

# Update on the pharmacogenomics of pain management

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**Abstract:** Pharmacogenomics is the study of genetic variants that impact drug effects through changes in a drug's pharmacokinetics and pharmacodynamics. Pharmacogenomics is being integrated into clinical pain management practice because variants in individual genes can be predictive of how a patient may respond to a drug treatment. Pain is subjective and is considered challenging to treat. Furthermore, pain patients do not respond to treatments in the same way, which makes it hard to issue a consistent treatment regimen for all pain conditions. Pharmacogenomics would bring consistency to the subjective nature of pain and could revolutionize the field of pain management by providing personalized medical care tailored to each patient based on their gene variants. Additionally, pharmacogenomics offers a solution to the opioid crisis by identifying potentially opioid-vulnerable patients who could be recommended a nonopioid treatment for their pain condition. The integration of pharmacogenomics into clinical practice creates better and safer healthcare practices for patients. In this article, we provide a comprehensive history of pharmacogenomics and pain management, and focus on up to date information on the pharmacogenomics of pain management, describing genes involved in pain, genes that may reduce or guard against pain and discuss specific pain management drugs and their genetic correlations.

**Keywords:** pharmacogenomics, pharmacogenetics, pain, anesthesiology, polymorphism, genetics

## Introduction

Pain affects approximately 100 million Americans and furthermore costs the US approximately \$600 billion per year.<sup>1</sup> According to the International Association for the Study of Pain, pain is defined as “an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage or described in terms of such damage”.<sup>2</sup> Pain can be acute or chronic; somatic or visceral; nociceptive, neuropathic, or inflammatory in nature. Nociceptive pain refers to the response to noxious stimuli and continues only in the maintained presence of noxious stimuli.<sup>3</sup> Inflammatory pain results from injury of tissues and subsequent activation of inflammatory markers, which sensitize nociceptive pathways resulting in patients experiencing pain with otherwise innocuous stimuli and heightens sensitivity of pain perception. Neuropathic pain is the maladaptive response of the nervous system to damage.<sup>4</sup> Lower back pain is the primary cause of disability worldwide and has a prevalence of 9.4%, which increases with age. Approximately 20% of US adults have chronic pain and it is one of the most common reasons adults seek medical care.<sup>5,6</sup> Chronic pain is particularly debilitating because it affects all aspects of life including physical, mental, social, occupational, and

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family environments.<sup>7</sup> Additionally, psychiatric disorders are common among patients with chronic pain and include depression (2–83%), anxiety (1–65%) and substance use disorders (1–25%).<sup>8</sup>

There are several options available to treat pain, including nonpharmacologic measures, pharmacotherapy, and surgical interventions. Opioids are commonly used to treat pain conditions however, they have the potential to be abused and to cause addiction. Misuse of prescription opioids (including abuse, dependence, and overdose) is a serious public health problem and costs approximately \$78 billion per year in the US.<sup>9</sup> The Centers for Disease Control and Prevention (CDC) officially declared fatal prescription drug overdose as an epidemic in 2012.<sup>10</sup> More recently in 2017, approximately 70,237 people died due to drug overdose (including illicit drugs and prescription drugs) of which, 25% were due to prescription opioids. And overall from 1999–2017, 218,000 people have died in the US from opioid overdoses. Taken together, opioids are clearly a potential danger to certain patients, but until recently, pain management physicians had no way to decipher which patients could become addicted. Pharmacogenomics can be a powerful tool to tackle the opioid epidemic, by which physicians could elucidate individual genetic variants in patients, and thus, patient potential for drug abuse.

Pharmacogenomics is the study of the role of the genome in drug response. It focuses on the genetic variants that impact drug effects through changes in a drug's pharmacokinetics (the study of how the organism affects the drug, ie, absorption, distribution, metabolism, elimination) or pharmacodynamics (the study of how a drug affects an organism, ie, physiologic, biochemical, and molecular effects of drugs on the body and involves receptor binding and chemical interactions).<sup>11</sup> In 1959, Friedrich Vogel first created the term “pharmacogenetics”, however, the origins of pharmacogenomics can be traced back to 510 BC. Pythagoras observed that some individuals ingesting fava beans experienced potentially fatal hemolytic anemia, whereas others did not. It was later found out to be due to an inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD).<sup>12</sup> Elliott Vesell and George Page showed that monozygotic twins displayed significantly less variability in antipyrine pharmacokinetics.<sup>13</sup> In the 1960s, Price Evans et al observed a considerable variation of isoniazid metabolism among certain individuals and believed it to be due to genetic factors.<sup>14</sup> Decades later, Blum et al showed that the genetic polymorphism in isoniazid acetylation was

due to inherited variants in the gene encoding N-acetyltransferase 2 (*NAT2*).<sup>15</sup> Subsequent studies showed the pattern of inheritance for many drug effects, and in 1987 *CYP2D6* (the hepatic cytochrome P450 2D6), the first polymorphic human drug metabolizing gene to be cloned.<sup>16</sup> For an explanation of gene nomenclature, see Table 1. Since then, hundreds of *CYP2D6* alleles have been identified. *CYP2D6* is highly polymorphic; it accounts only for 2–5% of the total hepatic P450 enzymes; however, it is involved in the metabolism of 25% of all drugs used in clinical practice.<sup>17</sup> Several commonly used opioids, including codeine, tramadol, hydrocodone, oxycodone are metabolized by *CYP2D6*. The analgesic effect of codeine stems from its conversion to morphine; and, the amount of morphine produced from the parent drug codeine can be highly variable between individuals depending on rate of metabolism of codeine, which is in turn dependent on the *CYP2D6* polymorphism of the individual. Individuals with certain gene alleles can be classified into metabolic categories: ultrarapid metabolizer (UM) with higher than normal function of the enzyme, extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) where an individual has little or no enzymatic action.<sup>18</sup> These differences reinforce the fact that individual patients vary significantly in their response to the “universal” doses of opioids that are used in practice where one dose of medicine can be ineffective to one person and lethal to another.

Several candidate genes involved in the metabolism of opioids (pharmacokinetic related candidate genes such as *CYP2D6*, *CYP3A4/A5*, *UGT2B7*, *ABCB1*, *ABCC3*, *SLC22A1*) and pharmacodynamic related candidate genes such as *OPRM1*, *COMT*, *KCNJ6*) are under investigation and seem promising for clinical use in the future.<sup>19</sup> Knowledge of pharmacogenomics is slowly being integrated into mainstream clinical practice. For example, Vanderbilt university is carrying out panel-based pharmacogenomic testing through the Vanderbilt Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment

**Table 1** Gene nomenclature explanation

CYP2C19*17	
CYP	Superfamily
2	Family
C	Subfamily
19	Gene
*17	Allelic variant

(PREDICT) program and has enrolled more than 10,000 patients.<sup>20</sup> StJude's Children's Research Hospital has developed the PG4KDS protocol which aims to use the pharmacogenetic tests in the electronic health record (EHR) to preemptively guide prescribing.<sup>21</sup> In 2016, ACPE (Accreditation Council for Pharmacy Education) incorporated pharmacogenomics into pharmacy education and pharmacogenomics is included as one of the factors that should be emphasized in the evidence-based clinical decision-making and medication therapy management aspects of clinical practice.<sup>22</sup>

Pharmacogenomics is rapidly evolving, and numerous efforts are in the pipeline to apply the knowledge of pharmacogenomics into clinical practice so as to offer better and safer healthcare to patients. In this article, we focus on the pharmacogenomics of pain management, describing genes involved in pain, genes that may reduce or guard from pain and discuss specific pain management drugs and their genetic correlation.

