Pharmacogenetic Testing for Pain Management

Summary

While multiple pharmacologic therapies are available for the management of acute and chronic pain, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain, and in the presence of adverse events. This has prompted interest in better targeting pain therapies through the use of pharmacogenetic testing of genes relevant to analgesic pharmacokinetics or pharmacodynamics.

Panels of genetic tests for genes that have shown some association with the pharmacokinetics or pharmacodynamics of analgesic medications have been developed to aid in the management of pain. The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that evaluate associations of many different genetic variants and response to analgesic medication, risk of adverse events, and addiction risk. The largest body of evidence is related to the association of the OPRM1 A118G single nucleotide polymorphism (SNP) with analgesic response and addiction risk, which has not consistently demonstrated significant associations. For other genes included in commercially-available pain management panels, the body of evidence evaluating associations between polymorphism and analgesic response, adverse effects, or addiction risk is small. At present, the clinical utility of pharmacogenetic testing in pain management is poorly defined. No published studies were identified that report on ways that clinical management of pain and/or patient outcomes are associated with pharmacogenetic testing. Therefore, genetic testing panels for pain management are considered investigational for all indications.

Related Policies
2.04.38 Cytochrome P450 Testing
2.04.48 Genetic Testing for Warfarin Dose
2.04.51 Genetic Testing for Tamoxifen Treatment
2.04.110 Genetic Testing for Mental Health Conditions

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for pain management is considered investigational for all indications.
Policy Guidelines

Commercially-available genetic tests for pain management consist of panels of single nucleotide polymorphisms (SNPs) or (less commonly) individual SNP testing. SNPs that have been implicated in pain management include the following (see also Table 1):

- 5HT2C (serotonin receptor)
- 5HT2A (serotonin receptor)
- SLC6A4 (serotonin transporter)
- DRD1 (dopamine receptor)
- DRD2 (dopamine receptor)
- DRD4 (dopamine receptor)
- DAT1 or SLC6A3 (dopamine transporter)
- DBH (dopamine beta-hydroxylase)
- COMT (catechol-O-methyl-transferase)
- MTHFR (methylene tetrahydrofolate reductase)
- γ-Aminobutyric acid (GABA) A receptor
- OPRM1 (μ-opioid receptor)
- OPRK1 (κ-opioid receptor)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome P450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

Background

Pain is a universal human experience and an important contributor to both outpatient and inpatient medical visits. The Institute of Medicine’s (IOM) Committee on Advancing Pain Research, Education, and Care reports that common chronic pain conditions affect at least 116 million adults in the United States. Chronic pain may be related to cancer, or be what is termed “chronic non-cancer pain,” which may be secondary to a wide range of conditions, such as migraines, low back pain, or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, and physical and occupational therapy, and complementary/alternative therapies. Nonetheless, IOM reports that many individuals receive inadequate pain prevention, assessment, and treatment. Given that pain is an individual and subjective experience, assessing and predicting response to pain interventions, including pain medications, is challenging.

Overview of Pain Management

A variety of medication classes are available to manage pain: non-opioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDS), opioid analgesics, which target central nervous system pain perception, and a variety of classes of adjuvants, including antiepileptic drugs (e.g., gabapentin, pregabalin), antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors), and topical analgesics. The management of chronic pain has been driven, in part, by the World Health Organization’s analgesic ladder for pain management, which was developed for the management of cancer-related pain, but has been applied to the management of other forms of pain. The ladder outlines a stepped approach to pain management, beginning with non-opioid analgesia, and proceeding to a weak opioid (eg, codeine), with or without an adjuvant for persisting pain and subsequently to a strong opioid (eg, fentanyl, morphine), with or without an
adjuvant for persisting or worsening pain. A wide variety of opioids are available in short- and long-acting preparations and administered through variety of routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.

For acute pain management, particularly postoperative pain, systemic opioids and non-opioid analgesics remain a mainstay of therapy. However, there has been growing interest in using alternative, nonsystemic treatments in addition to or as an alternative to systemic opioids. These options include neuraxial anesthesia, including intraoperative epidural or intrathecal opioid injection, which can provide pain relief for up to 24 hours postoperatively, and postoperative indwelling epidural anesthesia with opioids and local anesthetics, which may be controlled with a patient-controlled anesthesia (PCA) pump. Postoperative peripheral nerve blocks may also be used.

While available pain management therapies are effective for many patients, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain. In addition, many opioids are associated with significant risk of adverse effects, ranging from mild (eg, constipation) to severe (eg, respiratory depression), and are associated with risk of dependence, addiction, and abuse. Limitations in currently-available pain management techniques have led to interest in the use of pharmacogenetics to improve the targeting of therapies and prediction and avoidance of adverse effects.

Genetics of Pain Management
Genetic factors may contribute to range of aspects of pain and pain control, including predisposition to conditions that lead to pain, pain perception, and the development of comorbid conditions that may affect pain perception. The currently-available genetic tests relevant to pain management assess single nucleotide polymorphisms (SNPs) in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes. These genetic associations may be relevant for several clinical purposes:

- **Drug selection or avoidance:**
  - To identify individuals likely or not likely to respond to a specific medication.
  - To identify individuals at high risk of adverse drug reactions.
  - To identify individuals at high risk of opioid addiction or abuse.

