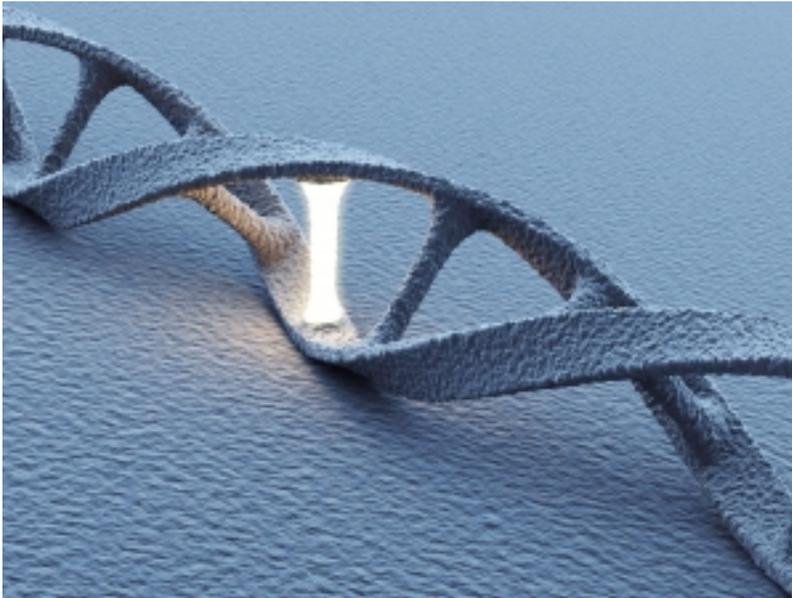


Pharmacogenetics and Pain Management

Clinical use and interpretation of the common pharmacogenetic tests.

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[3]In recent years, pharmacogenetic testing has become more common in pain management. During this time, a few cytochrome P450 (CYP450) enzymes have been identified as being particularly important to the metabolism of certain pharmaceutical agents commonly used in pain treatment, such as opioids, antidepressants, and anti-inflammatory agents.

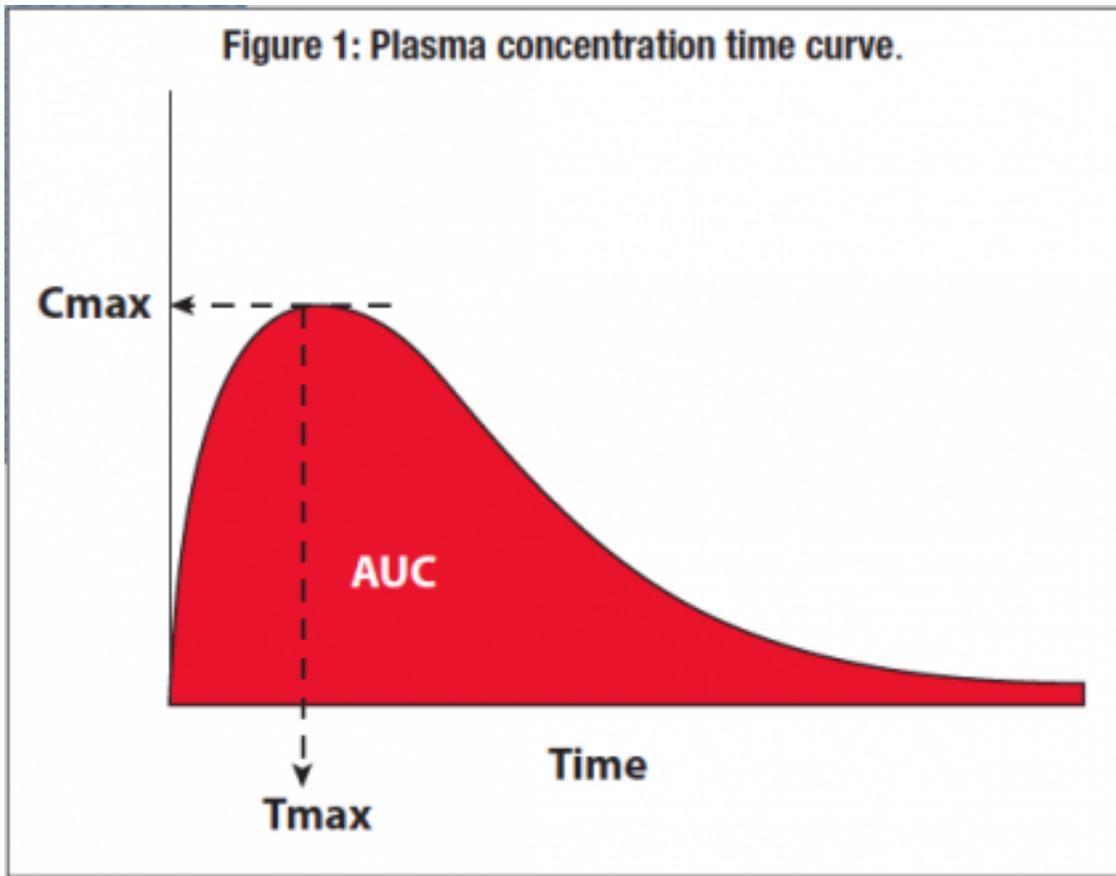
More recently, 2 non-cytochrome P450 “pharmacodynamic” genetic tests have been identified that help explain opioid dosage requirements in pain patients. The first measures, opioid mu receptor 1 (OPRM1), which determines the ability of opioids to bind to the mu opioid receptor site. The other measures catechol-o methyltransferase (COMT), the enzyme that degrades catecholamines in the central nervous system.

