Enzymes

The liver is the main site of opioid metabolism, in which opioids are dealkylated by cytochrome P450 enzymes [29]. Different enzymes metabolize different opioids. For example, CYP2D6 is the main enzyme involved in the metabolism of codeine, hydrocodone, and oxycodone. Another cytochrome P450 enzyme, CYP3A5, is involved in the metabolism of the opioids fentanyl and oxycodone. UGT2B7 is involved in drug glucuronidation, which is related to improved analgesic effects [30]. Genetic polymorphisms of these drug-metabolizing enzymes can yield 0- to 10,000-fold differences in drug

Table 1 Drug transporter genetic variations associated with clinical outcomes

Gene	Phenotype/ genotype	Functionally important allelic variant(s)	Effects associated with variant allele(s)	References
ABCB1	TT	C.3435C>T	Increases the incidence of RD in adults	[14]
	GG/GA	rs9282564	Increases the incidence of RD in children	
ABCC3	GG	rs739923	Significantly prolongs PACU stay associated with RD	[16, 17]
	AA	rs4148412		
OCT1		Multiple SNPs, including rs12208357 rs72552763 GAT deletion	Increases risk for morphine-related PONV and RD, leading to a prolonged PACU stay	[20]

RD, respiratory depression; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting

efficacy [31], thus affecting the incidence of opioid-related adverse reactions.

CYP2D6

Because of its extensive enzyme activity, CYP2D6 is generally classified according to its unique genotype [32]. According to the activity of CYP2D6 allele-related enzymes, CYP2D6 genotypes are divided into ultrafast metabolite (UM), extensive or normal metabolite (EM/NM), intermediate metabolite (IM), or poor metabolite (PM) phenotypes [33]. Many studies have shown that CYP2D6 polymorphisms are associated with adverse events after opioid intake. Candiotti et al. [34] found that the copy number of the CYP2D6 allele influenced the success or failure of ondansetron for PONV prevention. Another comparative study showed that UM patients with three active alleles of CYP2D6 vomited more than EM or PM patients [35]. This effect is because codeine, tramadol, and hydrocodone are degraded into morphine, nortramadol, and hydroxymorphinone, respectively, by CYP2D6. The degradation products of codeine, tramadol, and hydrocodone have stronger analgesic efficacy and lead to an increase in the incidence of adverse reactions, while CYP2D6 PM will lead to a decrease in degradation and reduced effects [36]. In contrast, a case report suggests that CYP2D6 UM status predisposes patients to severe respiratory depression [37]. These findings suggest that

choosing which metabolic type of opioid to administer based on the individual's CYP2D6 genotype may lead to improved, individualized dosing and reduced adverse reactions to opioids after surgery.

FAAH

The fatty acid amide hydrolase (FAAH) gene encodes the FAAH enzyme that hydrolyzes endocannabinoids such as anandamide and other classes of lipids [38, 39]. Anandamide acts on cannabinoid (CB) receptors and potentiates opioid action, as evidenced by its ability to attenuate naloxone-induced morphine withdrawal in mice [40, 41]. Hence, in patients receiving opioids such as morphine, factors that increase anandamide levels or decrease anandamide hydrolysis would be expected to potentiate opioid effects, such as in individuals with FAAH variants that reduce function, thus affecting anandamide hydrolysis. Sadhasivam et al. [42] showed a significant correlation between FAAH SNP rs324420 and refractory PONV after tonsillectomy and a prolonged stay in the recovery room due to opioid-induced RD. Chidambaran et al. [43] also proved a significant correlation between the FAAH SNP rs324420 and morphine-induced RD by analyzing the hypercapnic ventilatory response (HCVR). In addition, they found that the incidence of PONV in individuals with the AA genotype of rs11576941 was 2.14 times higher

than that in those with other genotypes. In the future, prospective genotyping could be used to predict the potentially high incidence of opioid-induced RD and PONV in children with certain FAAH gene mutations, which is conducive to promoting personalized pain management.

PDE3A

SNP rs12305038 is a missense variant in exon 1 of the PDE3A gene, which encodes phosphodiesterase 3A. This protein belongs to a class of enzymes that degrades cGMP and cAMP and is an important regulator of cyclic nucleotide signaling in numerous pathways [44]. Phosphodiesterase (PDES) is involved in the morphine addiction pathway (HSA05032 KEGG pathway), as well as the bitter and sweet signaling pathways of the morphine addiction pathway [45]. In the European Opioid Genetics Study (EPS), Colombo et al. [46] calculated and analyzed the nausea and vomiting score (NVS) after opioid analgesia in 1494 cancer patients and found a strong correlation between PDE3A rs12305038 and NVS. Thus, mutations in these taste-altering enzymes may also modulate the response to nausea and vomiting.

UGT2B7

The biological significance of UGT2B7 C802T mutations in the opioid response remains controversial. Some studies have shown that the T allele is associated with a higher morphine-6-glucoside (M6G)/morphine plasma ratio [47], resulting in improved analgesic effects due to the increased potency of M6G [48]. Other published studies have shown no relationship between the genotype and the M6G-to-morphine ratio and a lack of improved analgesic effects associated with M6G [49, 50]. Among the studies on the relationship between this gene and opioid adverse reactions, a Japanese study found that 802T carriers had a lower frequency of nausea than noncarriers among cancer patients administered morphine for analgesia [51]. Contradictory results suggest that C802T decreases opioid requirement among postpartum patients and increases risk for CNS depression among mothers and their breastfeeding infants [8]. To date, few studies on the

relationship between UGT2B7 gene polymorphisms and morphine pharmacokinetics have been conducted, and related adverse reactions need to be further studied (Table 2).