- **Dose optimization:**
  - Identify individuals who are likely to require higher or lower doses of a drug.
  - Estimate the dose and dosing frequency.

Genes related to these clinical scenarios include, broadly speaking, those involved in neurotransmitter uptake, clearance, and reception; opioid reception; and hepatic drug metabolism. Panels of genetic tests have been developed and have been proposed for use in the management of pain. Genes that have been identified as being relevant to pain management and that are included in currently available panels are summarized in Table 1.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Gene Product Function</th>
<th>Potential Role in Pain Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT2C (serotonin receptor)</td>
<td>Xq23</td>
<td>1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine</td>
<td>Polymorphisms (i.e., 102T/C) have been associated with variation in pain threshold</td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td>13q14-21</td>
<td>Another serotonin receptor subtype</td>
<td>Fibromyalgia, TMJ syndrome, migraine</td>
</tr>
<tr>
<td>SLC6A4 (serotonin transporter)</td>
<td>17q11.2</td>
<td>Clear serotonin metabolites from the synaptic spaces in the CNS</td>
<td>DRD4 VNTR have been associated with presence of pain related disorders</td>
</tr>
<tr>
<td>DRD1 (dopamine receptor)</td>
<td>5q35.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD2 (dopamine receptor)</td>
<td>11q23.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 (dopamine receptor)</td>
<td>11q15.5</td>
<td>G-protein-coupled receptors that have dopamine as their ligands.</td>
<td>DRD4 VNTR have been associated with presence of pain related disorders (fibromyalgia, TMJ syndrome, migraine)</td>
</tr>
<tr>
<td>DAT1 or SLC6A3 (dopamine transporter)</td>
<td>5q15.33</td>
<td>Mediates dopamine reuptake from synaptic spaces in the CNS.</td>
<td></td>
</tr>
<tr>
<td>DBH (dopamine beta-hydroxylase)</td>
<td>9q34.2</td>
<td>Catalyzes the hydroxylation of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons.</td>
<td>DRD4 VNTR have been associated with presence of pain related disorders (fibromyalgia, TMJ syndrome, migraine)</td>
</tr>
<tr>
<td>COMT (catechol-O-methyltransferase)</td>
<td>22q11.21</td>
<td>Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine and norepinephrine.</td>
<td>Val158Met polymorphism has been associated with alterations in emotional processing and executive function. Other polymorphisms have been associated with pain sensitivity.</td>
</tr>
<tr>
<td>MTHFR (methylene tetrahydrofolate reductase)</td>
<td>1p36.22</td>
<td>Converts folic acid to methylfolate, a precursor to the norepinephrine, dopamine, and serotonin neurotransmitters.</td>
<td>Multiple polymorphisms have been identified, which are associated with a wide variety of clinical disorders</td>
</tr>
<tr>
<td>γ-Aminobutyric acid (GABA) A receptor</td>
<td>5q34</td>
<td>Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter.</td>
<td></td>
</tr>
<tr>
<td>OPRM1 (μ-opioid receptors)</td>
<td>6q25.2</td>
<td>G-protein coupled receptor that is the primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone.</td>
<td>A118G polymorphism (rs1799971) has been associated with reduced pain sensitivity and opioid requirements.</td>
</tr>
<tr>
<td>OPRK1 (κ-opioid receptor)</td>
<td>8q11.23</td>
<td>Binds the natural ligand dynorphin and synthetic ligands.</td>
<td></td>
</tr>
<tr>
<td>UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)</td>
<td>4q13.2</td>
<td>Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds.</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Locus</td>
<td>Gene Product Function</td>
<td>Potential Role in Pain Management</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cytochrome P450 genes:</td>
<td></td>
<td>Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics.</td>
<td>CYP2D6 is the primary metabolizer for multiple oral opioids; metabolizer phenotype has been associated with variability in opioid effects</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>22q13.2</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>10q23.33</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10q23.33</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>7q22.1</td>
<td>Same as above</td>
<td>Involved in the metabolism of up to 60% of clinically used drugs.</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>19q13.2</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>15q24.1</td>
<td>Same as above</td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; CYP: cytochrome; TMJ temporomandibular joint; UG: uridine diphosphate glycosyltransferase; VNTR: varying number of tandem repeats;

Commercially Available Genetic Tests for Pain Management
Several test labs market panels of tests or individual tests designed to address one or more aspects of pain management, including but not limited to drug selection, drug dosing, or prediction of adverse events. Specific polymorphisms included in the panels are shown in Table 2.

- GeneSight Analgesic (Assurex Health, Mason, OH) is a genetic panel test that is intended to analyze “how patients’ genes can affect their metabolism and possible response to FDA [Food and Drug Administration]-approved opioids, NSAIDS [nonsteroidal anti-inflammatory drugs] and muscle relaxants commonly used to treat chronic pain.” Results are provided with a color coded report based on efficacy and tolerability which displays which medications should be used as directed, used with caution, or used with increased caution and more frequent monitoring. The company’s website does not specify the testing methods. Publications describing other tests provided by the company specify that testing is conducted via SNP sequencing performed via multiplex polymerase chain reaction (PCR).