All pain practitioners who prescribe opioids should know that a patient with an OPRM1 with a low sensitivity rating and/or a COMT with a high activity rating likely will require a higher opioid dose than normal to obtain relief from a severe pain problem.

This article presents an up-to-date status and review of the pharmacogenetic markers that have relevance to pain practice.

Classification of Pharmacogenetic Biomarkers

Pharmacogenetic (PGx) biomarkers can be classified into 2 general categories—pharmacokinetic (PK) and pharmacodynamic (PD) biomarkers. Pharmacokinetics is what the body does to the drug (illustrated in Figure 1 of a plasma concentration time profile), whereas pharmacodynamics is what the drug does to the body.



AUC, area under the curve; Cmax, maximum concentration; Tmax, time of maximum concentration

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[4]

Different examples of PK biomarkers include CYP2D6, CYP2C9, and CYP2B6. If a drug is metabolized via one of these CYP pathways, variations in the genetic code for these enzymes may result in differences in the activity or the expressed amount of enzyme and, therefore, differences in the blood levels of drug. This, in turn, can influence the effectiveness and toxicity of the medication.

Transporters are another type of PK biomarker. Transporters move drugs in and out of cells. Variation in the genes that code for transporters also may result in changes in blood levels. Different examples of pharmacokinetic biomarkers include CYP2D6, CYP2C9 and CYP2B6.

Examples of PD response to an opioid include analgesia, sedation, respiratory depression, and constipation. Some PD biomarkers are the actual molecular receptors of a drug and, thus, they can impact drug response directly. OPRM1 is one example. Multiple studies have found that variation in the gene that codes for this receptor is associated with analgesic and addiction response.

Some PD biomarkers affect drug response indirectly. Examples include variation in human leucocyte antigen genes that influence risk of hypersensitivity to drugs such as the anticonvulsant carbamazepine or the non-steroidal anti-inflammatory drug meloxicam. COMT is another example that will be discussed below.

Generally speaking, the understanding of PK biomarkers is more advanced than that of PD biomarkers. This is because PK genes can be analyzed, and then the changes in blood levels of a drug secondary to the genetic variation can be objectively measured, allowing for a very clear cause and effect

relationship.

Measuring the association between a gene responsible for PD response can be much more challenging to accomplish in an objective manner. Pain, for example is influenced by gender, age, ethnicity, and many environmental factors other than genetics. There also is no perfect tool for monitoring an individual's pain level.

Another challenge with PD biomarkers is that the mechanism of action of drugs is not always fully understood. This can make it very difficult to elucidate the therapeutic consequences of a particular genetic mutation. Mutations resulting in changes to the receptor binding site or receptor density may or may not result in a predictable response. PD biomarkers that are indirectly associated with drug response may be even more challenging to understand and predict.