POLYMORPHISMS AFFECTING PHARMACODYNAMIC FACTORS

CHRM3 (M3 Muscarinic Acetylcholine Receptor)

M3 muscarinic acetylcholine receptor, one of five subtypes (M1–M5) of muscarinic receptors, is the predominant muscarinic subtype mediating acetylcholine-induced airway smooth muscle contraction, found throughout the CNS and peripheral tissue [52]. Recently, three studies have revealed the association between the CHRM3 rs2165870 polymorphism and PONV risk, with conflicting results. A genome-wide association study (GWAS) explored the association between a number of loci and PONV risk [53]. They observed that the CHRM3 rs2165870 polymorphism GG + AA genotype only was associated with PONV risk, even after repeated adjustment. Two subsequent studies have shown that the CHRM3 rs2165870 polymorphism AA or GA genotype is associated with an increased risk for PONV [54, 55]. Wang et al. [56] found that the AA genotype or allele of the CHRM3 rs2165870 polymorphism increased the risk for PONV in the Chinese Han population. Further studies showed that carriers of the AA genotype or A allele responded to ondansetron treatment within 2 h postoperatively, while the effect of ondansetron for PONV was reduced 2–24 h postoperatively in these patients. These studies suggest that the CHRM3 rs2165870 polymorphism may be an important marker to predict ondansetron response among PONV patients. Clinicians should use other drugs to inhibit PONV in patients with AA genotype 2–24 h after surgery. The possible reason for the difference in research results is the difference in experimental design. Some studies adopt the DNA-pooling approach to conduct GWAS studies, which is cost-effective and has low reliability. It is also easier to make strong correlation on the statistical strength of the

Table 2 Drug-metabolizing enzyme genetic variations associated with clinical outcomes

Gene	Phenotype/ genotype	Functionally important allelic variant(s)	Effects associated with variant allele(s)	References
CYP2D6	UM		Increases the incidence of RD but has no significant effect on PONV	[29, 32]
	EM			
	PM			
	IM		Decreases the incidence of RD	
FAAH	AA	Multiple SNPs, including rs324420, rs11576941, and rs4141694	High risk for morphine-induced respiratory depression and PONV in children; decreased hypercarbic ventilator response and impending respiratory depression in the pediatric postoperative setting	[15, 37]
	CC		Less risk for PONV and RD than children with CA and AA genotypes	[37]
PDE3A		rs12305038	Strongly correlated with PONV	[40]
UGT2B7		C802T	Some studies have shown that C802T can reduce the incidence of PONV, while contradictory results suggest that C802T decreases opioid requirement among postpartum patients and an increases risk for CNS depression among mothers and their breastfeeding infants	[24, 45]

EM, extensive metabolizer (normal); IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer; RD, respiratory depression; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting

identified associations. Other studies using the individual SNP-genotyping approach have shown the opposite [46].

OPRM1

OPRM1 encodes the μ -opioid receptor, which is the main target receptor of opiates. An SNP of OPRM1, A118G, has been a major focus of opioid response pharmacogenetics research. Hwang et al. [57] recently showed in a meta-analysis that the OPRM1-A118G polymorphism is associated with interindividual differences in postoperative opioid responses. In reviews and subsequent studies, some authors investigated the effect of the OPRM1-A118G polymorphism on postoperative adverse reactions after anesthesia, primarily PONV. Although A118G has been reported to be associated with

postoperative side effects, the results of different studies have varied widely. Zhang et al. [58] found that AA, AG, and GG genotypes showed no significant differences in effects on nausea and vomiting. Liu also studied the association between the A118G polymorphism and the incidence of postoperative nausea, vomiting, and itching. After Bonferroni correction, no significant difference in PONV incidence was found between the A genotype group and the G + G genotype group [59]. On the other hand, Lee et al. [60] randomly assigned 416 patients who underwent local mastectomy under general anesthesia to the general intravenous anesthesia group (T group) and inhalation anesthesia group (I group). The results showed that the PONV score of OPRM1 patients in the AA and AG T groups was significantly lower

than that of those in the I group. In the GG-type patients, there were no differences in any parameters between the T and I groups. It is suggested that polymorphisms of the μ -opioid receptor can affect the occurrence of PONV, thus affecting the choice of anesthesia method and improving the anesthesia experience of patients. Kong et al. [61] showed in the latest meta-analysis of the relationship between OPRM1 and PONV that the A118G polymorphism (rs1799971) may be associated with postoperative vomiting, but not with nausea, itching, or dizziness. The contradictions in these studies suggest that larger, well-designed studies with greater ethnic variation are required to validate the association between OPRM1 and PONV.