- Proove Biosciences (Irvine, CA) offers several genetic panels that address pain control. The Proove® Opioid Risk Panel is a panel of 12 genes that is intended to predict opioid abuse and failure of opioid therapy. Genetic testing results are provided with along with an overall “Dependence Risk Index.” The company also markets the Proove® Pain Perception panel, which is a panel test for single nucleotide polymorphisms (SNPs) in several genes related to pain perception, including COMT and at least 3 other genes. Results are provided with a report which stratifies patients’ pain sensitivity based on COMT haplotype. Genetic testing for these panels is conducted by sequencing of target regions with reverse-transcription polymerase chain reaction (rtPCR).

- Pain Medication DNA Insight™ (Pathway Genomics, San Diego, CA) is a panel test intended to identify genetic variants that affect how an individual will respond to the analgesic effects of certain types of pain medications. The result report includes the genotype/SNP for each gene included, along with a description of the toxicity risk, dose required, medication efficacy, or plasma concentration based on genotype results for a range of medications used for pain
management, primarily opioids. The testing method is not specified on the company’s website.

- Millennium PGT (Pain Management) (Millennium Health, San Diego, CA) is a genetic panel test intended to help physicians select pain medication. The panel includes analysis of 11 genes related to pain management; results are provided with a proprietary “Millennium Analysis of Patient Phenotype” report that provides decision support for medications that may be affected by the patient’s genotype.

Other laboratories, including CompanionDx (Houston, TX), and AlBioTech (Richmond, VA), which markets the PersonaGene Genetic Panel, offer panels of CYP450 genes. Panels that are restricted to CYP450 genes are beyond the scope of this policy and are discussed in MPRM Policy 2.04.38 (Cytochrome P450 Testing).

In addition to the available panel tests, several labs offer genetic testing for individual genes that are included in some of the panels, including MTFHR, CYP450 genes, and OPRM1.

**Table 2: Genes Included in Genetic Panels for Pain Management**

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<tr>
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</thead>
<tbody>
<tr>
<td>SLC6A4 (5-HTT; serotonin transporter)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5HT2C (serotonin receptor)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DRD1 (dopamine receptor)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DRD2 (dopamine receptor)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DRD4 (dopamine receptor)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>DAT1 (dopamine transporter)</td>
<td>X</td>
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<tr>
<td>DA beta-hydroxylase</td>
<td>X</td>
<td>X</td>
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<tr>
<td>COMT (catechol O-methyltransferase)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>MTHFR</td>
<td>X</td>
<td>X</td>
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<tr>
<td>GABA</td>
<td>X</td>
<td>X</td>
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<tr>
<td>OPRK1 (κ-opioid receptor)</td>
<td>X</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>OPRM1 (μ-opioid receptor)</td>
<td>X</td>
<td>X</td>
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<tr>
<td>VKORC1</td>
<td></td>
<td>X</td>
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<tr>
<td>UGT2B15</td>
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<td>X</td>
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<td></td>
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<tr>
<td>CYP genes</td>
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<tr>
<td>CYP2D6</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>CYP2C19</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>CYP3A4</td>
<td>X</td>
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<tr>
<td>CYP1A2</td>
<td>X</td>
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<tr>
<td>CYP2C9</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>CYP2B6</td>
<td></td>
<td>X</td>
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<td>X</td>
<td></td>
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<tr>
<td>CYP3A5</td>
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</tbody>
</table>
Regulatory Status

No U.S. Food and Drug Administration (FDA)-approved genetic tests for pain management were identified. The Proove Narcotic Risk and Pain Perception panel, the GeneSight Analgesic panel, the Pathway Genomics Pain Medication DNA Insight panel, and the Millennium PGT (Pain Management) panel are laboratory-developed tests that are not subject to FDA approval. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Rationale

The evaluation of a genetic test’s clinical utility focuses on 3 main principles: (1) analytic validity (the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent); (2) clinical validity (the diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

In the case of genetic testing for pain management, testing is not used primarily as a diagnostic test; rather, testing is used to guide medication management, in one of the following ways:

- Drug selection or avoidance:
  - To identify individuals likely or not likely to respond to a specific medication.
  - To identify individuals at high risk of adverse drug reactions.
  - To identify individuals at high risk of opioid addiction or abuse.
- Dose optimization:
  - Identify individuals who are likely to require higher or lower doses of a drug.
  - Estimate the dose and dosing frequency.

Analytic Validity

Information on analytic validity of the test is lacking. No published studies were identified that specifically evaluated the analytic validity of the test as performed commercially. There was no information identified in the published literature or from the manufacturers’ websites concerning the genetic testing methods used for analysis. As a result, it is not possible to determine the analytic validity of the testing process.

