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REVIEW

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.¹ 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".² 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.³ 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.⁴ 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.^{5,6} Chronic pain is particularly debilitating because it affects all aspects of life including physical, mental, social, occupational, and

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

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.9 The Centers for Disease Control and Prevention (CDC) officially declared fatal prescription drug overdose as an epidemic in 2012.¹⁰ 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).¹¹ 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).¹² Elliott Vesell and George Page showed that monozygotic twins displayed significantly less variability in antipyrine pharmacokinetics.¹³ 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.¹⁴ 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).¹⁵ 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.¹⁶ 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.¹⁷ 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.¹⁸ 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.¹⁹ 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	I Gene	nomenclature	expl	anation
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CYP2C19*17	
СҮР	Superfamily
2	Family
С	Subfamily
19	Gene
*17	Allelic variant

(PREDICT) program and has enrolled more than 10,000 patients.²⁰ 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.²¹ 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.²²

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.²³ By providing information about the location and magnitude of harmful stimuli, acute pain heightens vigilance and promotes appropriate responses to address the stimuli.²⁴ 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.^{25,26}

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

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.²⁷ 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.²⁷

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.²⁷

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.^{28,29} Conditions associated with neuropathic pain include diabetes, HIV infection, alcohol abuse, vitamin or mineral deficiencies, and vasculitis.²⁹ Neuropathic pain is relatively common and occurs in



Figure I Types of chronic pain.

25% of diabetic patients and 35% of HIV-positive patients.²⁸ Clinically, neuropathic pain must be differentiated from nociceptive pain because management differs between the two.²⁹ 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.²⁸

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.^{30,31} Unfortunately, up to 50% of cancer patients have inadequate pain control and 25% actually die in pain.³⁰ 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.³¹

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.³² An inverse relationship between socioeconomic status and chronic widespread pain prevalence has also been described.³³ 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.³⁴ 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.³⁵

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.³⁶ In adolescents, perceived stress may be related

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

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.⁴⁰

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.⁴⁰ Studies examining sex-related differences in opiate utilization in the postoperative period have found that men consume more morphine postoperatively than women.⁴¹

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.^{33,35,42} 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.⁴³ Psychological factors such as anxiety and depression have been described as risk factors for the development of tension headaches.³⁹ 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 psychologic factors, the strength of this inverse relationship is lessened.³³ 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.43

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.⁴⁴ Epigenetic mechanisms are thought to play a role in both the expression of pronociceptive genes and the evolution of acute pain into chronic pain.⁴⁵ 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.⁴⁵ Additionally, polymorphisms involving the serotonin 5-HT2A receptor, serotonin transporter, and dopamine-4 receptor are more common in patients with fibromyalgia.⁴⁵ 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.⁴⁶

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.⁴⁷ 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.⁴⁸ African Americans also have lower thresholds for pain, cold, heat, pressure, and ischemia compared to Caucasions.⁴⁹ 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.⁵⁰ 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.⁵¹ Australian women also rate menstrual pain as more intense compared to Chinese women.⁵² Swedes report more frequent pain in lower back, neck, shoulders, hands, and elbows compared to Sami (northern Scandinavian indigenous individuals) men and women.53 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.⁵⁴ This same group also reported different emotional responses to chronic pain and pain intensity within a group of individuals classified as white.⁵⁵ 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.^{81,82,120} 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

CYP2D6 genetics		
Туре	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%

 Table 2 Ethnic differences in CYP2D6 activity

Notes: Data from these studies.81,82

of neuropathic pain. A study examining IL-6 infusions intrathecally revealed IL-6 causes increased neuronal responses and hyperalgesia to temperature changes.⁵⁶ 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.⁵⁷

Tumor necrosis factor alpha (TNF α) is a pro-inflammatory cytokine that mediates its effects via the surface receptors TNFR1 and TNFR2 and activation of NFkB. TNF α promotes regulation of pathways of apoptosis, pain, and inflammatory responses. Neurons and nociceptors contain TNF α receptors, and TNF α 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 α .⁵⁷

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 α 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.⁵⁷ 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.⁵⁸

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.⁵⁹

The enzyme GTP cyclohydrolase (GTPCH) is encoded by the *GCH1* 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 *GCH1* 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.⁶⁰

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 3.⁶¹ 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.⁶¹ 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.⁶² See Table 3.