DRD2 Taq IA (Dopamine D2 Receptor TaqIA)

The dopamine receptor antagonists metoclopramide and haloperidol have been successfully used to prevent and treat PONV, suggesting that DRD2 may play a role in the occurrence and development of PONV. Previous studies have shown that the DRD2 TaqIA polymorphism is associated with DRD2 density in the striatum [62] and caudate nucleus [63]. Individuals carrying the A2A2 allele have higher DRD2 density and are more sensitive to dopaminergic stimulation, thus indicating a higher incidence of PONV. Nakagawa et al. [64] analyzed the relationship between dopamine D2 receptor TaqIA polymorphisms and PONV occurrence. The study included 1070 patients, 303 of whom underwent gastrointestinal surgery. The presence of PONV was analyzed at 6 and 24 h postoperatively. They found that the A2A2 allele of the dopamine D2 receptor Taq IA polymorphism increased the risk for PONV in the first 6 h after surgery. Frey et al. [65] also found a significant correlation between the TaqIA A2 allele and PONV history in 306 patients with strabismus after surgery. Due to the lack of studies on the relationship between this polymorphism and PONV, these results cannot be confirmed, and further studies are needed.

5-HT3B Receptor

The 5-HT₃ receptor is a ligand-gated ion channel with five distinct subunits (5-HT_{3a}, B, C, D, and E) [66]. A common polymorphism in the 5-HT_{3b} subunit is the deletion of -100_-102AAG [67]. Kim et al. [68] found that in patients treated with remifentanyl during anesthesia, the incidence of PONV was higher in Asian-American patients with two alleles of the 5-HT_{3B} receptor gene (deletion/deletion genotype) than in those with other genotypes (insertion/deletion and insertion/insertion) 2 h after the first postoperative drug administration. Screening for this gene deletion in patients at high risk for PONV may have some significance in guiding the drug treatment of PONV.

lncRNA MIR4300HG

In addition to the genetic factors of SNPs mentioned above, in other PONV-associated genes, the effect of SNPs on PONV was smaller than that of clinical factors [67, 69]. But mutations in unknown genes may also play an important role in PONV regulation. Exploring this question requires additional genotyping and genome-wide testing. Sugino et al. [70] designed and developed a Japanese-specific DNA chip for high-throughput SNP genotyping based on whole-genome sequencing. Then, they identified a novel SNP (rs11232965) associated with PONV in the lncRNA miR4300Hg.1070 in Japanese patients. This suggests a potential molecular mechanism of PONV and may enable the prediction of PONV occurrence (Table 3).

PGx Advocates for Preoperative Genetic Screening to Guide Analgesic Protocols and Personalize Precision Medicine

I. PGx Can Be Used for the Preoperative Screening of Severe Adverse Reactions to Perioperative Anesthesia and Analgesia

The most clinically useful genes to identify in the preoperative decision-making phase are those known to present potentially life-threatening anesthesia reactions or adverse effects. Pharmacogenetic testing may take several different forms. Clinicians possibly order single-gene tests through large laboratory companies.

Table 3 Association between genetic polymorphism related to pharmacodynamics and adverse drug reactions to opioids

Gene	Phenotype/ genotype	Functionally important allelic variant(s)	Effects associated with variant allele(s)	References
CHRM3	AA/GA/ GG	rs2165870	The risk of PONV was increased	[46–48]
	AA		The response to ondansetron was weakened 2–24 h after surgery	[49]
OPRM1		A118G (rs1799971)	The incidence of PONV is lower in patients with the AA/AG type after general intravenous anesthesia	[53] [54]
DRD2 Taq IA	A2A2		The A2A2 allele of the DRD2 Taq IA polymorphism increased the risk of PONV in the first 6 h postoperatively	[57]
5-HT3B		-100-102AAG deletion	The incidence of PONV was higher in patients with AAG deletion in the two alleles of the 5-HT3B receptor gene	[61]
lncRNA MIR4300HG		rs11232965	The lncRNA miR4300HG may be a potential correlation with the incidence of PONV, but current studies still lack sufficient evidence	[63]

RD, respiratory depression; PONV, postoperative nausea and vomiting

Patients can be referred to physician medical geneticists or genetic counselors, although many of these clinics in the United States focus on prenatal genetic testing or cancer genetics. At some institutions, preoperative evaluation clinics partner with a third-party vendor to offer pharmacogenetic testing via saliva samples at the time of the preoperative clinic visit. This panel possibly includes the hyperthermia (RYR1) and pseudocholinesterase deficiency (BCHE) genes, as well as those involved in opioid metabolism. This will offer the opportunity to identify patients at risk before administering anesthesia and reduce adverse effects [71]. Of course, given the high cost of this technique and the uncertainty of its effectiveness, we do not recommend genetic testing as a routine preoperative examination at present.

PGx can also guide the selection of analgesics following major abdominal surgery. Senagore et al. [72] evaluated a consecutive series of patients undergoing open or laparoscopic

colorectal and major ventral hernia surgery who received pharmacogenetic testing prior to surgery (PGx group) and compared them to a historical group (H group) of patients who underwent the same operations but were managed with their standard enhanced recovery protocol. The overall benefit of analgesia score (OBAS) was used to assess the combined impact on analgesia, patient satisfaction, and the impact of drug-associated side effects [73]. The results demonstrated a significantly lower OBAS rating ($p < 0.01$) for the PGx group than for the H group, representing a reduction in the score. Similarly, the pain subscore of the OBAS demonstrated a statistically significant improvement in analgesia reported by patients in the PGx group. This indicates that PGx-guided postoperative analgesia not only achieves good analgesic effects but also reduces related adverse reactions.