Clinical Validity

Evidence on the clinical validity of genetic testing for pain management consists primarily of genome-wide association studies (GWAS) that correlate specific genetic polymorphisms with pain medication requirements or measures of pain control and case-control and cohort studies that report differences in pain medication requirements or measures of pain control for different genotypes. A comprehensive review of the GWAS and case control studies for all of these genes is beyond the scope of this policy. However, some of the representative literature, with a focus on studies published within the last 10 years, in this area is discussed below.
Genetic Variants and Analgesic Requirements
A variety of studies have evaluated the association of various genes with pain sensitivity or efficacy of pain medication, either elicited directly via subject report of pain or indirectly via analgesic dose requirement. Studies that evaluate the association between single nucleotide polymorphisms (SNPs) and analgesic dose requirements may provide a more objective outcome measurement of pain control; although this design makes it difficult to separate the effects of genotype on pain sensitivity from those of genotype on pain medication efficacy, these types of studies most directly translate to the clinical use of dose optimization.

Genetic Variants and Analgesic Requirements: Multiple-Gene Studies
Several studies have evaluated the association between multiple genes and SNPs and pain control. Klepsted et al reported results of a large genetic association study which evaluated the impact of variability in multiple genes on opioid use for cancer pain among 2294 cancer pain patients. Patients were enrolled from 17 European centers and were considered eligible if they had malignant disease and were using an opioid for moderate or severe pain (step III or higher on the World Health Organization treatment ladder for cancer pain). The authors assessed a large number of SNPs in multiple candidate genes which had previously been associated with pain control:

- OPRM1 (mu opioid receptor; 9 SNPs);
- OPRD1 (delta opioid receptor; 3 SNPs);
- OPRK1 (kappa opioid receptor; 1 SNP);
- ARRB (beta-arrestin; 7 SNPs);
- GNAZ (G nucleotide-binding protein 1; 1 SNP);
- HIN1 (histidine trinucleotide binding protein 1; 5 SNPs);
- Stat6 (signal transducer and activator of receptor 6; 3 SNPs);
- ABCB1 (p-glycoprotein transporter; 8 SNPs);
- COMT (catechol-O-methyltransferase; 6 SNPs);
- ADRA21 (alpha 2A adrenergic receptor; 3 SNPs);
- MC1R (melanocortin 1 receptor; 1 SNP);
- TACR1 (neurokinin 1 receptor; 10 SNPs);
- GCH1 (GTP cyclohydrolase 1; 3 SNPs);
- DRD2 (dopamine receptor D2; 11 SNPs);
- DRD3 (dopamine receptor D3; 8 SNPs);
- HTR3A, -3B, -2A, -3C, -3D, -3E, 1 and 4 (serotonin receptors; 36 SNPs);
- HRH1 (histamine receptor H1; 4 SNPs);
- CNR1 (cannabinoid receptor 1; 3 SNPs.

The patients’ primary opioids were morphine (n = 830), oxycodone (n = 446), fentanyl (n = 699), or other opioids (n = 234). Patients were randomly divided into 2 groups, with 2/6s serving as a development sample and 1/3 serving as a validation sample. The authors used a 10% false discovery rate for determining SNPs associated with the outcome measure using the Benjamini-Hochberg approach. Ten SNPs investigated had a minor allele frequency of less than 0.05 and/or were not in Hardy–Weinberg equilibrium and were excluded from further analyses. For the primary outcome of opioid dosage, no SNPs were consistently associated with dosage in both the development and validation samples. The authors note that their study design (cross-sectional evaluation of cancer
patients already managed with opioids) does not allow the determination of the relative genetic influence of pain perception and opioid efficacy.

In another relatively large study, Lotsch et al evaluated the effect of SNPs in multiple candidate genes on pain control among 352 patients treated in outpatient tertiary care centers. The authors assessed the following SNPs:

- **OPRM1** (mu opioid receptor) 118A>G;
- **COMT** (catechol-O-methyltransferase) 472G>A;
- **ABCB1** (p-glycoprotein transporter) 1236C>T, 2677G>T(A), and 3435C>T;
- **MC1R** (melanocortin 1 receptor) 29insA, 451C>T, 478C>T, and 880G>C;
- Functionally impaired CYP2D6 *41 allele;

Patients were managed with multiple opioids, most commonly oral tilidine (N=81; 15.6%), oral tramadol (N=81; 15.6%), and intravenous or subcutaneous morphine (N=74; 14.3%). Opioid doses were converted to oral morphine equivalents. In linear regression, the ABCB1 3435C>T polymorphism was the only factor significantly associated with opioid dose (P=0.004). In linear regression, the OPRM1 118A>G polymorphism was also significantly associated with opioid dose (P=0.041). No genetic associations were found with opioid-related adverse effects, including nausea/vomiting, constipation, fatigue, or laboratory abnormalities.