 Table 3 Phenotypic effects of SNPs on drug metabolism

Drug given	Prodrug		Active drug	
Metabolizer level	Poor	Rapid	Poor	Rapid
Drug exposure Drug activity Adverse effects	Decreased conversion Decreased efficacy Increased if prodrug is toxic	Increased conversion Increased efficacy Increased if active compound is toxic	Decreased inactivation Increased efficacy Increased if drug is toxic	Increased inactivation Decreased efficacy 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.⁶³ 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.⁶⁴ 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.⁶⁵

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.⁶⁶

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.⁶⁷

CACNA2D3 encodes the alpha-2/delta protein in voltage-gated Ca2+ 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.⁶⁸

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.⁶⁹ 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.⁷⁰

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.⁷¹

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.⁷²

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.⁷³

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.⁷⁴

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 postoperatively to achieve adequate analgesic effects, supporting that these specific SNPs cause decreased transport activity.⁷⁵ 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.⁷⁶ 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.^{77,78}

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

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 involed 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

Cytokines

IL-10 dampens proinflammatory cytokines IL-6 associated with pain TNFa promotes inflammation and cell death

Receptors

OPRM1 Mu-opioifd hypermethylation \downarrow analgesia ADRA2 a2 GPCR agonism \downarrow 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 acitvity change analgesia

lon 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 calciuim Cchannel SNP | pain and head sensitivity

Figure 2 Biological polymorphisms involved in pain.

metabolite formation.⁸³ 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).⁸⁴ 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.⁸⁵

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.⁷⁶ 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 adiministered 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.⁸⁶ 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) μ g*h*L⁻¹ in EMs and 16 (10–24) μ g*h*L⁻¹ in UMs relative to individuals with the PM phenotype (0.5 μ g*h*L⁻¹, *P*=0.02).

The codeine-CYP2D6 interaction is the only opioidgene 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.⁸⁷ 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.⁸⁸ 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).⁸⁹ In UMs, respiratory depression may occur, and has been described in at least one case report to date.⁸⁹ 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.⁸⁸ 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 μ -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.⁸⁷ 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.⁹⁰ 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.⁹¹

Oxycodone and oxymorphone

Oxycodone and oxymorphone are metabolized by CYP450 and to a lesser extent, UDP-glucuronosyltransferases (UGT), specifically UGT2B7.92 The UGTs are a secondary metabolizing system responsible for the formation of glucuronides. Geneticvariability in the enzyme 2B7 exisits, however, the in vitro and in vivo functional significance of these allele variants are not well defined.⁹³ 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.⁹⁴ 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.⁹⁵ Given the complex interplay between oxycodone metabolism and its associated pharmacogenetics, current CPIC guidelines recommend further studies before definitive treatment guidance can be given.⁸⁷

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-2.⁹⁶ 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.⁸⁰

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.⁹⁷ 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.⁹⁸

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.⁹⁹ 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.¹⁰⁰ Additionally, variability of the prostaglandin-endoperoxidase synthase 1 and 2 genes (PTGS1 and PTGS2) influences response to particular NSAIDs.⁹⁹ PTGS1 encodes for COX1, and PGTS2 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.¹⁰¹

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*.⁷⁸ 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.¹⁰²

Remifentanil

Remifentanil 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. Remifentanil is a specific mu-type-opioid receptor agonist. There is evience to suggest increased pain sensitivity in Met158 individuals following treatment with remifentanil. As previsouly 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.¹⁰³ 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 µ-opioid system response to prolonged pain.^{104,105} A cohort study investigating repeated thermal-pain stimulation both before and after one single dose of opiate in caucasions showed that individuals with the Val158 genotype did not respond to either the initial noxious stimulus or the analgesic response to remifentanil.¹⁰⁶ Yet, reported pain in Met15 individuals were higher following repeated heat stimulation and postremifentanil 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 opioidinduced hyperalgesia.¹⁰²

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.¹⁰⁷ 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 CYP2D19.¹⁰⁷