II. Clinical Implementation of Genotype Guidance Can Be Used to Monitor Analgesic Security Profiles and Limit Adverse Drug Effects in Patients with Chronic Pain (CP)

The CYP2D6 gene is highly polymorphic, with over 100 alleles defined. UMs with multiple gene copies are at increased risk for adverse drug effects, including life-threatening toxicities, compared to NMs. For patients with PM, IM, or UM phenotypes (based on genotype results), pharmacists recommend avoiding codeine, hydrocodone, oxycodone, and tramadol. The Clinical Pharmacogenetics Implementation Consortium (CPIC) developed guidelines that recommend monitoring the responses of patients administered codeine [74]. In a precision medicine-guided treatment for cancer pain pragmatic clinical trial [75], 142 patients were evaluable, of whom 43 consented for the pharmacogenomics team. Anxiety, appetite, depression, drowsiness, fatigue, nausea, pain, shortness of breath, and well-being were evaluated on a scale from 0 (no symptoms) to 10 (worst severity), using the Edmonton Symptom Assessment Scale. In the pharmacogenomics team, subjects were tested for multiple SNP genotypes, including catechol-o-methyl transferase (COMT), OPRM1 (A118G), and the CYP family. Physicians reviewed the results of genetic tests and adjusted the treatment regimen based on the literature and CPIC guidelines. At the end of the trial, while there was no significant difference in pain improvement between the two groups based on whether or not there was a pharmacogenomics test, 15 of the 43 patients in the genetic testing group had an actionable genotype for therapy modification and showed significantly more improvement in their pain than the other patients in the group (73% vs. 46%). This trial is unique because it will provide prospective data on pain-related outcomes with clinical implementation of genotype-guided pain management in a real-world setting.

Pharmacogenomic-guided prescription applied to chronic pain and in other therapeutic areas has been shown to be a rational tool for precision medicine [76]. If this intervention proves beneficial, it could significantly improve pain management and limit adverse drug

effects, which are common issues with opioids (Fig. 1).

III. Future Perspective of PGx in Clinical Practice

The implementation of PGx in clinical practice is still challenging. Medical personnel do not have the ability to effectively genotype the efficacy or adverse reactions of specific drugs, so it is difficult to use PGx as a tool to improve treatment [77]. This may be the greatest obstacle limiting the clinical use of PGx. The CPIC and the Dutch Pharmacogenetics Working Group have worked tirelessly to identify the best matches between several genes and drugs and have published relevant guidelines. These guidelines help clinicians select the most appropriate drug based on the genotype of the patient to achieve the best efficacy while minimizing adverse reactions. Unfortunately, patients encountered in clinical work are highly variable, and there is not a one-to-one correspondence between genotype and specific drug. Specific drugs often act on different genetic targets, resulting in adverse reactions that are difficult to be explained simply by a single genotype. However, for patients with severe adverse drug reactions, drug monitoring in combination with PGx may still be beneficial.

In addition, the cost of PGx gene testing also restricts its clinical application. Codeine is commonly used to treat postpartum pain in the United States, but this drug can cause drowsiness and respiratory depression in infants, which can lead to death in severe cases. Prenatal testing for specific genotypes of codeine is available, but Moretti et al.'s study showed that an additional \$7700 was needed to avoid one adverse event in the infant [78]. Such low efficiency is harder to afford by ordinary people. Of course, if the number of patients who agree to genetic testing increases, the cost can be spread evenly and reduced.

CONCLUSION

Precision medicine requires that postoperative analgesia treatment achieve the best analgesic effect with minimum adverse reactions. PGx