## Types of pain

### Acute pain

Acute pain is characterized by pain that has an inciting event, is sudden in onset, is time-limited, and has the potential to develop into a pathological condition.<sup>23</sup> By providing information about the location and magnitude of harmful stimuli, acute pain heightens vigilance and promotes appropriate responses to address the stimuli.<sup>24</sup> In this way, acute pain is characterized as having a useful biological purpose. Acute pain typically lasts less than 3 months and its treatment involves interrupting painful nociceptive signals and addressing their underlying cause.<sup>25,26</sup>

### Chronic pain

In contrast to acute pain, chronic pain is a disease state that serves no biological purpose, lacks a recognizable endpoint, and if related to disease or injury, extends beyond

the time period expected for healing.<sup>25</sup> Chronic pain usually lasts longer than 3–6 months and is considered a unique clinical entity.<sup>26</sup> Many patients with chronic pain additionally experience changes involving emotion, behavior, and affect.<sup>24</sup> Chronic pain can be subdivided into several etiologies (see Figure 1).<sup>26</sup> Treatment of chronic pain involves a multidisciplinary approach and the utilization of various therapeutic strategies.<sup>25</sup>

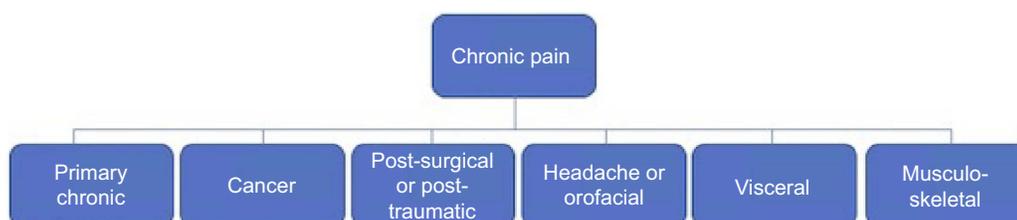
## Inflammatory pain

Inflammatory pain is due to the excitability of peripheral nociceptive fibers due to anti-inflammatory mediators such as cytokines, chemokines, bradykinin, prostaglandins, and proteases.<sup>27</sup> These mediators are released by injured tissues and activated immune cells in response to harmful stimuli and interact with one of the following categories of receptors: G-protein coupled receptors, tyrosine kinase receptors, and ionotropic receptors. Regardless of the receptor utilized, the result of these receptor-ligand interactions is the lowering of action potential threshold via depolarization and subsequent hyperexcitability of sensory neurons.<sup>27</sup>

Both acute and chronic pain are characterized by regulation of gene expression within the sensory neuron, which includes modification in the expression of receptors implicated in pain sensation. Changes in receptor transcription during acute inflammation involves local changes at the site of inflammation. In contrast, chronic inflammation prompts transcriptional changes at the level of the dorsal root ganglion.<sup>27</sup>

## Neuropathic pain

Neuropathic pain is caused by malfunction of the somatosensory nervous system and is characterized by both positive and negative symptoms such as sensations of burning and evoked pain.<sup>28,29</sup> Conditions associated with neuropathic pain include diabetes, HIV infection, alcohol abuse, vitamin or mineral deficiencies, and vasculitis.<sup>29</sup> Neuropathic pain is relatively common and occurs in



**Figure 1** Types of chronic pain.

25% of diabetic patients and 35% of HIV-positive patients.<sup>28</sup> Clinically, neuropathic pain must be differentiated from nociceptive pain because management differs between the two.<sup>29</sup> Current first-line medications for the treatment of neuropathic pain include serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, gabapentin, and pregabalin. Second-line options include transdermal patches of capsaicin or lidocaine. Opioids are reserved as third-line agents.<sup>28</sup>

## Cancer pain

Up to 80% of patients with invasive cancer experience cancer pain, and the number of cancer diagnoses is estimated to reach 20 million by the year 2025.<sup>30,31</sup> Unfortunately, up to 50% of cancer patients have inadequate pain control and 25% actually die in pain.<sup>30</sup> As such, cancer pain is a significant clinical problem and optimizing its management is important. Although the exact pathophysiology is not fully understood, cancer pain is thought of as a distinct pain entity resulting from complicated interactions between neoplastic cells and cells of the patient's immune and neurological systems. Opioids are the most effective pharmacologic agents in the treatment of cancer pain.<sup>31</sup>

## Other factors that result in individual pain differences

### Environmental factors

Environmental factors likely contribute to the multifactorial causes of individual pain symptom differences among patients. Associations between pain severity and demographic factors such as race, ethnicity, preferred language, sex, and age have been reported.<sup>32</sup> An inverse relationship between socioeconomic status and chronic widespread pain prevalence has also been described.<sup>33</sup> For instance, lower levels of education were found to be significantly and inversely related to more severe pain and functional impairment in women with chronic pelvic pain.<sup>34</sup> Additionally, living in less affluent areas is associated with frequent analgesic use and increased morbidity of chronic noninflammatory musculoskeletal pain when compared to patients living in more affluent areas.<sup>35</sup>

The relationship between stress, illness, and pain is complex. While short-term stress has several positive effects, such as enhanced immune system activity, chronic stress may contribute to illness and variances in pain perception.<sup>36</sup> In adolescents, perceived stress may be related

to variation in pain intensity and probability of reporting pain.<sup>37</sup> Stress is also thought to potentiate pain in patients with fibromyalgia.<sup>38</sup> Along with other environmental and psychological factors, stress has also been described as a risk factor for the development of tension headaches.<sup>39</sup>

The interplay between pharmacologic agents may also contribute to individual pain differences amongst patients. The use of certain psychoactive drugs such as benzodiazepines or selective serotonin reuptake inhibitors in patients undergoing surgery has been associated with significantly higher utilization of morphine postoperatively when compared to patients who did not take such drugs preoperatively.<sup>40</sup>

### Biological factors

Age and gender also contribute to differences in pain management and pain perception. Age-dependent differences in distribution, metabolism, and elimination of various medications make age a critical consideration for medication dose requirements. For example, advanced age has been associated with increased sensitivity to the analgesic effects of morphine.<sup>40</sup> Studies examining sex-related differences in opiate utilization in the postoperative period have found that men consume more morphine postoperatively than women.<sup>41</sup>

### Psychological factors

The interaction between depression and pain symptoms is a growing area of study, and numerous reviews have described associations between depression and pain.<sup>33,35,42</sup> Both the prevalence of pain in depressed cohorts and the prevalence of depression in pain cohorts are higher than when these two conditions are examined in isolation.<sup>43</sup> Psychological factors such as anxiety and depression have been described as risk factors for the development of tension headaches.<sup>39</sup> Additionally, it has been suggested that psychological factors may contribute to the observation that low socioeconomic status is inversely associated with higher levels of chronic pain. After controlling for psychological factors, the strength of this inverse relationship is lessened.<sup>33</sup> Thus while it is generally accepted that that pain symptoms and psychological factors such as depression are common comorbidities, a thorough understanding of the interplay between the two is complicated and not fully understood.<sup>43</sup>

### Genetic factors

Individual responses to opioids have been examined using twin studies, which estimate that 24–60% of the variances

in cold-pressor pain and heat pain are attributable to genetic factors.<sup>44</sup> Epigenetic mechanisms are thought to play a role in both the expression of nociceptive genes and the evolution of acute pain into chronic pain.<sup>45</sup> Interestingly, single nucleotide polymorphisms (SNPs) within specific genes (*caspase 9*, *interleukin 16*) increase the rate of self-reporting of pain by patients without interfering with the progression of underlying disease processes.<sup>45</sup> Additionally, polymorphisms involving the serotonin 5-HT<sub>2A</sub> receptor, serotonin transporter, and dopamine-4 receptor are more common in patients with fibromyalgia.<sup>45</sup> Harnessing the genetic polymorphisms in transporters, receptors, drug-metabolizing enzymes, and other drug targets linked to individual differences in the efficacy and the toxicity of drugs can revolutionize the field of pain management.