The biomarkers included in Genelex's analgesic panel include both PK and PD biomarkers. The PK biomarkers included are CYP2D6, CYP2C9, CYP3A4, CYP3A5, and CYP2B6. The PD biomarkers included are OPRM1 and COMT.

Pharmacokinetic Biomarkers

PK biomarkers are all very similar with regards to clinical interpretation and indication for testing. CYP2D6, CYP2C9, and CYP2B6 genes have a poor, intermediate, and normal metabolizer phenotype. CYP2D6 and CYP2C19 also have an ultra rapid metabolizer phenotype. CYP3A4 has an intermediate and normal metabolizer phenotype and CYP3A5 has a non-expresser, intermediate expresser, and expresser phenotype. For CYP3A5, the majority of patients are non-expressers, which is the equivalent of a poor metabolizer.

The indication for testing is the same for all PK biomarkers—the results of therapeutic drug monitoring are not within normal limits and the drug is known to be metabolized by the enzyme being genotyped (tested). Other contributing factors—such as drug interactions, the timing of analysis relative to dose administration, compliance, prescribing error, and malabsorption—should be ruled out prior to testing. In pain management, therapeutic drug monitoring may apply to blood levels, urinary drug screening (UDS), and oral fluid/saliva sampling.

The following 3 cases illustrate when PK testing may be indicated:

Case Example #1

JS was a 43-year-old man who developed chronic neck pain after a motor vehicle accident. As a new patient, he underwent a standard medical history and physical examination. After he was assessed for risk, he was de-termined to be a candidate for opioid therapy and he agreed to a pain contract. According to the terms of the contract, UDS is to be completed at the first visit, monthly after initiating opioid therapy, and randomly.

The initial screening (before opioid use) was unremarkable, but the second screening conducted 1 month later was abnormal, showing no hydromorphone present, despite the patient being on a scheduled dose of hydrocodone (Table 1).

Test	Flag Results	Unit	Reference Value
Confirmation - Opiates	Positive	ng/mL	<100
Codeine	Negative	ng/mL	<100
Hydrocodone	Positive	ng/mL	<100
Hydromorphone	Negative	ng/mL	<100
Morphine	Negative	ng/mL	<100
Oxycodone	Negative	ng/mL	<100
Oxymorphone	Negative	ng/mL	<100



[5]

Hydrocodone is metabolized to hydromorphone by CYP2D6. Review of the patient’s medication list showed no concomitant drugs that would interfere with the metabolism of hydrocodone (ie, CYP2D6 inhibitors such as paroxetine, fluoxetine, bupropion, duloxetine, quinidine, etc.). Furthermore, the patient claimed to be taking all medications as prescribed.

The patient agreed to PGx testing to see how he metabolized the hydrocodone. Results showed that the patient was a CYP2D6 poor metabolizer, which helped explain why hydromorphone was undetectable with the UDS and restored the physician’s trust in the patient.

A second indication would be if the patient has in the past or currently is experiencing adverse drug reactions or treatment failure to a medication known to be metabolized by the enzyme being considered for testing. Similar to the first indication, other factors such as drug interactions should be ruled out prior to ordering the genetic test based on this indication.

Case Example #2

A 5 and a half year-old boy underwent ambulatory adenotonsillectomy. Upon returning home from surgery around 6 hours later, he received a single 20-mg dose of tramadol. The following morning, the boy was found extremely lethargic by his parents and rushed to the emergency room (ER). Upon arrival to the ER he was comatose, with pin-point pupils, minimal respiratory effort, frequent episodes of apnea, and an oxygen saturation rate of 48% in room air.

Tramadol is metabolized by CYP2D6 to O-desmethyltramadol (M1) and other metabolites. Genetic testing of CYP2D6 was conducted and the results indicated that the boy was a CYP2D6 ultra rapid metabolizer, which was consistent with both the clinical presentation as well as the urinary drug concentrations of M1.¹ Figure 2 illustrates the differences in AUC between confirmed CYP2D6 phenotypes and patients who received I.V. bolus tramadol 3 mg/kg.² Fortunately he made a full recovery with non-invasive ventilation and intravenous naloxone.