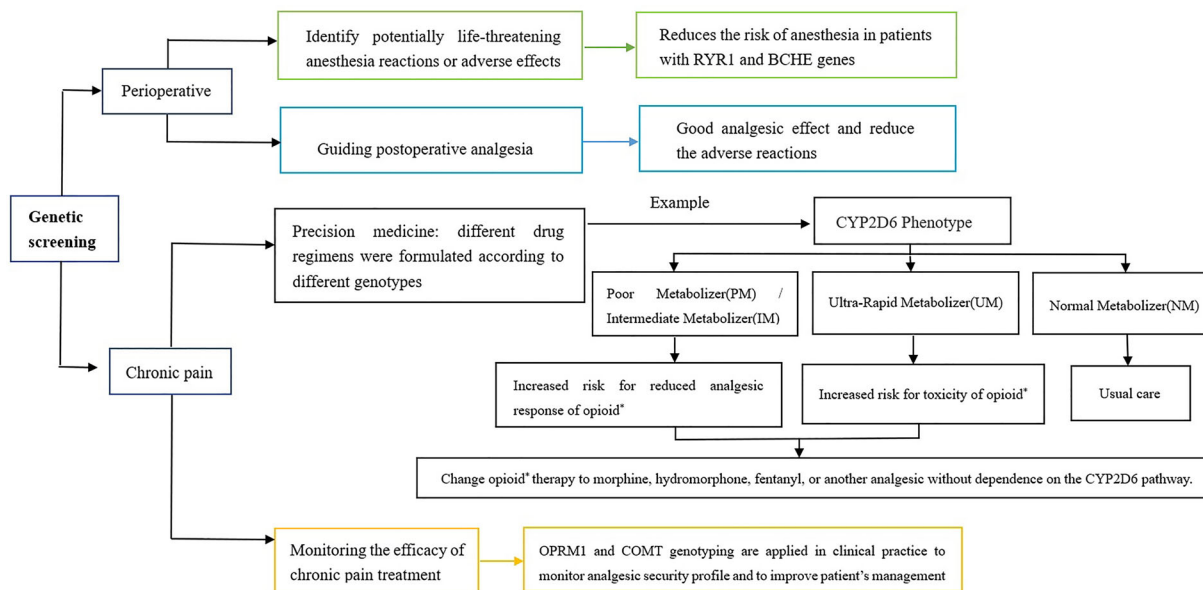


Fig. 1 Clinical application of genetic screening. RYR1, hyperthermia; BCHE, pseudocholinesterase deficiency; OPRM1, μ -opioid receptor gene; COMT, catechol-o-methyl transferase; *codeine, hydrocodone, oxycodone, and tramadol

could help physicians avoid risks and adverse experiences resulting from RD and PONV, but there is insufficient evidence to confirm which gene polymorphism predicts postoperative adverse reactions to opioids. To date, the application of PGx in the analgesia field has been limited to isolated, single-center studies with a small sample size; there is a lack of evidence-based medicine approaches, and the conclusions are often contradictory. There is also a lack of evidence-based study of the positive effects of PGx on analgesia approaches. It is also important to note that individual responses to opioids are determined by polygenetic inheritance, and the role of any single gene is limited. This results in a low cost-effectiveness ratio for genetic testing, which is the greatest obstacle to the application of PGx in precision medicine.

In future research, we should pay attention to the interactions among SNPs in multiple genes and the interaction between genes and the environment; additionally, it is necessary to conduct a large number of multicenter and multiethnic studies.

ACKNOWLEDGEMENTS

The authors thank the patient for participating in this project.

Funding. This work was supported by Key R&D Program of Zhejiang (No. 2022C03081) and Ningbo Yinzhou district agricultural and social development science and technology project fund (No. 20180229). The Rapid Service Fee was funded by Key R&D Program of Zhejiang.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Authorship Contributions. Jinsong Zhao and Zhiying Feng contributed to the concept of the manuscript and outline. Jinsong Zhao, Shihong Cai and Long Zhang were responsible for writing the manuscript. Yuefeng Rao, Xianhui

Kang and Zhiying Feng were responsible for editing.

Disclosures. Jinsong Zhao, Shihong Cai, Long Zhang, Yuefeng Rao, Xianhui Kang and Zhiying Feng have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

1. Babu KM, Brent J, Juurlink DN. Prevention of opioid overdose. *N Engl J Med*. 2019;380(23):2246–55.
2. Marchand K, Tallon C, Katan C, Fairbank J, Fogarty O, Pellatt K, et al. Improving treatment together: a protocol for a multi-phase, community-based participatory, and co-design project to improve youth opioid treatment service experiences in British Columbia. *Addict Sci Clin Pract*. 2021;16(1):53.
3. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol*. 2013;75(1):60–78.
4. Pasternak GW. Mu opioid pharmacology: 40 years to the promised land. *Adv Pharmacol*. 2018;82:261–91.
5. Stein C. Opioid analgesia: recent developments. *Curr Opin Support Palliat Care*. 2020;14:112–7.
6. Vijayvargiya P, Camilleri M, Vijayvargiya P, Erwin P, Murad MH. Systematic review with meta-analysis: efficacy and safety of treatments for opioid-induced constipation. *Aliment Pharmacol Ther*. 2020;52(1):37–53.
7. Smith M, Kong D, Kuo A, Imam M, Williams C. Analgesic opioid ligand discovery based on non-morphinan scaffolds derived from natural sources. *J Med Chem*. 2022;65(3):1612–61.
8. Yang J, Bauer BA, Wahner-Roedler DL, Chon TY, Xiao L. The modified WHO analgesic ladder: is it appropriate for chronic non-cancer pain? *J Pain Res*. 2020;13:411–7.
9. Ma J, Li W, Chai Q, Tan X, Zhang K. Correlation of P2RX7 gene rs1718125 polymorphism with post-operative fentanyl analgesia in patients with lung cancer. *Med (Baltim)*. 2019;98(7):e14445.
10. Ho KWD, Wallace MR, Staud R, Fillingim RB. OPRM1, OPRK1, and COMT genetic polymorphisms associated with opioid effects on experimental pain: a randomized, double-blind, placebo-controlled study. *Pharmacogenomics J*. 2020;20(3):471–81.
11. Tanaka R, Sato J, Ishikawa H, Sato T, Shino M, Ohde Y, et al. Influence of genetic variants of opioid-related genes on opioid-induced adverse effects in patients with lung cancer: A STROBE-compliant observational study. *Med (Baltim)*. 2021;100(44):e27565.
12. Singh A, Zai C, Mohiuddin AG, Kennedy JL. The pharmacogenetics of opioid treatment for pain management. *J Psychopharmacol*. 2020;34(11):1200–9.
13. Nigam SK. What do drug transporters really do? *Nat Rev Drug Discov*. 2014;14(1):29–44.
14. Ahmed S, Choudhry Z, Bhatti J. Impact of genetic polymorphisms on opioid misuse: a scoping review. *Pharmacogenomics*. 2019;20(9):685–703.
15. Kuhlmann I, Hjelmar-Petersen R, Overgaard M, Dornonville-de-la-Cour K, Zwisler S, Bjerregaard-Stage T, et al. No significant influence of OCT1 genotypes on the pharmacokinetics of morphine in adult surgical patients. *Basic Clin Pharmacol Toxicol*. 2022;130(1):93–102.