## Ethnic factors

There is considerable evidence suggesting ethnicity is also a factor in pain differences.<sup>46</sup>

For example, African Americans report greater pain and suffering compared to Caucasians for conditions such as glaucoma, AIDS, migraine, jaw pain, headache, postoperative pain, angina pectoris, joint pain, arthritis, myofascial pain.<sup>47</sup> Furthermore, 27% of African Americans and 28% of Hispanics over 50 years old report having severe pain most of the time, compared to only 17% of non-Hispanic white individuals.<sup>48</sup> African Americans also have lower thresholds for pain, cold, heat, pressure, and ischemia compared to Caucasians.<sup>49</sup> American Indians, Alaska Natives and Aboriginal people of Canada also have a higher prevalence of pain symptoms and painful conditions compared to the general US population.<sup>50</sup> Individuals from Singapore and individuals of Malayan descent have a lower pain severity compared

to Chinese individuals, whereas Indian individuals report greater pain severity compared to Malayan and Chinese individuals.<sup>51</sup> Australian women also rate menstrual pain as more intense compared to Chinese women.<sup>52</sup> Swedes report more frequent pain in lower back, neck, shoulders, hands, and elbows compared to Sami (northern Scandinavian indigenous individuals) men and women.<sup>53</sup> There are also intra-ethnic differences that should be accounted for. For example, one study examining European individuals found significant differences in the way in which pain was expressed by individuals from different European countries, yet there were no reported differences in pain perception.<sup>54</sup> This same group also reported different emotional responses to chronic pain and pain intensity within a group of individuals classified as white.<sup>55</sup> This group included Hispanic, old American (third-generation US born non-Hispanic Caucasian), Irish, Italian, French-Canadian and Polish heritages. The Hispanic group reported significantly higher pain intensity ratings, followed by Italians. Overall, there is a wide variety of individual differences in pain, especially when considering ethnicity. Health-care providers should take these differences into account when treating patients for pain.<sup>81,82,120</sup> See Table 2.

## Biological polymorphisms involved in pain

### Cytokines

Pathological pain involves the release of pro-inflammatory cytokines from activated macrophages in response to stress or injury. In contrast, some cytokines produced, such as IL-10, have anti-inflammatory properties that act in opposition to the pro-inflammatory cytokines.

IL-6 is a pro-inflammatory cytokine linked to responses to nerve injury and has effects on regeneration and feelings

**Table 2** Ethnic differences in CYP2D6 activity

CYP2D6 genetics		
Type	Activity	Ethnic differences
Poor metabolizer	None	Asian: 0-1.2%, African American: 2–5%, Ethiopian/Nigerian: 1.8-8.1%, Caucasians: 3–10%, Mexican American/Hispanic: 2.2–6.6%
Intermediate metabolizer	Low	Asian: 51%, Caucasian: 1-2%, Ethiopian/Nigerian: NA, Mexican American/Hispanic: NA
Extensive metabolizer	Normal	Most individuals fall into this category
Ultrarapid metabolizer	High	Asian: 0.9%, Danes and Finns: 1%, Ethiopian/Nigerian: 29-30%, Greeks: 10%, Mexican American/Hispanic: 1.7%, North Americans (white): 0.8-4.3%, Portuguese: 10%, Saudis: 20%

**Notes:** Data from these studies.<sup>81,82</sup>

of neuropathic pain. A study examining IL-6 infusions intrathecally revealed IL-6 causes increased neuronal responses and hyperalgesia to temperature changes.<sup>56</sup> Another study analyzing inflammatory cytokines and pain reported that following primary total knee arthroplasty, there is a positive correlation between serum IL-6 concentrations and the degree of pain reported postoperatively.<sup>57</sup>

Tumor necrosis factor alpha (TNF $\alpha$ ) is a pro-inflammatory cytokine that mediates its effects via the surface receptors TNFR1 and TNFR2 and activation of NF $\kappa$ B. TNF $\alpha$  promotes regulation of pathways of apoptosis, pain, and inflammatory responses. Neurons and nociceptors contain TNF $\alpha$  receptors, and TNF $\alpha$  injections into nerves lead to degeneration of the nerve distal to the point of injection and hyperalgesia. Both effects are eliminated with administration of systemic TNF binding protein, which blocks the effects of TNF $\alpha$ .<sup>57</sup>

IL-10 is an anti-inflammatory cytokine that dampens the activity of the pro-inflammatory cytokines by preventing their release from macrophages. IL-10 also diminishes the effects of IL-6 and TNF $\alpha$  through receptor blockade. Some clinical studies have found evidence suggesting that low levels of serum IL-10 contribute to chronic pain states or patients with chronic, diffuse inflammation.<sup>57</sup> Another study found that administration of IL-10 postmyocardial infarction reduced inflammation enough within the ventricle to promote and facilitate healing of the damaged myocardium.<sup>58</sup>

## Enzymes

Catechol O-methyl transferase (COMT) is an enzyme present at nerve terminals and is responsible for the degradation of the catecholamines dopamine, epinephrine, and norepinephrine. Different haplotypes of COMT enzyme expression are associated with variations in pain sensitivity through differences in pain processing. A study involving patients with diagnoses of chronic pain conditions associated with the

Val(158)Met polymorphism with a poorly functioning COMT enzyme, causing increased sensitivity to perioperative pain and fibromyalgia. Reduced levels of functioning COMT enzyme was also linked to increased responsiveness to opioids for the treatment of chronic pain.<sup>59</sup>

The enzyme GTP cyclohydrolase (GTPCH) is encoded by the *GCHI* gene and is involved in the pathway leading to the production of tetrahydrobiopterin (BH4). The level of BH4 is positively correlated with pain sensitivity following injury to sensory neurons. SNPs within the *GCHI* gene are linked to pain sensitivity, with some variations being protective from pain and others exacerbating it. This concept has been primarily studied in African Americans with sickle cell disease, with the presence of variant rs8007267 being protective from chronic pain and variant rs3783641 being associated with increased crisis pain.<sup>60</sup>

*CYP2D6* is a well-studied cytochrome P450 enzyme responsible for the metabolism of many opioid analgesics. There are more than 80 unique alleles of *CYP2D6*, and variations in expression affect drug metabolism and alter the efficacy of these drugs, see Table 3.<sup>61</sup> Extensive metabolizers have two wild-type alleles, which allow regular enzyme activity and predictable drug responses. In one extreme are the poor metabolizers, with two nonfunctional alleles, leading to near absent enzyme activity. Conversely, some individuals inherit either multiple copies of the functional allele, or an overactive promoter that results in increased gene transcription and elevated enzyme activity. Intermediate metabolizers have an allele with reduced functionality and impaired enzymatic activity.<sup>61</sup> Studies show that 7–10% of the Caucasian population may be poor *CYP2D6* metabolizers, meaning that these individuals are at risk for failure of drug therapy in prodrugs that require activation by this enzyme, or they are at risk for toxicity in drugs that require breakdown by this enzyme.<sup>62</sup> See Table 3.