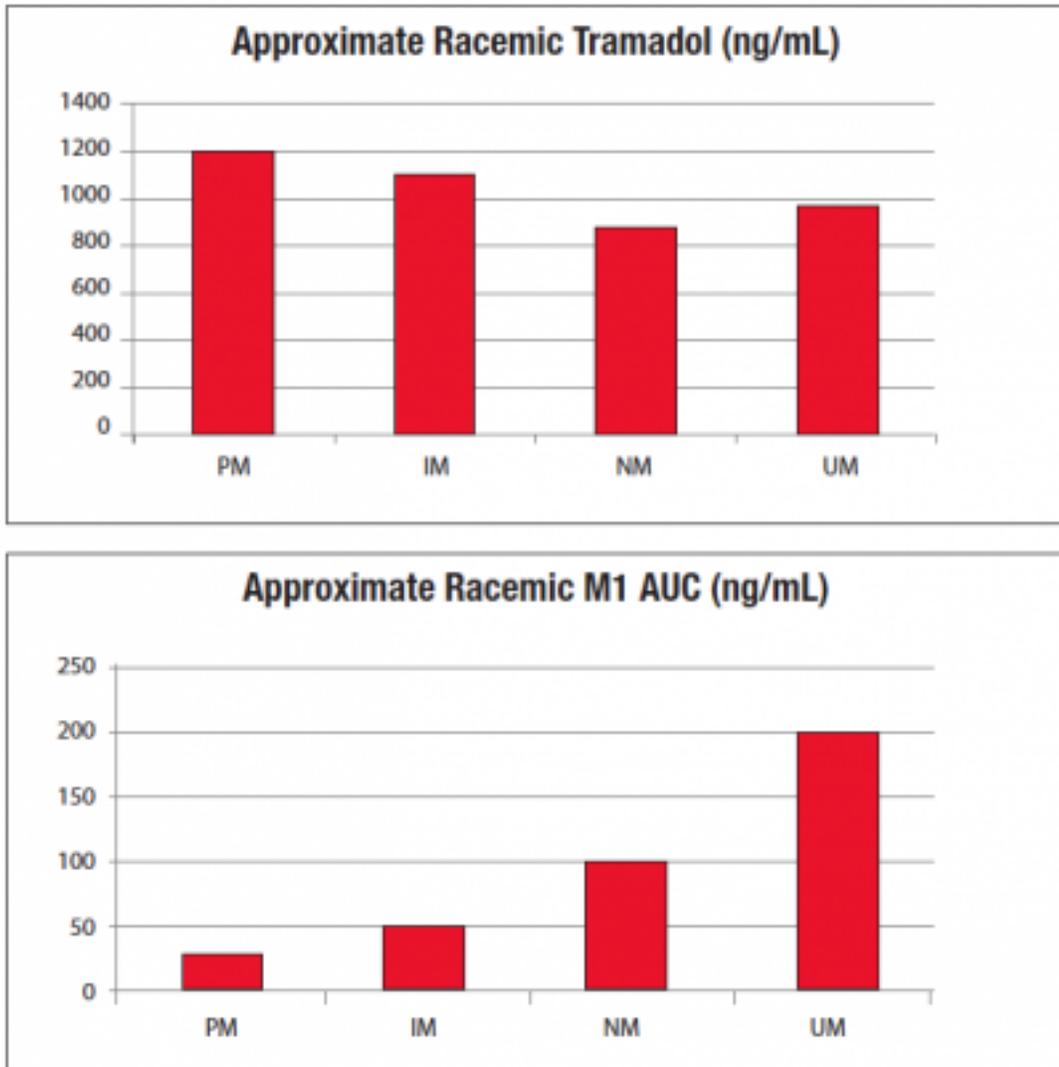


Figure 2. Tramadol and O-desmethytramadol (M1) AUC in different CYP2D6 phenotypes. AUC, area under the curve; IM, immediate metabolizer; NM, normal metabolizer; PM, poor metabolizer; UM, ultra rapid metabolizer

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[6]

Case Example #3

A third indication for PD testing is for the prospective use of PGx data. This may be appropriate to predict variation in metabolism prior to initiating drug therapy. The value of this approach is the most promising because it aims to prevent problems before they happen.

FT was a 65-year-old man with chronic cancer pain. His pain had not been controlled with fentanyl and hydrocodone/acetaminophen, and methadone was being considered as a therapeutic option. However, the patient was stable on the antidepressant citalopram and there was a risk of additive QTc prolongation with this combination. It is determined that the benefits of continuing citalopram and trying methadone likely outweigh the risks, but the physician first wanted to know whether the patient would metabolize methadone normally.