16. Brown JA, Faley SL, Shi Y, Hillgren KM, Sawada GA, Baker TK, et al. Advances in blood–brain barrier modeling in microphysiological systems highlight critical differences in opioid transport due to cortisol exposure. *Fluids Barriers CNS*. 2020;17(1):38.
17. Mora-Lagares L, Pérez-Castillo Y, Minovski N, Novič M. Structure-function relationships in the human P-glycoprotein (ABCB1): insights from molecular dynamics simulations. *Int J Mol Sci*. 2022;23(1):362.
18. Thompson S, Koszdin K, Bernards C. Opiate-induced analgesia is increased and prolonged in mice lacking P-glycoprotein. *Anesthesiology*. 2000;92(5):1392–9.
19. Meineke I, Freudenthaler S, Hofmann U, Schaeffeler E, Mikus G, Schwab M, et al. Pharmacokinetic modelling of morphine, morphine-3-glucuronide and morphine-6-glucuronide in plasma and cerebrospinal fluid of neurosurgical patients after short-term infusion of morphine. *Br J Clin Pharmacol*. 2002;54(6):592–603.
20. Sadhasivam S, Chidambaran V, Zhang X, Meller J, Esslinger H, Zhang K, et al. Opioid-induced respiratory depression: ABCB1 transporter pharmacogenetics. *Pharmacogenomics J*. 2015;15(2):119–26.
21. Chidambaran V, Venkatasubramanian R, Zhang X, Martin L, Niu J, Mizuno T, et al. ABCC3 genetic variants are associated with postoperative morphine-induced respiratory depression and morphine pharmacokinetics in children. *Pharmacogenomics J*. 2017;17(2):162–9.
22. Venkatasubramanian R, Fukuda T, Niu J, Mizuno T, Chidambaran V, Vinks A, et al. ABCC3 and OCT1 genotypes influence pharmacokinetics of morphine in children. *Pharmacogenomics*. 2014;15(10):1297–309.
23. Hasselstrom J, Sdwe J. Morphine pharmacokinetics and metabolism in humans enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. *Clin Pharmacokinet*. 1993;24(4):344–54.
24. Tzvetkov M, dos Santos-Pereira J, Meineke I, Saadatmand A, Stingl J, Brockmüller J. Morphine is a substrate of the organic cation transporter OCT1 and polymorphisms in OCT1 gene affect morphine pharmacokinetics. *Biochem Pharmacol*. 2013;86(5):666–78.
25. Fukuda T, Chidambaran V, Mizuno T, Venkatasubramanian R, Ngamprasertwong P, Olbrecht V, et al. OCT1 genetic variants influence the pharmacokinetics of morphine in children. *Pharmacogenomics*. 2013;14(10):1141–51.
26. Balyan R, Zhang X, Chidambaran V, Martin L, Mizuno T, Fukuda T, et al. OCT1 genetic variants are associated with postoperative morphine-related adverse effects in children. *Pharmacogenomics*. 2017;18(7):621–9.
27. Shu Y, Leabman M, Feng B, Mangravite L, Huang C, Stryke D, et al. Evolutionary conservation predicts function of variants of the human organic cation transporter, OCT1. *Proc Natl Acad Sci USA*. 2003;100(10):5902–7.
28. Singh O, Chan J, Lin K, Heng C, Chowbay B. SLC22A1-ABCB1 haplotype profiles predict imatinib pharmacokinetics in Asian patients with chronic myeloid leukemia. *PLoS ONE*. 2012;7(12):e51771.
29. Gerhard G, Kaniper S, Paynton B. Fentanyl overdoses and pharmacogenetics. *Pharmacogenet Genomics*. 2020;30(1):5–8.
30. Baber M, Bapat P, Nichol G, Koren G. The pharmacogenetics of opioid therapy in the management of postpartum pain: a systematic review. *Pharmacogenomics*. 2016;17(1):75–93.
31. Smith H. Opioid metabolism. *Mayo Clin Proc*. 2009;84(7):613–24.
32. Crews K, Gaedigk A, Dunnenberger H, Klein T, Shen D, Callaghan J, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther*. 2012;91(2):321–6.
33. The Human Cytochrome P450 (CYP) Allele Nomenclature Database. <http://www.cypalleles.ki.se>. Accessed Aug 2014.
34. Candiotti K, Birnbach D, Lubarsky D, Nhuch F, Kamat A, Koch W, et al. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology*. 2005;102(3):543–9.
35. Janicki P. Cytochrome P450 2D6 metabolism and 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Med Sci Monit*. 2005;11(10):RA322–328.
36. Lötsch J, Rohrbacher M, Schmidt H, Doehring A, Brockmüller J, Geisslinger G. Can extremely low or high morphine formation from codeine be predicted prior to therapy initiation? *Pain*. 2009;144:119–24.
37. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, et al. Codeine intoxication associated with