**Genetic Variants and Analgesic Requirements: OPRM1 Genotype**

The largest body of research assessing the association between SNPs in a specific gene and pain management appears to be for OPRM1 genotype, most often for the A118G SNP (rs1799971). These studies are summarized in Table 3.
<table>
<thead>
<tr>
<th>Study</th>
<th>SNP</th>
<th>Population</th>
<th>Primary Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al (2006)</td>
<td>OPRM1</td>
<td>120 patients undergoing total knee arthroplasty treated with morphine PCA who required rescue morphine</td>
<td>• No. of morphine PCA demands (1st 24 h, 2nd 24 h, and 1st 48 h postoperatively)</td>
<td>• Total morphine dose</td>
</tr>
<tr>
<td></td>
<td>A118G</td>
<td>SNP</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginosar et al (2013)</td>
<td>OPRM1</td>
<td>125 nulliparous women receiving combined spinal epidural-fentanyl anesthesia for labor</td>
<td>• Time to first request for additional analgesia</td>
<td>• No difference in time to request for additional analgesia or VAS at request for analgesia for AA homozygotes vs heterozygotes (GA) and homozygotes (GG) carrying G allele:</td>
</tr>
<tr>
<td></td>
<td>A118G</td>
<td>SNP</td>
<td>• Pain intensity at first request for additional anesthesia on VAS</td>
<td>o Time to analgesia request: 110.1 min for AA vs 108.3 min for GA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Intensity of anesthetic-related pruritus on VAS</td>
<td>o VAS (0-100) at analgesia request: 57.6 for AA vs 55.0 for GA and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in presence or intensity of pruritus based on genotype</td>
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</tr>
<tr>
<td>Ginosar et al (2009)</td>
<td>OPRM1</td>
<td>99 patients receiving alfentanil PCA for extracorporeal shock wave lithotripsy</td>
<td>• PCA bolus requests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A118G</td>
<td>SNP</td>
<td>• Alfentanil dose</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Alfentanil plasma concentration</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Verbal analog pain scores</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Compared with wild-type AA genotype, heterozygotes (GA) and homozygotes (GG) carrying G allele had:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o Higher alfentanil dose over 20 min (75.4 µg/kg vs 51.4 µg/kg; p=0.004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o Higher no. of boluses attempted over 25 min (7.2 vs 3.4; p=0.015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o Higher mean plasma alfentanil concentration (177 ng/mL vs 139 ng/mL; p=0.034)</td>
</tr>
</tbody>
</table>
### Table 3: Summary of Clinical Validity Studies of OPRM1 Genotype and Pain Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Genotype/Dosage/Procedure</th>
<th>Pain Management Outcomes</th>
</tr>
</thead>
</table>
| Hayashida et al (2008)13     | Multiple OPRM1 SNPs; 138 patients undergoing major abdominal surgery receiving continuous postop epidural opioid analgesia with rescue systemic opioids and/or NSAIDs | - Postoperative opioid equivalent dose requirement  
- NRS pain score                                                     |
| Kolesnikov et al (2011)15    | OPRM1 A118G SNP and COMT; 102 patients undergoing lower abdominal hysterectomy or myomectomy managed postop with intravenous PCA with morphine | - 48-h cumulative postop morphine dose  
- OPRM1 A118G and COMT G1947A polymorphisms alone were not associated with 48-h morphine consumption  
- Joint OPRM1/COMT polymorphisms were significantly associated with 48-h morphine consumption:  
  - For OPRM1 G carriers and COMT G carriers: total morphine dose 51.9 mg  
  - For OPRM1 wild-type homozygotes: total morphine dose 66.2 mg |
| Zhang et al (2010)17         | OPRM1 A118G SNP; 177 women undergoing total abdominal hysterectomy or myomectomy managed postop with intravenous PCA with fentanyl | - 24-h mean pain intensity on VAS  
- 24-h fentanyl consumption  
- OPRM1 A118G polymorphisms were not associated with initial VAS scores or first 24-h mean VAS scores  
- OPRM1 A118G polymorphisms showed significant association with 24-h fentanyl consumption (p<0.05 for linear trend):  
  - For A/A homozygotes: mean 24-h fentanyl consumption 363 µg |

**BIS:** bispectral index; **BPI:** Brief Pain Inventory; **CI:** confidence interval; **ED50:** median effective dose; **NRS:** numeric rating scale; **NSAIDs:** nonsteroidal anti-inflammatory drugs; **PCA:** patient-controlled anesthesia; **postop:** postoperative; **SNP:** single nucleotide polymorphism; **VAS:** visual analog scale; **VNTR:** varying number of tandem repeats.
Genetic Variants and Analgesic Requirements: CYP450 Genotype

A full review of the association between CYP450 genotypes and medications used for pain is beyond the scope of this policy (please refer to MPRM Policy 2.04.38, “Cytochrome P450 Genotyping.”) However, a summary of recent studies focusing on CYP2D6 metabolism status and pain management, primarily in the use of opioid medications, is outlined below.

**CYP450 and Metabolism of Multiple Opioids.** Jannatto et al evaluated the association between steady-state concentrations of the opioids methadone, oxycodone, hydrocodone, and tramadol and CYP2D6 genotype among 61 patients being treated for chronic pain. Most patients (54%) were extensive metabolizers (EM), while 41% were intermediate metabolizers (IM) and 5% were poor metabolizers (PM). No statistically significant associations were seen with CYP2D6 metabolizer status and opioid steady state concentration. For CYP2D6 EMs, 21% had complete pain relief, 58% had partial pain relief, and 21% had no relief, whereas for CYP2D6 IMs, 20% had complete pain relief, 68% had partial pain relief, and 12% had no pain relief, while all CYP2D6 PMs had partial pain relief (statistical comparison not reported).