Methadone is a racemic mixture of R- and S-methadone. CYP2B6 metabolizes S-methadone and, to a

lesser extent, R-methadone. Although R-methadone is associated with the therapeutic effect, S-methadone preferentially blocks the hERG current.^{3,4} Testing reveals that the patient is a CYP2B6 normal metabolizer and clinicians decide to initiate methadone therapy.

Although there are plenty of exceptions to this rule, many classes of medications can be matched with an enzyme pathway, making the clinical interpretation of CYP450 testing fast and convenient (Table 2).

CYP2D6	CYP2C9	CYP3A4/5	CYP2B6
Amitriptyline	Celecoxib	Codeine	Methadone
Codeine	Flurbiprofen	Diazepam	
Desipramine	Ibuprofen	Fentanyl	
Diazepam	Meloxicam	Hydrocodone	
Hydrocodone	Piroxicam	Oxycodone	
Imipramine		Methadone	
Methadone			
Nortriptyline			
Oxycodone			
Tramadol			
Venlafaxine			



[7]

For example, the opioids codeine, hydrocodone, oxycodone, and tramadol are metabolized by CYP2D6 to active metabolites. Other pathways such as CYP3A4 also may be involved in their metabolism (Table 2, above, and Figure 3). Opioids that avoid CYP450 metabolism include oxymorphone, hydromorphone, morphine, and tapentadol, making these good choices to avoid common metabolism-based drug interactions. Other drug classes highly dependent on the CYP2D6 pathway that are used adjunctively for pain include the tricyclic antidepressants (amitriptyline and nortriptyline) and duloxetine. Most NSAIDs on the other hand are highly dependent on CYP2C9 for metabolism.

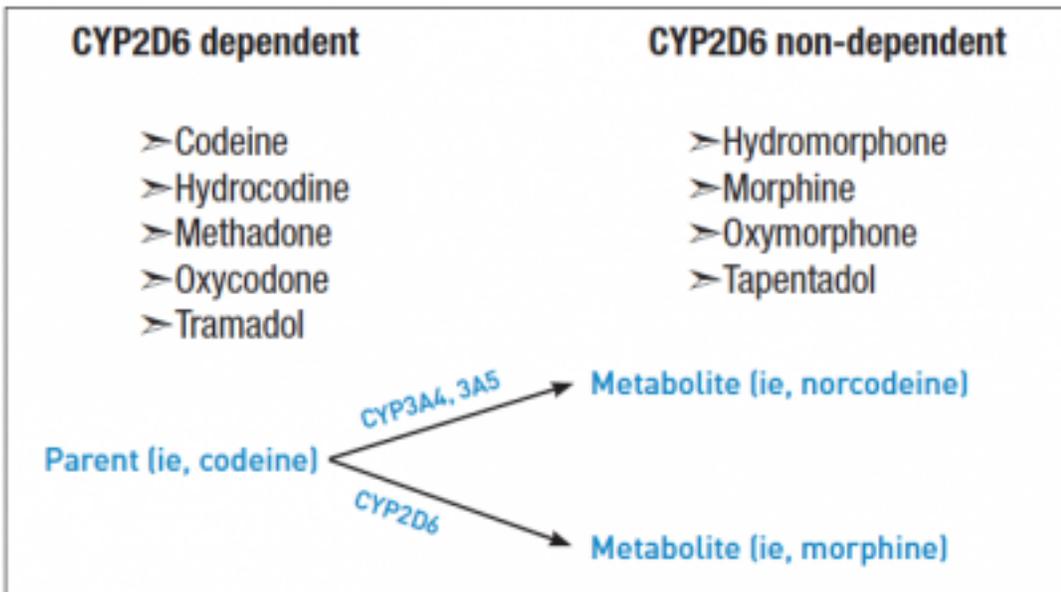


Figure 3. Opioid Metabolism



[8]

There are obvious advantages to understanding enzyme pathways, and a patient’s baseline metabolic capacity. In 2014, Pergolizzi et al proposed a simple strategy for dealing with the great amount of genetic variation and drug interaction potential for these pathways.⁵ Simply put, choosing an opioid (or another drug) not metabolized by the CYP450 pathways doesn’t guarantee you will not have problems, but it significantly decreases the chances.⁵

Although this certainly is an ideal scenario, barriers such as insufficient insurance coverage can prevent providers from adopting this mechanistic-based approach to prescribing. Thus, knowing how a drug is metabolized and having a baseline understanding of a patient’s metabolic capacity is necessary to anticipate and adjust for potential problems. Table 3 can be used as a tool to predict possible responses based on genetic variation and drug interaction.