- ultrarapid CYP2D6 metabolism. *N Engl J Med.* 2004;351(27):2827–31.
38. Scavone J, Sterling R, Van Bockstaele E. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience.* 2013;248:637–54.
39. Devane W, Hanus L, Breuer A, Pertwee R, Stevenson L, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Sci (N Y).* 1992;258(5090):1946–9.
40. Vela G, Ruiz-Gayo M, Fuentes J. Anandamide decreases naloxone-precipitated withdrawal signs in mice chronically treated with morphine. *Neuropharmacology.* 1995;34(6):665–8.
41. Yamaguchi T, Hagiwara Y, Tanaka H, Sugiura T, Waku K, Shoyama Y, et al. Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice. *Brain Res.* 2001;909:121–6.
42. Sadhasivam S, Zhang X, Chidambaran V, Mavi J, Pilipenko V, Mersha T, et al. Novel associations between FAAH genetic variants and postoperative central opioid-related adverse effects. *Pharmacogenomics J.* 2015;15(5):436–42.
43. Chidambaran V, Pilipenko V, Spruance K, Venkatasubramanian R, Niu J, Fukuda T, et al. Fatty acid amide hydrolase-morphine interaction influences ventilatory response to hypercapnia and postoperative opioid outcomes in children. *Pharmacogenomics.* 2017;18(2):143–56.
44. Francis S, Blount M, Corbin J. Mammalian cyclic nucleotide phosphodiesterases: molecular mechanisms and physiological functions. *Physiol Rev.* 2011;91(2):651–90.
45. Amrein H, Bray S. Bitter-sweet solution in taste transduction. *Cell.* 2003;112(3):283–4.
46. Colombo F, Pintarelli G, Galvan A, Noci S, Corli O, Skorpen F, et al. Identification of genetic polymorphisms modulating nausea and vomiting in two series of opioid-treated cancer patients. *Sci Rep.* 2020;10(1):542.
47. Sawyer M, Innocenti F, Das S, Cheng C, Ramírez J, Pantle-Fisher F, et al. A pharmacogenetic study of uridine diphosphate-glucuronosyltransferase 2B7 in patients receiving morphine. *Clin Pharmacol Ther.* 2003;73(6):566–74.
48. Portenoy R, Thaler H, Inturrisi C, Friedlander-Klar H, Foley K. The metabolite morphine-6-glucuronide contributes to the analgesia produced by morphine infusion in patients with pain and normal renal function. *Clin Pharmacol Ther.* 1992;51(4):422–31.
49. Holthe M, Rakvåg T, Klepstad P, Idle J, Kaasa S, Krokan H, et al. Sequence variations in the UDP-glucuronosyltransferase 2B7 (UGT2B7) gene: identification of 10 novel single nucleotide polymorphisms (SNPs) and analysis of their relevance to morphine glucuronidation in cancer patients. *Pharmacogenomics J.* 2003;3(1):17–26.
50. Lötsch J, Kobal G, Stockmann A, Brune K, Geislinger G. Lack of analgesic activity of morphine-6-glucuronide after short-term intravenous administration in healthy volunteers. *Anesthesiology.* 1997;87(6):1348–58.
51. Fujita K, Ando Y, Yamamoto W, Miya T, Endo H, Sunakawa Y, et al. Association of UGT2B7 and ABCB1 genotypes with morphine-induced adverse drug reactions in Japanese patients with cancer. *Cancer Chemother Pharmacol.* 2010;65(2):251–8.
52. Xiaofei-Cheng QY, Liu J, Ye J, Xiao GZH, Pan Y, Li X, Hao R, et al. Constitutional 763.3 Kb chromosome 1q43 duplication encompassing only CHRM3 gene identified by next generation sequencing (NGS) in a child with intellectual disability. *Mol Cytogenet.* 2019;12:16.
53. Janicki P, Vealey R, Liu J, Escajeda J, Postula M, Welker K. Genome-wide Association study using pooled DNA to identify candidate markers mediating susceptibility to postoperative nausea and vomiting. *Anesthesiology.* 2011;115(1):54–64.
54. Klenke S, de Vries G, Schiefer L, Seyffert N, Bachmann H, Peters J, et al. Genetic contribution to PONV risk. *Anaesthesia Crit Care Pain Med.* 2020;39(1):45–51.
55. Klenke S, de Vries G, Schiefer L, Seyffert N, Bachmann H, Peters J, et al. CHRM3 rs2165870 polymorphism is independently associated with postoperative nausea and vomiting, but combined prophylaxis is effective. *Br J Anaesth.* 2018;121(1):58–65.
56. Wang J, Li Y, Zheng C, Sun Y, Yang J. CHRM3 rs2165870 polymorphism correlates with postoperative nausea and vomiting incidence and the efficacy of ondansetron in a Chinese Han population. *Pharmacogenom Personal Med.* 2020;13:319–26.
57. Hwang I, Park J, Myung S, Ahn H, Fukuda K, Liao Q. OPRM1 A118G gene variant and postoperative opioid requirement: a systematic review and meta-analysis. *Anesthesiology.* 2014;121(4):825–34.
58. Zhang W, Chang Y, Kan Q, Zhang L, Lu H, Chu Q, et al. Association of human micro-opioid receptor gene polymorphism A118G with fentanyl analgesia consumption in Chinese gynaecological patients. *Anaesthesia.* 2010;65(2):130–5.