**CYP450 and Metabolism of Tramadol.** Kirschheiner et al evaluated the association between CYP2D6 genotype and tramadol pharmacokinetics and pharmacodynamics among 25 healthy volunteers given tramadol (11 considered ultrarapid metabolizers [UM], 11 EMs, and 5 PMs based on CYP2D6 genotype). The maximum plasma concentration of tramadol’s active metabolite were significantly higher for UM subjects than for EM subjects (mean difference 14 ng/mL; 95% CI 2 to 26 ng/mL; P=0.005). The mean increase in pain tolerance from baseline to 4 hours after tramadol intake was -1 second, 20 seconds, and 36 seconds in the PM, EM, and UM groups, respectively. UMs demonstrated a stronger miosis after tramadol (maximum decrease in pupillary diameter after tramadol: 1 mm, 1.4 mm, and 2.2 mm for PM, EM, and UM groups, respectively). The authors conclude that UMs were more sensitive to the effects of tramadol.

In an earlier case control study, Wang et al reported an association between CYP2D6 *10 C188T polymorphisms and post-operative tramadol consumption in 71 patients following gastrectomy.

**CYP450 and Metabolism of Codeine.** Kirschheiner et al evaluated the association between CYP2D6 genotype and codeine metabolism among 25 healthy volunteers given a single 30 mg dose of codeine (11 UMs, 11 EMs, and 5 PMs based on CYP2D6 genotype). The area under the curve (AUC) for plasma concentration of morphine (the active metabolite of codeine) versus time was significantly greater for UMs (16 μg hour/L vs 11 μg hour/L; P=0.02). UMs were more likely to report sedation than EMs (91% vs 50%; P=0.03).

**CYP450 and Metabolism of Oxycodone.** In another, case-control study, Zwisler et al evaluated the association between CYP2D6 polymorphisms and intravenous oxycodone requirements following surgery (primarily thyroid or hysterectomy) in 270 patients. The authors found no difference between total oxycodone consumption between CYP2D6 EMs and PMs (EM 14.7 mg vs PM 13 mg; P=0.42).
CYP450 and Metabolism of Fentanyl. Liao et al evaluated the association between CYP3A4 polymorphisms and interactions with OPRM1 A118G polymorphisms and post-operative fentanyl requirements among 97 undergoing radical gastrectomy. Patients with the CYP3A4 *1B/*1B genotype used less fentanyl via PCA in the 48 hours after surgery compared with patients in the *1/*1 group (16.3 μg/kg vs 22.5 μg/kg; P=0.032). Although OPRM A118G polymorphisms were not significantly associated with cumulative fentanyl dose at 24 or 48 hours post-surgery, the joint genotype combination between CYP3A4 and OPRM1 was significantly associated with 48 hour cumulative fentanyl dose (P=0.021). VAS scores and frequency of adverse effects (nausea, vomiting, and dizziness) did not differ significantly across CYP3A4 groups.

Zhang et al reported no association between CYP3A5*3 polymorphisms and 24-hour post-operative fentanyl consumption in 203 women following total abdominal hysterectomy or myomectomy.

Genetic Variants and Analgesic Requirements: Other Gene Associations

While the largest body of research related to the clinical validity of genetic testing for pain management appears to be related to OPRM1 and CYP450 SNPs, the association of multiple other genes and response to analgesics has been reported. A summary of studies evaluating the association of some of these other genes and pain management outcomes is shown in Table 4.
### Table 4: Summary of Clinical Validity Studies of Other Genes and Pain Management