**Table 3** Phenotypic effects of SNPs on drug metabolism

Drug given	Prodrug		Active drug	
	Poor	Rapid	Poor	Rapid
Metabolizer level				
Drug exposure	Decreased conversion	Increased conversion	Decreased inactivation	Increased inactivation
Drug activity	Decreased efficacy	Increased efficacy	Increased efficacy	Decreased efficacy
Adverse effects	Increased if prodrug is toxic	Increased if active compound is toxic	Increased if drug is toxic	Decreased if drug is toxic
				Increased if drug is toxic

## Ion channels

Transient receptor potential (TRP) channels are found throughout peripheral afferent nerves and are responsive to many intra- and extracellular mechanical, chemical, osmotic, and thermal stimuli.<sup>63</sup> TRP channels are pronociceptive, responding mostly to noxious inflammatory stimuli. Therefore polymorphisms that make TRP less sensitive, such as *Ile585Val* in TRPV1, have been shown to decrease the experience of pain in patients with knee osteoarthritis.<sup>64</sup> Additionally, TRP channel polymorphisms can change the somatosensory nature of pain—different people will have varying heat, cold, or mechanical pain thresholds from polymorphisms in TRP channels.<sup>65</sup>

Voltage-gated potassium channels play a significant role in nociceptive signaling and regulation of pain pathways. *KCNS1* is a genetic polymorphism in the voltage-gated potassium channels that leaves individuals susceptible to pain associated with HIV, back pain, and phantom limb pain following amputation. *KCNS1* is expressed in tissues all throughout the body. The role of this ion channel was confirmed with *KCNS*-knockout mice exhibiting a predisposition to neuropathic pain and enhanced sensitivity to mechanical pain.<sup>66</sup>

*CACNG2* encodes for the protein stargazin that is needed for trafficking and ion flow through glutamatergic AMPA receptors in the nervous system. Polymorphisms in *CACNG2* have been linked to susceptibility to neuropathic pain. A study investigating neuropathic pain in breast cancer patients following mastectomy found that a specific 3 SNP haplotype of *CACNG2* was linked to the tendency to develop phantom breast pain, confirming *CACNG2* as a modifier of neuropathic pain.<sup>67</sup>

*CACNA2D3* encodes the alpha-2/delta protein in voltage-gated Ca<sup>2+</sup> channels and has been documented to contribute to nociceptive pain response to noxious heat. In humans, a specific SNP has been located that leads to reduced pain sensitivity to heat and chronic back pain postsurgically. Interestingly, when studied in mice, mutant *CACNA2D3* exhibited impaired pain and heat sensitivity, but had intense activation of sensory brain regions including sight, smell, and hearing, showing impaired transmission of signals between high-order pain pathways with possible cross-activation of other sensory pathways in the brain.<sup>68</sup>

## Receptors

*OPRM1* is the human mu-opioid receptor gene that is known to play a role in the analgesic effects of opioids.

Inadequate pain management in cancer patients has been linked to hypermethylation of *OPRM1*, yielding a decreased response to the analgesic effects of opioids. Chronic or high-dose use of opioids was correlated with this hypermethylation and downregulation of receptors, confirming a mechanism of tolerance.<sup>69</sup> Furthermore, the presence of a specific *A118G* polymorphism in *OPRM1* leads to a less active receptor that has been linked to individuals with reduced analgesic responses to morphine postoperatively.<sup>70</sup>

ADRA2 is an alpha-2-adrenergic G protein-coupled receptor that plays a significant role in the regulation and release of sympathetic nervous system neurotransmitters. Pharmacologically, this receptor is the target of pain control therapies, such as central acting alpha-2 agonists, that reduce the release of sympathetic neurotransmitters and relieve symptoms of opioid withdrawal. Alpha-2 adrenergic receptors located in the spinal column dorsal horns, when activated with an agonist, inhibit the release of substance P and the activity of the nociceptive neurons, leading to analgesia. This is illustrated by the clinical use of clonidine, an alpha-2 agonist, in the treatment of chronic pain as well as opioid withdrawal symptoms.<sup>71</sup>

Dopamine receptor D2 (DRD2) is a G-protein coupled receptor that inhibits adenylyl cyclase. This receptor is well-known as the site of action of many antipsychotic drugs, but it has also been studied in migraine headaches. A specific SNP rs1800497 was linked to increased prevalence of migraine headaches in Chinese females, leading to the proposal of the possible use of DRD2 antagonists in the prevention of treatment of migraine headaches.<sup>72</sup>

## Transporters

DAT-1 is a transporter that regulates the reuptake of dopamine into the presynaptic neuron from the synaptic cleft. Polymorphisms in this transporter have been linked to individual differences in cold pain tolerance in healthy subjects. The specific polymorphism studied was a 40 base-pair repeat in the transporter within the 3' untranslated region that led to decreased transport and low activity of dopamine, suggesting that low dopaminergic activity yields higher sensitivity to pain.<sup>73</sup>

The serotonin transporter (5HTT) is responsible for serotonin's reuptake from the synaptic cleft. Specific polymorphisms known as the 5-HT transporter-linked polymorphic region (5-HTTLPR) has been studied intensely in patients with chronic pain, looking at high-, intermediate-, and low-expressing groups. A study analyzing the variations of the triallelic 5-HTTLPR and perception of

heat pain found that individuals with high levels of serotonin transporter expression had lower pain thresholds for heat pain than those with intermediate levels of expression, highlighting the complex role of serotonin in pain modulation.<sup>74</sup>

ABCB1 is an ATP-binding cassette transporter responsible for transport of various molecules across membranes, including the blood–brain barrier, and is a member of the multidrug resistance family of transporters. ABCB1 transports various opioid analgesics across the blood–brain barrier, and specific polymorphisms are linked to changes in analgesic effects of these drugs. In a study of lung cancer patients undergoing radical operations, patients possessing homozygous rs2032582 and rs1128503 loci consumed significantly higher doses of sulfentanil post-operatively to achieve adequate analgesic effects, supporting that these specific SNPs cause decreased transport activity.<sup>75</sup> See Figure 2.