59. Liu J, Hu D, Jiang Y, Xi H, Li W. Association between single nucleotide polymorphisms in the OPRM1 gene and intraoperative remifentanyl consumption in northern Chinese women. *Pharmacology*. 2014;94:273–9.
60. Lee S, Kim J, Park S, Oh C, Kim S. Effects of μ -Opioid receptor gene polymorphism on postoperative nausea and vomiting in patients undergoing general anesthesia with remifentanyl: double blinded randomized trial. *J Korean Med Sci*. 2015;30(5):651–7.
61. Kong Y, Yan T, Gong S, Deng H, Zhang G, Wang J. Opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) and postoperative nausea and vomiting. *Am J Transl Res*. 2018;10(9):2764–80.
62. Thompson J, Thomas N, Singleton A, Piggott M, Lloyd S, Perry E, et al. D2 dopamine receptor gene (DRD2) Taq1 A polymorphism: reduced dopamine D2 receptor binding in the human striatum associated with the A1 allele. *Pharmacogenetics*. 1997;7(6):479–84.
63. Noble E. The D2 dopamine receptor gene: a review of association studies in alcoholism and phenotypes. *Alcohol (Fayetteville, NY)*. 1998;16(1):33–45.
64. Nakagawa M, Kuri M, Kambara N, Tanigami H, Tanaka H, Kishi Y, et al. Dopamine D2 receptor Taq IA polymorphism is associated with postoperative nausea and vomiting. *J Anesth*. 2008;22(4):397–403.
65. Frey U, Schnee C, Achilles M, Silvanus M, Esser J, Peters J. Postoperative nausea and vomiting: the role of the dopamine D2 receptor TaqIA polymorphism. *Eur J Anaesthesiol*. 2016;33(2):84–9.
66. Fasching P, Kollmannsberger B, Strissel P, Niesler B, Engel J, Kreis H, et al. Polymorphisms in the novel serotonin receptor subunit gene HTR3C show different risks for acute chemotherapy-induced vomiting after anthracycline chemotherapy. *J Cancer Res Clin Oncol*. 2008;134(10):1079–86.
67. Rueffert H, Thieme V, Wallenborn J, Lemnitz N, Bergmann A, Rudlof K, et al. Do variations in the 5-HT3A and 5-HT3B serotonin receptor genes (HTR3A and HTR3B) influence the occurrence of postoperative vomiting? *Anesth Analg*. 2009;109(5):1442–7.
68. Kim M, Lee J, Choi E, Kim E, Choi S. Association of 5-HT3B receptor gene polymorphisms with the efficacy of ondansetron for postoperative nausea and vomiting. *Yonsei Med J*. 2015;56(5):1415–20.
69. Hayase T, Sugino S, Moriya H, Yamakage M. TACR1 gene polymorphism and sex differences in postoperative nausea and vomiting. *Anaesthesia*. 2015;70(10):1148–59.
70. Sugino S, Konno D, Kawai Y, Nagasaki M, Endo Y, Hayase T, et al. Long non-coding RNA MIR4300HG polymorphisms are associated with postoperative nausea and vomiting: a genome-wide association study. *Hum Genomics*. 2020;14(1):31.
71. Chaturvedi R, Alexander B, Court AA, et al. Genomics testing and personalized medicine in the pre-operative setting: Can it change outcomes in postoperative pain management? *Best practice & research. Clin Anaesthesiol*. 2020;34(2):283–95.
72. Senagore A, Champagne B, Dosokey E, Brady J, Steele S, Reynolds H, et al. Pharmacogenetics-guided analgesics in major abdominal surgery: further benefits within an enhanced recovery protocol. *Am J Surg*. 2017;213(3):467–72.
73. Lehmann N, Joshi G, Dirkmann D, Weiss M, Gulur P, Peters J, et al. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth*. 2010;105(4):511–8.
74. Crews K, Gaedigk A, Dunnenberger H, Leeder J, Klein T, Caudle K, 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.
75. Patel JN, Boselli D, Hamadeh IS, Pharm L, et al. Pain management using clinical pharmacy assessments with and without pharmacogenomics in an oncology palliative medicine clinic. *JCO Oncol Pract*. 2020;16:e166–74.
76. Lazaridis K. Improving therapeutic Odyssey: preemptive pharmacogenomics utility in patient care. *Clin Pharmacol Ther*. 2017;101(1):39–41.
77. Just K, Steffens M, Swen J, Patrinos G, Guchelaar H, Stingl J. Medical education in pharmacogenomics—results from a survey on pharmacogenetic knowledge in healthcare professionals within the European pharmacogenomics clinical implementation project Ubiquitous Pharmacogenomics (U-PGx). *Eur J Clin Pharmacol*. 2017;73(10):1247–52.
78. Moretti M, Lato D, Berger H, Koren G, Ito S, Ungar W. A cost-effectiveness analysis of maternal CYP2D6 genetic testing to guide treatment for postpartum pain and avert infant adverse events. *Pharmacogenomics J*. 2018;18(3):391–7.