Table 3. Clinical Consequences of Opioid Cytochrome P450 Drug Interactions

Opioid	CYP2D6 Inhibition or Patient is PM	Patient is CYP2D6 UM (enzyme not inducible by other drugs)	CYP3A4 Inhibition	CYP3A4 Induction	CYP2B6 Inhibition or PM
Codeine	Decreased analgesia (less morphine produced); UDS may show no metabolite present	Increased analgesia and toxicity (more morphine produced)	Increased analgesia and toxicity (more codeine and possibly more morphine)	Decreased analgesia (decreased codeine and morphine)	N/A
Hydrocodone	Possible decreased analgesia and/or increased toxicity (more hydrocodone and less hydromorphone produced); UDS may show fewer or absent metabolite present	Possible increased analgesia and toxicity (more hydromorphone produced); UDS may show fewer or no parent molecules present	Increased analgesia and toxicity (more hydrocodone and possibly more hydromorphone)	Decreased analgesia (decreased hydrocodone and hydromorphone)	N/A
Methadone	Increased analgesia and toxicity risk	Decreased analgesia risk	Increased analgesia and toxicity risk	Decreased analgesia risk	Increased toxicity (QTc prolongation risk)
Oxycodone	Possible decreased analgesia and/or increased toxicity (more oxycodone and less oxymorphone produced); UDS may show fewer or absent metabolite present	Possible increased analgesia and toxicity (more oxymorphone produced); UDS may show fewer or no parent molecules present	Increased analgesia and toxicity (more oxycodone and possibly more oxymorphone)	Decreased analgesia (decreased oxycodone and oxymorphone)	N/A
Tramadol	Decreased analgesia and increased risk of pro-serotonergic side effects, including a decrease in seizure threshold	Increased analgesia and toxicity	Slight increased analgesia and risk of toxicity	Possible decreased analgesia	Slight increased analgesia and risk of toxicity
Hydromorphone	N/A	N/A	N/A	N/A	N/A
Morphine	N/A	N/A	N/A	N/A	N/A
Oxymorphone	N/A	N/A	N/A	N/A	N/A
Tapentadol	N/A	N/A	N/A	N/A	N/A

NA, not applicable; PM, poor metabolizer; UDS, urine drug screen; UM, ultra rapid metabolizer



[9]

Pharmacodynamic Biomarkers

As stated earlier, the clinical utility of many PD biomarkers is less robust than that of PK biomarkers. This is, in part, due to the fact that the mechanism of action of drugs is not always fully understood.

Two PD biomarkers associated with pain response include OPRM1 and COMT. Variation in the gene that codes for OPRM1 have been associated with differences in the response to opioids, naltrexone, and substances of abuse (Table 4).⁶⁻⁸

Parameter	High Sensitivity (AA)	Intermediate Sensitivity (AG)	Low Sensitivity (GG)
Opioid dose and response ⁶	Normal opioid dose needed to achieve pain relief	Normal to slightly increased opioid dose needed to achieve pain relief	Increased opioid dose needed to achieve pain relief; slight protection from opioid-induced nausea ⁷
Naltrexone response for alcohol dependence ⁸	Poorer response to naltrexone treatment in alcoholics, including increased risk of relapse	Increased success to naltrexone treatment in alcoholics	Increased success to naltrexone treatment in alcoholics, including lower relapse rates
Opioid/heroin addiction risk ⁶	Typical risk of opioid addiction in Asians	Increased risk factor of opioid addiction in Asians	Increased risk factor of opioid addiction in Asians

OPRM1, opioid mu receptor 1

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[10]

The variant most well studied for the OPRM1 receptor is 118A>G. While the mechanism of the variation is not fully understood there are a couple different working hypotheses.^{9,10} One proposal is that the G mutation results in decreased OPRM1 expression resulting in decreased receptor density. Compared to individuals without this mutation, those with it may require higher opioid doses to achieve analgesia because there is less receptor to bind to.¹⁰ A second hypothesis suggests that with G allele mutation, individuals express a normal amount of OPRM1 receptor, but it's mutated such that endogenously produced endorphins bind more tightly to the receptor. This results in the patient requiring a higher opioid dose to displace the natural endorphin binding.⁹ Of course, the true mechanism involved could be neither of these hypotheses or a combination of them both.