<table>
<thead>
<tr>
<th>Study</th>
<th>Gene(s)</th>
<th>Population</th>
<th>Primary Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
</table>
| Aoki et al (2010) | 5HT2A   | 135 patients status after open abdominal surgery, managed with continuous epidural anesthesia with opioids | • Intraoperative fentanyl dose and postop PCA fentanyl dose  
• Spontaneous pain intensity on 100-mm VAS | • 24-h postop fentanyl use higher with shorter DRD4 VNTR: fentanyl dose 4.09 µg/kg for SHORT/SHORT vs 2.24 µg/kg for any LONG (p=0.0118)  
• 3-h VAS scores did not significantly differ among VNTR groups |
| Aoki et al (2013) | DRD4    | 355 patients undergoing mandibular sagittal split ramus osteotomy          | • Daily morphine dose  
• Measure of “average pain” in the prior 24 h using BPI | • COMT Val158Met polymorphism was associated with morphine requirements (p=0.025):  
  o For Val/Val genotype (N=44): mean 24-h morphine requirement,  
  o For Val/Met genotype (N=96): mean 24-h morphine requirement,  
  o For Met/Met genotype (N=67): mean 24-h morphine requirement,  
• Other symptoms, including pain scores and adverse effect symptoms, did not differ significantly across groups |
| Jensen et al (2009) | COMT    | 43 healthy subjects subjected to thermal pain after short-acting opioid (remifentanil) administration | • Pain intensity on VAS after 5 blocks of 30-s heat administration | • At all 5 points, presence of met allele was associated with higher pain scores:  
  o For met homozygotes vs val homozygotes: p=0.010 (difference in normalized pain score at time 5 estimated from chart: ≈ 0.5)  
  o For met homozygotes vs val-met heterozygotes: p=0.042 (difference in normalized pain score at time 5 estimated from chart: ≈ 0.25)  
• Analgesia was induced by remifentanil in all groups without separating different genotype groups (p=0.042) |
| Rakvag et al (2005) | COMT    | 207 cancer patients receiving morphine therapy                              | • Daily morphine dose  
• Measure of “average pain” in the prior 24 h using BPI | • COMT Val158Met polymorphism was associated with morphine requirements (p=0.025):  
  o For Val/Val genotype (N=44): mean 24-h morphine requirement,  
  o For Val/Met genotype (N=96): mean 24-h morphine requirement,  
  o For Met/Met genotype (N=67): mean 24-h morphine requirement,  
• Other symptoms, including pain scores and adverse effect symptoms, did not differ significantly across groups |
| Kim et al (2006)  | COMT    | 207 multiple adults undergoing 3rd molar extraction including at least 1 impacted 3rd molar | • Daily morphine dose  
• Measure of “average pain” in the prior 24 h using BPI | • COMT Val158Met polymorphism was associated with morphine requirements (p=0.025):  
  o For Val/Val genotype (N=44): mean 24-h morphine requirement,  
  o For Val/Met genotype (N=96): mean 24-h morphine requirement,  
  o For Met/Met genotype (N=67): mean 24-h morphine requirement,  
• Other symptoms, including pain scores and adverse effect symptoms, did not differ significantly across groups |

**COMT**

• COMT SNP5 (rs740603) showed significant association with maximum postop pain (p=0.039):
SLC6A2

- SLC6A2 SNP2 (rs40434) showed significant association with analgesia onset time (p=0.011):
  - For G/G homozygotes: mean, 20.2 min (95% CI, 9.7 to 30.6)
  - For A/G heterozygotes: mean, 9.5 min (95% CI, 7.8 to 11.2)
  - For GG homozygotes: mean, 11.3 min (95% CI, 7.3 to 15.3)

SLC6A4

- SLC6A4 SNP1 (rs2066713) showed significant association with onset of postop pain (p=0.025):
  - For T/T homozygotes: mean, 145.7 min (95% CI, 124.3 to 167.0)
  - For T/C heterozygotes: mean, 124.4 min (95% CI, 115.4 to 133.5)
  - For C/C homozygotes: mean, 117.6 min (95% CI, 105.2 to 130.0)

Kim et al (2013)

- Multiple 196 patients undergoing laparoscopic or total abdominal hysterectomy managed postop with intravenous PCA with fentanyl

OPRM1

- OPRM1 A118G polymorphism was not associated with 48-h fentanyl consumption:
  - For A/A homozygotes: mean cumulative fentanyl dose, 1044.9 µg
  - For A/G heterozygotes: mean cumulative fentanyl dose, 1019.8 µg
  - For G/G homozygotes: mean cumulative fentanyl dose, 1013.5 µg

CYP3A4

- CYP3A4*18 and *3 polymorphisms not significantly associated with 48-h fentanyl consumption

ABCB1

- ABCB1 2667G→A/T and 3435C→T polymorphisms not significantly associated with 48-h fentanyl consumption

Kosek et al (2009)

- 5-HTT 43 healthy subjects subjected to thermal pain after short-acting opioid (remifentanil) administration
- Pain intensity on VAS after 5 blocks of 30-s heat administration
- For triallelic 5-HTTLPR:
  - At baseline, no differences between mean VAS after painful stimulus between high-, intermediate-, and low-expressing groups
  - After remifentanil administration, subjects with low 5-HTT expression had better analgesia vs subjects homozygous for 5-HTTLPR LA allele (p<0.02; VAS absolute difference estimated from chart: ≈20 mm).
Genetic Variants and Medication-Related Adverse Effects
Some studies have evaluated the association between genetic variants and medication-related adverse effects, which translate to a clinical use of dose optimization (to avoid an unwanted effect) OR to drug selection or avoidance (to identify individuals at high risk of adverse effects).

Genetic Variants and Medication-Related Adverse Effects: CYP2D6 and Respiratory Depression/CNS Depression
There has been particular interest in the evaluation of the role of CYP2D6 in the metabolism of codeine and other narcotics in children, particularly after tonsillectomy/adenoidectomy, and in nursing mothers after several cases of fatal overdoses. Codeine is metabolized to its active metabolite, morphine, via CYP2D6 activity. Individuals with higher than average CYP2D6 activity may have increased morphine formation, leading to higher toxicity risk, whereas those with lower than average CYP2D6 activity may have reduced morphine formation, leading to insufficient pain relief.