## Opioid receptor polymorphisms

Variations in the mu, kappa, and delta opioid receptors also play a significant role in the opioid response. Over 100 variants of the opioid receptor mu 1 gene (*OPRM1*) have been identified. The most studied allele, 118 A>G polymorphism (*rs1799971*), is prevalent in 2–48% of the

population.<sup>76</sup> This particular mutation results in an increased binding of beta-endorphins to the mu opioid receptor, and is hypothesized provide higher pain relief in homozygotes, and thus decreased daily requirements for morphine.<sup>77,78</sup>

Polymorphisms with similar clinical relevance have been found for the *OPRK1* and *OPRD1* genes as well.  $\kappa$ -opioid receptor activation is responsible for spinal analgesia and is responsible for similar adverse effects as the  $\mu$ -receptor (respiratory depression, sedation, and dysphoria), while the  $\delta$ -opioid receptor is implicated in dysphoria and psychomimetic effects.<sup>76</sup> These receptors, particularly the  $\delta$ -receptor, have importance with regards to addiction as mentioned in the buprenorphine section, and thus serve as potential future targets of targeted addiction therapy.<sup>79,80</sup>

## Genetic polymorphisms associated with drugs used to treat pain

### Morphine

Morphine is metabolized through glucuronidation via *UGT2B7* and *UGT1A1*, forming the active metabolite morphine 6-glucuronide as well as the inactive metabolite morphine 3-glucuronide. *UGT2B7* is the primary enzyme involved in biotransformation, accounting for 60% of

## Biological polymorphisms involved in pain

### Enzymes

COMT ↓ enzyme activity linked to ↑ pain and ↓ opioid responsiveness

GTP cyclohydrolase level of BH4 produced correlates with pain sensitivity

CYP2D6 variants affect drug metabolism and efficacy

### Ion channels

TRP pro-nociceptive, polymorphisms change perception

Voltage gated potassium channel *KCNS1* polymorphism with ↑ sensitivity to neuropathic/mechanical pain

*CACNG2* stargazin channel *CACNG2* polymorphisms modify neuropathic pain

*CANA2D3* voltage gated calcium channel SNP ↓ pain and head sensitivity

### Cytokines

IL-10 dampens proinflammatory cytokines

IL-6 associated with pain

TNF $\alpha$  promotes inflammation and cell death

### Receptors

*OPRM1* Mu-opioid hypermethylation ↓ analgesia

*ADRA2*  $\alpha 2$  GPCR agonism ↓ SNS pain response

*DED2* GPCR SNP linked to increased migraines

### Transporters

DAT-1 ↓ dopaminergic activity ↑ cold pain sensitivity

5HTT ↑ expression ↓ heat pain threshold

ABCB1 transports drugs across BBB, SNPs changing transport activity change analgesia

Figure 2 Biological polymorphisms involved in pain.

metabolite formation.<sup>83</sup> While numerous studies detail the effects of genetic polymorphisms on morphine's biotransformation, efficacy to treatment, and potential for toxicity, guidelines to support dose selection of morphine are lacking. Genotypes related to morphine's ability to treat pain, such as the GG genotype for *OPRM1*, may help inform appropriate dose selection. In one study, patients with the GG genotype often require higher daily doses of morphine to achieve appropriate levels of analgesia, in comparison to the wild-type A allele (225+143 mg/day vs 97+89 mg/day in those with the A allele for *OPRM1*,  $P=0.006$ ).<sup>84</sup> Another study showed variability for the development of respiratory depression in individuals with polymorphisms for the p-glycoprotein transporter *ABCB1*, resulting in extended hospital stay.<sup>85</sup>

## Codeine

Codeine is a prodrug metabolized by *O*-demethylation to the active analgesic morphine via the *CYP2D6* pathway. This mechanism accounts for about 10% of the overall elimination of codeine. *CYP2D6* activity can vary considerably among individuals, as there are approximately 100 different variants of the genes that have been identified to date.<sup>76</sup> The most clinically significant polymorphisms arise from those harboring two loss of function variants, also known as poor metabolizers, and those harboring at least three normal function variants, also known as ultrarapid metabolizers. Poor metabolizers produce low plasma concentrations of the active morphine metabolite, and thus are less likely to achieve adequate pain control with codeine. Ultrarapid metabolizers, however, run the risk of reaching supratherapeutic levels of morphine. Furthermore, there is a relationship between the metabolism of codeine and morphine when the drugs are administered at the same time. Genotypic differences in *UGT2B7*, which is responsible for metabolizing morphine into morphine-6-glucuronide and morphine-3-glucuronide, can impact codeine's therapeutic effect. In particular, the *UGT2B7\*2/\*2* genotype, which results in a reduced function of the enzyme, has been associated with higher toxicity. Several pharmacokinetic studies have illustrated the effects of these phenotypes on metabolite formation. In one study, a single dose of 30 mg codeine was administered to 12 UM individuals in comparison to 11 EMs and three PMs.<sup>86</sup> Significant differences were detected between EM and UM groups for areas under the plasma concentration versus time curves (AUCs) for morphine with a median

(range) AUC of 11 (5–17)  $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$  in EMs and 16 (10–24)  $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$  in UMs relative to individuals with the PM phenotype (0.5  $\mu\text{g}\cdot\text{h}\cdot\text{L}^{-1}$ ,  $P=0.02$ ).

The codeine-*CYP2D6* interaction is the only opioid-gene interaction that currently has an actionable Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for pharmacogenetic-based recommendations, primarily due to the severe nature the toxicities related to rapid metabolism phenotypes in young users, such as respiratory depression.<sup>87</sup> On the basis of these guidelines, it is strongly recommended that UMs and PMs should avoid codeine due to potential for toxicity and lack of efficacy, respectively. Recent updates by the US Food and Drug Administration (FDA) to the label for both codeine and tramadol also contraindicate the use of codeine for pain or cough in patients younger than 12 years of age.<sup>88</sup> Furthermore, the FDA warns against the use of codeine in obese adolescents and those with obstructive sleep apnea or severe lung disease.

## Tramadol

Tramadol, like codeine, is also a prodrug bioactivated by the *CYP2D6* enzyme, through which it is metabolized to its active metabolite *O*-desmethyltramadol (ODT). Similar to codeine, tramadol's effects are impacted by individuals with UM and PM phenotypes. In one study, tramadol failed to provide adequate pain relief at 48 hours following surgery in patients with the *CYP2D6* polymorphism ( $P<0.001$ ).<sup>89</sup> In UMs, respiratory depression may occur, and has been described in at least one case report to date.<sup>89</sup> The same cautions were made by the FDA in response to tramadol as were made for codeine in April 2017, namely a contraindication for the use of tramadol in individuals less than 18 years of age following tonsillectomy or adenoidectomy.<sup>88</sup> Although there is no CPIC guideline for tramadol, its metabolism by *CYP2D6* would make it an unsuitable alternative to codeine and thus be treated in a similar fashion to codeine with regards to cautions and recommendations for use.