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,

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Drug	Clinical utility	Genes	Phenotypic effect of the genetic variant	
Codeine	Management of mild- to moderately-severe pain	CYP2D6	Poor metabolizers may fail to reach adequate analgesia	
		UGTB7	Ultrarapid metabolizers may reach high levels of morphine following low to	
			standard dosing leading to increased risk of toxic systemic concentrations of	
			morphine ^{87,88,108}	
			Loss of function mutation in UGTB7 is associated with decreased metabolism	
			of morphine, resulting in increased risk of toxicity ⁸⁶	
Tramadol	Management of pain severe enough to require an opioid analgesic and for which alternative	CYP2D6	Poor metabolizers fail to reach adequate analgesia ⁸⁷	
	nonopioid treatments are inadequate		Ultrarapid metabolizers may experience life-threatening serotonin or opioid	
			receptor-mediated adverse events ⁸⁹	
Hydrocodone	Management of pain severe enough to require daily around-the-clock opioid, long-term	CYP2D6	CYP2D6 enzyme demethylates hydrocodone into hydromorphone, which has	
	treatment and for which alternative treatment options are inadequate	CYP3A4	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 ^{87,90}	
			Poor CYP2D6 metabolizers may not reach desired analgesic effect with	
_			standard dosing	
Oxycodone	Pain management in patients for whom alternative treatment options are ineffective, not	CYP3A4	Patients designated as PMs have been reported to need more oxycodone to	
	tolerated, or would be otherwise inadequate to provide sufficient management of pain	CYP2D6	achieve adequate analgesia	
			Complex phenotypic effects impacted by parent drug's inherent analgesic	
			effect ^{94,95}	
			Weak evidence suggests a higher risk of side effects such as respiratory	
			depression, tiredness, or nausea	
Morphine	Management of pain severe enough for which alternative treatments are inadequate that	ABCBI	Associations between ABCB1 polymorphisms and prolonged recovery	
_	require an opioid analgesic	OPRM I	room stays and postoperative morphine requirement ^{83,85}	
			GG genotype for OPRMI associated with increased requirement for post-	
			operative opioids ⁸⁵	
Diamorphine	Not recommended clinical utility to date	hCE-I	Variation in OPRK1 and OPRD1 may be connected to potential for	
_		hCE-2	addiction ^{80,96}	
		OPRKI		
_		OPRDI		
Fentanyl	Surgery: adjunct to general or regional anesthesia; preoperative medication; analgesic	OPRM I	Variations in median effective dose required to exhibit analgesia among	
_	during anesthesia and in the immediate postoperative period	ABCBI	polymorphisms such as ABCB197	
_	Transdermal device: acute postoperative pain			
_	Transdermal patch: management of pain in opioid-tolerant patients			
	Transmucosal: management of breakthrough cancer pain in opioid-tolerant patients			
			(Continued)	1

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

Table 4 (Cont	inued).		
Drug	Clinical utility	Genes	Phenotypic effect of the genetic variant
Buprenorphine	Use for moderate to severe pain	CYP3A4	OPRD/ SNPs such as rs58111 and rs529520 may help predict outcomes of
	Opioid dependence	OPRDI	buprenorphine use in treating opioid dependence ⁹⁸
NSAIDS	Pain for which an opioid analgesic is not required	CYP2C9	Two variants of CYP2C9, CYP2C9*2 and CYP2C9*3, result in decreased
		PTGS1,	inactivation of NSAID, increasing risk for side effects such as GI bleed ¹⁰⁰
		PTGS2	Mutations resulting in varying concentrations of PTGS1/2 associated with
			variable response based on selectivity of NSAID for COX1 or COX2 ¹⁰⁰
Ketamine	Induction and maintenance of general anesthesia and procedural sedation/analgesia	CYP2B6,	Decreased enzyme binding and reduced drug clearance in polymorphisms
		CYP3A4,	have been noted, but clinical significance has yet to be identified. ¹⁰¹
		CYP2C	
Lidocaine	Local and regional anesthesia by infiltration, nerve block, epidural, or spinal techniques	SCN9A	Reduced efficacy in polymorphisms ¹⁰²
		MCRI	
Abbreviations: PM	I, poor metabolizer; NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.		

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which transcribe opioid receptor mu 1 and catechol-Omethyltransferase respectively, are relatively well categorized in their effect on acute postoperative, cancer-related, and chronic pain.^{109,110} 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.¹⁰⁹ 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.¹¹¹

Improving pain management necessitates expanding upon the clinical features analyzed when making treatment decisions.¹¹¹ Pharmacogenomics can provide valuable information to guide drug choice and dosing for more effective, safer treatments.^{111,112} CYP2D6 tests-including full sequence analysis and targeted variant analyses utilizing PCR-are available to determine a patient's metabolizer level of codeine.^{18,111} 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 treatment¹¹² 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.¹¹² 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.¹¹³ 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.¹¹¹

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.¹¹³ 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.¹¹¹ The precision of the developed formula proved to be low, but promising nonetheless.¹¹¹ 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.¹⁰¹

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.¹¹⁴ 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.¹⁰¹ 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 longterm 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.^{101,114} For example, studies exploring ethnicitybased 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.

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

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

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.¹¹³ 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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