It also is important to point out that studies are conflicting with some showing no association at all, some showing only a weak association and others showing association in the opposite direction.⁷ Still other studies seem to suggest an association only in patients with Asian ancestry.¹¹ Another important consideration when interpreting the associated findings of PD biomarkers and opioid response is the clinical situation in which the studies took place. A majority of OPRM1 PGx studies have looked at closely monitored patients receiving opioid therapy for postoperative pain control. Thus, extrapolating these finding to other clinical scenarios, such as the ambulatory care setting, should be done with caution and, ideally, further studies should be carried out in these clinical settings.

A second PD biomarker that has been associated with pain response is COMT (Table 5). COMT is an enzyme that functions to inactivate catecholamines (dopamine, norepinephrine, and epinephrine). Genetic variation has been associated with three phenotypes which can be described as high activity, intermediate activity and low activity. The consequence of having the low-activity phenotype is an increased presence of neurotransmitters relative to those with the high-activity phenotype. Because these neurotransmitters influence nearly all physiologic processes, COMT variation has been associated with numerous diseases and medication responses, including response to antipsychotics, stimulants, antidepressant and Parkinson's disease drugs.

COMT High Activity (Val/Val)	COMT Intermediate (Val/Met) and Low Activity (Met/Met)
<ul style="list-style-type: none"> • Increased breakdown of neurotransmitters • Higher pain threshold—"warrior" • Decreased opioid receptor density • Increased opioid requirements 	<ul style="list-style-type: none"> • Decreased breakdown of neurotransmitters • Lower pain threshold—"worrier" • Increased opioid receptor density • Decreased opioid requirements

COMT, catechol-o-methyltransferase

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[11]

With regards to opioids and pain management, studies have found that individuals with the high-activity phenotype may require higher doses of opioid relative to individuals with the low-activity phenotype. The proposed mechanism is that high-activity COMT results in less neurotransmitter response and, therefore, less signal transduction during painful stimuli, resulting in a higher pain threshold.¹² It has also been postulated that these individuals have less downstream opioid receptor density. The end result is that when these individuals experience pain, it may be quite severe and the opioid dose required for relief is high. Indeed these individuals have been called "warriors."¹³⁻¹⁵

Individuals with low-activity phenotype have the opposite association. Studies have shown that these patients may require lower opioid doses. The proposed mechanism is that with lower COMT activity, there are more catecholamines present and, thus, increased neurotransmission during painful stimuli and a lower pain threshold. When an opioid is used, the dose may not need to be as high compared to a high-activity patient because the painful stimuli is not as severe. Furthermore, the downstream results of having more neurotransmitter (because of low COMT activity) are increased opioid receptor density and, thus, an easier target for the opioid, so that not as much of it is needed. Individuals with this phenotype have been called "worriers."¹⁴

Summary

The genes discussed in this brief overview are by no means the only ones associated with pain medication. For example, in a review by Trescott, the author reviewed 23 genes that have been associated with pain treatment.¹⁶ Undoubtedly, in the future, testing of some of these genes will have a practical clinical value.

A select set of PK and PD genetic markers that have relevance to pain management have been identified. Testing for specific genetic abnormalities may help pain practitioners select the most effective therapeutic agent while avoiding drug-drug interactions. One of the best uses of CYP450 enzyme testing is to identify pain patients who have abnormalities in this system, so that they can be treated with an opioid that doesn't use this system—such as hydromorphone, oxycodone, tapentadol, or morphine. It is possible to genetically test for opioid receptor binding sensitivity and COMT enzymatic activity. Pain patients with a low opioid receptor binding sensitivity (OPRM1) and/or high COMT activity likely will require a higher opioid dosages than normal to adequately control severe pain.

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