## Hydrocodone

Hydrocodone, a semisynthetic opioid, follows metabolism via *CYP2D6* and *CYP3A4* to form hydromorphone and norhydrocodone respectively. These are further conjugated by UGT enzymes into water soluble metabolites that are excreted by the kidneys. Importantly, hydromorphone's affinity for the  $\mu$ -opioid receptor is far higher than that of

hydrocodone, up to 100-fold greater. Like tramadol and codeine, variations in *CYP2D6* have an impact on analgesia from hydrocodone.<sup>87</sup> At least one study determined that patients who underwent cesarean section delivery and were determined to be UMs of *CYP2D6* had approximately a 10-fold increase in hydromorphone plasma concentration compared to those with PM phenotype.<sup>90</sup> Based on this profile, hydrocodone may not be a good alternative to codeine or tramadol based on the CPIC guidelines for codeine. This recommendation is based mainly on hydrocodone's role as a substrate for *CYP2D6*, rather than from robust evidence. Given this status, CPIC currently recommends more research for this particular drug with respect to the impact of genetic polymorphisms. Recent studies have shown an opportunity to use hydrocodone pharmacogenetics to tailor responses to therapy, while at the same time assessing conversion of hydrocodone to hydromorphone in the body.<sup>91</sup>

### Oxycodone and oxymorphone

Oxycodone and oxymorphone are metabolized by *CYP450* and to a lesser extent, UDP-glucuronosyltransferases (UGT), specifically UGT2B7.<sup>92</sup> The UGTs are a secondary metabolizing system responsible for the formation of glucuronides. Genetic variability in the enzyme 2B7 exists, however, the *in vitro* and *in vivo* functional significance of these allele variants are not well defined.<sup>93</sup> Like hydrocodone, oxycodone is metabolized via the specific enzymes *CYP3A4* and *CYP2D6* into noroxycodone and oxymorphone, respectively. Unlike hydrocodone and tramadol, however, the parent drug for oxycodone exhibits some analgesic effect, and the drug also undergoes a more complex metabolic pathway than the previous two. *CYP3A4* mediates the primary metabolic pathway, accounting for more than 50% of the overall conversion of oxycodone. In similar fashion to codeine and tramadol, PMs of *CYP2D6* exhibit lower conversion into its active metabolites and thus exhibit a lower analgesic response as well as a lower potential for adverse effects in comparison to extensive metabolizers.<sup>94</sup> Moreover, UMs tend to have a much higher response and potential for side effects to doses of oxycodone. One study of cancer patients noted that differences in *CYP3A* impacted patient response to oxycodone.<sup>95</sup> Given the complex interplay between oxycodone metabolism and its associated pharmacogenetics, current CPIC guidelines recommend further studies before definitive treatment guidance can be given.<sup>87</sup>

### Diamorphine

Diamorphine, more commonly known by the street name "heroin" is metabolized into 6-monoacetylmorphine (6-MAM) primarily via the enzymes hCE-1 and partly by hCE-2.<sup>96</sup> Additionally, variations in loci for the kappa and delta opioid receptor genes *OPRK1* and *OPRD1* have been connected to the potential for addiction and dependence to diamorphine. Additional research involving these interactions could elucidate their role as targets for addiction therapy.<sup>80</sup>

### Fentanyl

Fentanyl is metabolized by the enzymes *CYP3A4* and *CYP3A5*. Variations in CYP enzymes have been demonstrated to impact plasma concentrations of fentanyl. In one study of 60 adult patients with cancer receiving transdermal fentanyl, the plasma concentration of fentanyl was shown to be twice as high in *CYP3A5\*3* homozygotes compared to *CYP3A5\*1* carriers.<sup>97</sup> The same study also showed that polymorphisms in the gene *ABCB1* can lead to significant changes in fentanyl plasma concentrations, with the *ABCB1 1236TT* variant being associated with a lower need for rescue medication. To date there have been no statistically significant findings for fentanyl-related adverse effects, in the previous study or current body of literature. As such, more research is needed before clinical adoption of fentanyl pharmacogenetics would be useful.

### Buprenorphine

Buprenorphine, a semisynthetic opioid, is metabolized via *CYP3A4*. Used mainly for treating opioid addiction, the drug exerts its effects at the *OPRD1* receptor. Most notably, the connection between specific SNPs such as rs58111 and rs529520 have been predictive of outcomes for the use of buprenorphine in treating opioid dependence, with the rs58111 SNP being associated with a more favorable response to buprenorphine.<sup>98</sup>

### Nonsteroidal anti-inflammatory drugs (NSAIDs)

Patient variability to NSAIDs is impacted by variations in select CYP enzymes, namely *CYP2C9*, which metabolizes many NSAIDs. Two allelic variants of *CYP2C9*, *CYP2C9\*2* and *CYP2C9\*3*, result in reduced inactivation of NSAID substrates by 50% and 15% respectively. This lower metabolism results in prolonged action of the drugs, and thus higher of side effects such as GI bleed.<sup>99</sup> A

prospective multicenter, study identified a higher rate of acute upper GI bleeding related to use of nonaspirin NSAIDs in patients with the *CYP2C9\*3* variant when compared to patients receiving aspirin, indicating the potential risk associated with certain NSAIDs in patients with the *CYP2C9\*3* loss-of-function allele.<sup>100</sup> Additionally, variability of the prostaglandin-endoperoxidase synthase 1 and 2 genes (*PTGS1* and *PTGS2*) influences response to particular NSAIDs.<sup>99</sup> *PTGS1* encodes for COX1, and *PTGS2* codes for COX2. Mutations resulting in a higher number of COX2 over COX1 were determined to respond better to selective agents such as rofecoxib, while agents with COX1 effects such as ibuprofen showed better pain response in individuals expressing more *PTGS1*.

### Ketamine

Ketamine metabolism occurs via N-demythylation by *CYP3A4*, *CYP2B6*, and *CYP2C*, with significant analgesic and sedative activity achieved through antagonism of the NMDA receptor. Despite there being several cytochrome enzymes involved in ketamine's metabolism, strong correlates between polymorphisms and clinical importance have yet to be identified.<sup>101</sup>

### Lidocaine

Lidocaine, a local anesthetic with activity at sodium channels, is metabolized via *CYP3A4*, and thus is theoretically impacted by influence of inducers and inhibitors of *CYP3A4*. The most pronounced effects on variation in clinical efficacy, however, are due to mutations in the sodium channel gene *SCN9A*.<sup>78</sup> One invitro study showed that the 395N>K mutation in this gene produces greater resistance to lidocaine, and another showed that individuals with phenotypes associated with red hair in the melanocortin-1 receptor gene (*MCR1*) had reduced efficacy to subcutaneous lidocaine.<sup>102</sup>

### Remifentanyl

Remifentanyl is a synthetic opioid analgesic drug that is potent and short-acting. It is used during surgery to treat pain and as an adjunct to anaesthetics. Remifentanyl is a specific mu-type-opioid receptor agonist. There is evidence to suggest increased pain sensitivity in Met158 individuals following treatment with remifentanyl. As previously mentioned, the COMT gene has variations that can affect opioid drug metabolism, specifically at the 158 codon where either Val or Met can be present. A 2006 study

suggested that individuals with Val alleles show increased COMT activity and have decreased prefrontal extracellular dopamine compared to those with the Met substitution.<sup>103</sup> Val158 alleles may also be associated with an advantage in the processing of aversive stimuli, or pain. Individuals who are homozygous for the Met158 allele show increased pain sensitivity, likely through a lower-functioning  $\mu$ -opioid system response to prolonged pain.<sup>104,105</sup> A cohort study investigating repeated thermal-pain stimulation both before and after one single dose of opiate in caucasians showed that individuals with the Val158 genotype did not respond to either the initial noxious stimulus or the analgesic response to remifentanyl.<sup>106</sup> Yet, reported pain in Met15 individuals were higher following repeated heat stimulation and postremifentanyl treatment, suggesting that the initial pain response is not mediated by COMT and may only present after the endogenous pain response is challenged. This reaction could be produced by an increased susceptibility of these individuals to opioid-induced hyperalgesia.<sup>102</sup>

### Escitalopram

Escitalopram is an SSRI used to treat autism spectrum disorder, but it can also be used to treat neuropathic pain. *CYP2C19* is the enzyme responsible for metabolizing escitalopram and individuals can carry up to 30 different alleles. The majority of patients will carry the *CYP2C19\*1*, *\*2*, or *\*17* alleles, where *\*17* allele is an ultrarapid metabolizer. A normal functioning enzyme is indicated by *CYP2C19\*1*, while *CYP2C19\*2* and *CYP2C19\*3* are the most common non-functioning alleles.<sup>107</sup> Ultrarapid metabolizers should be administered an alternative drug that is not metabolized by *CYP2D19*. Extensive and intermediate metabolizers should be administered medication normally. Poor metabolizers should have a 50% reduction in the recommended starting dose with a titration to the response dose or should be given a drug that is not metabolized by *CYP2D19*.<sup>107</sup>

See Table 4 for an overview of drugs, their clinical utility, associated polymorphisms and phenotypic effect of the genetic variant.

## Pharmacogenomics improving pain management

Pain-associated genetic factors vary with pain classification, but all classifications have some genetic component. The effect of polymorphisms in the *OPRM1* and *COMT* genes,

**Table 4** A list of drugs, their clinical utility, associated polymorphisms and phenotypic effect of the genetic variant

Drug	Clinical utility	Genes	Phenotypic effect of the genetic variant
Codeine	Management of mild- to moderately-severe pain	CYP2D6 UGTB7	Poor metabolizers may fail to reach adequate analgesia Ultrarapid metabolizers may reach high levels of morphine following low to standard dosing leading to increased risk of toxic systemic concentrations of morphine <sup>87,88,108</sup> Loss of function mutation in UGTB7 is associated with decreased metabolism of morphine, resulting in increased risk of toxicity <sup>86</sup> Poor metabolizers fail to reach adequate analgesia <sup>87</sup> Ultrarapid metabolizers may experience life-threatening serotonin or opioid receptor-mediated adverse events <sup>89</sup>
Tramadol	Management of pain severe enough to require an opioid analgesic and for which alternative nonopioid treatments are inadequate	CYP2D6	CYP2D6 enzyme demethylates hydrocodone into hydromorphone, which has stronger mu receptor binding activity. Ultrarapid metabolizers may reach higher levels of hydromorphone from conversion of hydrocodone and thus be at higher risk of toxicity <sup>87,90</sup> Poor CYP2D6 metabolizers may not reach desired analgesic effect with standard dosing
Hydrocodone	Management of pain severe enough to require daily around-the-clock opioid, long-term treatment and for which alternative treatment options are inadequate	CYP2D6 CYP3A4	Patients designated as PMs have been reported to need more oxycodone to achieve adequate analgesia Complex phenotypic effects impacted by parent drug's inherent analgesic effect <sup>94,95</sup> Weak evidence suggests a higher risk of side effects such as respiratory depression, tiredness, or nausea Associations between ABCB1 polymorphisms and prolonged recovery room stays and postoperative morphine requirement <sup>83,85</sup> GG genotype for OPRM1 associated with increased requirement for post-operative opioids <sup>85</sup> Variation in OPRK1 and OPRD1 may be connected to potential for addiction <sup>80,96</sup>
Oxycodone	Pain management in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain	CYP3A4 CYP2D6	Variations in median effective dose required to exhibit analgesia among polymorphisms such as ABCB1 <sup>97</sup>
Morphine	Management of pain severe enough for which alternative treatments are inadequate that require an opioid analgesic	ABCB1 OPRM1	
Diamorphine	Not recommended clinical utility to date	hCE-1 hCE-2 OPRK1 OPRD1	
Fentanyl	Surgery: adjunct to general or regional anesthesia; preoperative medication; analgesic during anesthesia and in the immediate postoperative period Transdermal device: acute postoperative pain Transdermal patch: management of pain in opioid-tolerant patients Transmucosal: management of breakthrough cancer pain in opioid-tolerant patients	OPRM1 ABCB1	

(Continued)

Table 4 (Continued).

Drug	Clinical utility	Genes	Phenotypic effect of the genetic variant
Buprenorphine	Use for moderate to severe pain Opioid dependence	CYP3A4 OPRD1	OPRD1 SNPs such as rs58111 and rs529520 may help predict outcomes of buprenorphine use in treating opioid dependence <sup>98</sup>
NSAIDs	Pain for which an opioid analgesic is not required	CYP2C9 PTGS1, PTGS2	Two variants of CYP2C9, CYP2C9*2 and CYP2C9*3, result in decreased inactivation of NSAID, increasing risk for side effects such as GI bleed <sup>100</sup> Mutations resulting in varying concentrations of PTGS1/2 associated with variable response based on selectivity of NSAID for COX1 or COX2 <sup>100</sup>
Ketamine	Induction and maintenance of general anesthesia and procedural sedation/analgesia	CYP2B6, CYP3A4, CYP2C	Decreased enzyme binding and reduced drug clearance in polymorphisms have been noted, but clinical significance has yet to be identified. <sup>101</sup>
Lidocaine	Local and regional anesthesia by infiltration, nerve block, epidural, or spinal techniques	SCN9A MGR1	Reduced efficacy in polymorphisms <sup>102</sup>

Abbreviations: PM, poor metabolizer; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.

which transcribe opioid receptor mu 1 and catechol-O-methyltransferase respectively, are relatively well categorized in their effect on acute postoperative, cancer-related, and chronic pain.<sup>109,110</sup> When patients are homozygous for the common amino acid substitution val158met, they require a dose of morphine that is significantly higher than homozygous met/met patients.<sup>109</sup> Similarly, cancer patients with a 118GG polymorphism in the *OPRM1* gene need a higher morphine dose than patients with 118AA (1,2,3). Other genes, such as *CREB1*, *GIRK2*, and *CACNA1E*, have similar consequences on the pain relieving effects of opioids.<sup>111</sup>

Improving pain management necessitates expanding upon the clinical features analyzed when making treatment decisions.<sup>111</sup> Pharmacogenomics can provide valuable information to guide drug choice and dosing for more effective, safer treatments.<sup>111,112</sup> *CYP2D6* tests—including full sequence analysis and targeted variant analyses utilizing PCR—are available to determine a patient's metabolizer level of codeine.<sup>18,111</sup> DNA is gathered via a buccal swab which prevents unnecessary burden on the patient while providing the clinician with a powerful tool to improve the patient's treatment.<sup>112</sup> Instead of analyzing a specific gene in relation to one treatment as in the case of codeine and *CYP2D6*, creating a pain-related gene panel would allow more informed and effective initial treatment by the clinician.<sup>112</sup> Panels already exist in this regard for laboratory experimentation, however, they are not FDA approved, nor are they ready to be implemented in the clinic.<sup>113</sup> Interpretation of pain is an incredibly complex pathophysiological process, which can only be partially explained by genetics, but studying and understanding variability in adverse effects and treatment effectiveness based on pharmacogenetics can benefit patient outcomes.<sup>111</sup>

An recent breakthrough study suggests a direct benefit of personalized patient medical care. Smith et al investigated *CYP2D6*-guided opioid therapy as a possible way to improve patient pain control. They found that, in fact, *CYP2D6* does improve pain control in *CYP2D6* intermediate and poor metabolizers. Patients experiencing chronic pain from seven different clinics were enrolled in the study. The patients were randomly assigned to either a *CYP2D6*-guided care group or a usual care group.

## Future directions

There are several major challenges for the future of pharmacogenomics in pain management. Primarily, the cost associated with implementing a pharmacogenomics

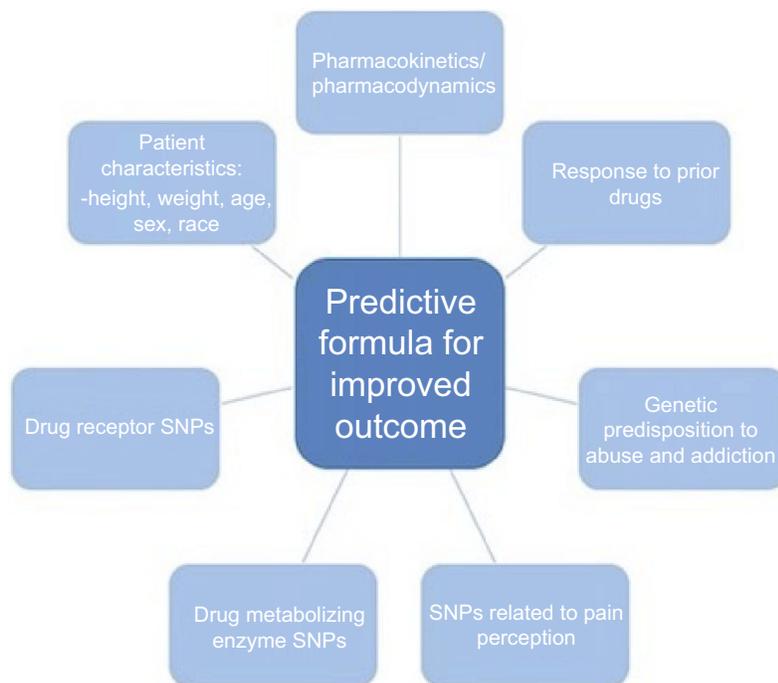
program is high and this can be a deterrent to health-care institutions. To address this, identifying patients who, based on the pharmacogenetics, may not respond to drug treatments, have a high risk of adverse events, or a high risk of drug abuse and addiction, could improve costs associated with chronic pain management and patient outcomes.<sup>113</sup> By developing predictive formulas for patient outcomes, physicians could utilize patient characteristics (height, weight, age, etc), genotypes from pharmacogenetic testing, and drug pharmacokinetics/pharmacodynamics along with additional predictive markers to better treat patients, see **Figure 3**. Yoshida et al used this approach to develop a predictive formula for postoperative fentanyl dose requirement using patients' SNP profile for several genes involved in pain relieving effects of opioids.<sup>111</sup> The precision of the developed formula proved to be low, but promising nonetheless.<sup>111</sup> Further study and identification of SNPs related to analgesics dosing, effectiveness, metabolism, and adverse effects will allow for new variables to be included in similar formulas to expand their predictive power.<sup>101</sup>

Furthermore, Next-Generation Sequencing (NGS), Illumina, Inc., San Diego, CA, USA is the new standard for sequencing technologies and is vital to understanding pharmacogenetics. The costs associated with NextGen Sequencing are decreasing, which will improve the affordability of genetic testing to the individual patient.<sup>114</sup> Testing

time is another major challenge associated with pharmacogenomics in pain management and cutting down on this testing time is crucial to the widespread acceptance of this system.<sup>101</sup> Patients in severe pain cannot afford to wait for results to return before receiving treatment, therefore, protocols should be in place to immediately help the patient while waiting for test results before a transition to the best long-term treatment option. Another challenge mentioned earlier, suggests that further research is needed to understand the pharmacogenetics behind both pain perception and pain management, especially to move beyond studying dosing and toxicity to investigate the efficacy of employing one pain relief medication versus another in an individual patient.<sup>101,114</sup> For example, studies exploring ethnicity-based genetic polymorphisms associated with metabolizer type have a variety of categorized results, even in recent studies. **Table 5** outlines several studies ranging from 2002–2018 which have overlapping polymorphisms associated with each category of metabolizer. More research is needed to make the results of these studies more consistent with one another. If these major challenges are addressed there is an increased likelihood that pharmacogenomics in the field of pain management will have a more widespread acceptance.

## Conclusion

A universal approach to health care, especially related to pain management, is no longer an option. Since all patients



**Figure 3** Predictive factors for personalized medicine.

**Table 5** Evidence for correlations between ethnicity or gene polymorphisms based on metabolizer status

	Poor metabolizer/none	Intermediate metabolizer/low	Extensive metabolizer/normal	Ultraprapid metabolizer/high
Bijl et al, 2007 <sup>115</sup>	*3, *4, *5, *6	*10, *41	*1, *2	“Ultraprapid metabolizers” (UMs) have >2 functional copies of the CYP2D6 gene and exhibit extremely high enzyme activity. Many genotyping assays determine the duplication of any CYP2D6 gene, including nonfunctional genes, leading to false positive UM assignment. In this way, genotyping will only detect 10–30% of CYP2D6 UMs.
Bernard et al, 2005 <sup>116</sup> Zhou 2009 <sup>117</sup>	*3, *4 *3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *18, *19, *20, *21, *38, *40, *42, *44, *56 and *62 *4/*4, *4/*5, *5/*5, *4/*6	*9, *10, *17, *41 *10, *17, *36 and *41	n/a *2	n/a n/a
Dean 2012 <sup>118</sup>		*4/*10, *5/*41	*1/*1, *1/*2, *2/ *2, *1/*41, *1/ *4, *2/*5, *1/ *10	*1/*1xN *1/*2xN
Gaedigk et al, 2017 <sup>119</sup>	*3, *4, *4xN, *5, *6, *7, *8, *11, *12, *36, *40, *42, *56	*9, *10, *17, *29, *41, *44, *49	*2, *35, *43, *45	*1xN, *2xN
Del Tredici et al, 2018 <sup>120</sup>	*3, *3xN, *4, *4xN, *4N, *5, *6, *6xN, *36, and *36xN	*9, *9xN, *10, *10xN, *17, *17xN, *29, *29xN, *36-*/10, *36-*/10xN, *36xN- *10, *36xN-*/10xN, *41, and *41xN	*1, *1xN, *2, *2xN, *2A, *2AxN, *35, and *35xN	n/a

have different responses to medications and pharmacogenomics now allows us to explain these differences in response, it is clear that individualized medicine tailored to each individual patient is the future of patient care. This should, however, be viewed with promise, as individualized patient-specific care can save money, improve patient experiences and improve patient outcomes. Monitoring the DNA polymorphisms in each patient can allow health-care providers to predict how a patient will respond to a drug and could potentially save a patient's life. This is of particular importance when considering the relationship between pain management and drug addiction. There are established genetic polymorphisms in individuals who abuse drugs, yet a clinician currently assesses the potential for abuse by interacting with the patient and reports from those close to the patient, thereby missing potentially crucial genetic predispositions to abuse.<sup>113</sup> Therefore, a health-care provider could prevent the possibility of a patient to abuse a drug based on their polymorphisms and suggest an alternate treatment regimen. **By applying the knowledge of pharmacogenomics into clinical practice health-care providers can offer safer comprehensive health care to patients.**

## Disclosure

The authors report no conflicts of interest in this work.

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