Madadi et al reported the results of a case-control study evaluating the association of maternal CYP2D6 polymorphisms and respiratory depression among infants of breastfeeding mothers treated with codeine. The study included 72 mother-child pairs whose mothers used codeine while breastfeeding, of which 17 (24%) of breastfed infants were reported to exhibit central nervous system (CNS) depression while their mothers used codeine. CNS depression was by maternal report. Two (11.8%) mothers of symptomatic infants were CYP2D6 UMs (in combination with a UGT2B7*2/*2 genotype), as compared to 0% of mothers among nonsymptomatic infants. Mothers of symptomatic cases were more likely to have a combined CYP2D6 UM and UGT2B7*2/*2 genotype than expected based on the average expected frequency (OR 8.4; 95% CI 4.7 to 47; P<0.001).

Genetic Variants and Medication-Related Adverse Effects: CYP2D6 and Other Adverse Effects
The effect of CYP450 genotype on outcomes other than respiratory depression has also been evaluated. Prows et al conducted a prospective study to evaluate factors, including CYP26 genotype, associated with codeine-related adverse drug events in children following tonsillectomy. The study enrolled 249 children aged 5 to 19 scheduled to undergo tonsillectomy. Symptoms were recorded in a symptom diary. Of 134 children who were given codeine, 106 (79%) reported at least 1 adverse event, most commonly lightheadedness and dizziness in white children and nausea and vomiting in African American children. The presence of a high risk CYP2D6 gene (EM or IM), compared with a low risk CYP2D6 gene (IM or PM), was associated with a higher ADR risk (P=0.044).

Candiotti et al evaluated the association of CYP2D6 gene copy number and the presence of postoperative nausea and vomiting after prophylaxis with the antiemetic ondansetron among 243 women undergoing general anesthesia. Eighty-eight women experienced postoperative nausea and/or vomiting requiring breakthrough medication. Metabolizer status based on number of functioning CYP2D6 copy numbers (PM, IM, EM, UM) was significantly associated with vomiting incidence, with vomiting occurring in 5/11 UMs (45.5%), compared with 1/12 PMs (8.3%), 5/30 IMs (16.7%), and 26/176 EMs (14.7%) (P=0.007 for UMs vs all other groups). However, nausea was not associated with genotype.
Genetic Variants and Medication-Related Adverse Effects: OPRM1 and Fentanyl-Associated Nausea and Vomiting
The association of other genes with analgesic-related adverse effects has also been reported. Zhang et al evaluated the association between the OPRM1 A118G polymorphism and fentanyl-associated postoperative nausea and vomiting among 165 women undergoing elective total abdominal hysterectomy or myomectomy who received fentanyl intravenous PCA postoperatively. The study found no statistically significant differences between genotype groups in terms of frequencies or scores of nausea and vomiting. Tsai et al evaluated the association between the OPRM1 A118G polymorphism and pruritus associated with epidural morphine used for postoperative analgesia among 212 women who received epidural morphine for post-Caesarian section analgesia. Pruritus was evaluated by the Itching Severity Scale (ISS 0–4), with significant pruritus considered to be an ISS score of 2-4. Among the 25 patients with OPRM1 genotype of GG, 3 (12%) had pruritus with ISS grade 2-4, while among the 187 patients with OPRM genotype AA or AG, 59 (31.6%) had significant pruritus (P=0.031). While this suggesting that OPRM1 genotype is associated with morphine-related pruritus, the study does not report morphine dose requirements for the different genotypes, making it difficult to exclude confounding by drug dose.

Genetic Variants and Addiction Risk
A number of studies have reported on the association between various genes and risk of addiction to or abuse of opioid pain medications and nonprescription opioids and other nonprescription substances, with some overlap between the two categories. Studies with a focus on genes associated with risk of addiction to or abuse of prescription medications, rather than cocaine, nicotine, or other substances, are outlined below. These studies would translate to a clinical use of drug selection or avoidance (to identify individuals in whom opioids should be used with caution). Other studies have evaluated the role of genotype in the efficacy of methadone therapy for a variety of addictions; while there is likely overlap between the genes involved in methadone metabolism and response and those involved in the metabolism and response of other opioids, studies evaluating methadone as a treatment for addiction are not included here.

Genetic Variants and Addiction Risk: OPRM1 and Opioid Dependence
In 2013, Haerian et al published a meta-analysis of studies evaluating the association between the OPRM1 A118G (rs1799971) polymorphism and opioid dependence. The authors identified 13 studies including 9385 subjects (N=4601 with opioid dependence and N=4784 controls) which reported OPRM1 genotypes for cases and controls. Most of the included studies (N=17) evaluated dependence on heroin, while the remaining evaluated dependence on opioids in general or opioids and cocaine. In pooled analysis of all included studies, the presence of the A allele (compared with the G allele) was not significantly associated with heroin dependence risk (pooled odds ratio [OR] 0.95; 95% CI 0.77 to 1.17). In pooled analysis evaluating risk of addiction to all opioids (excluding African-American subjects), the presence of the AA or AG genotype (compared with the GG genotype) was significantly associated with opioid dependence (pooled OR 0.78; 95% CI 0.63 to 0.97). The authors conclude that OPRM1 polymorphisms may be associated with opioid dependence among Asians.

In 2009, Coller et al published a meta-analysis of case-control studies evaluating the association between the OPRM1 A118G SNP allelic and genotypic frequencies and opioid dependence. The authors included 16 case-control studies (including 5169 subjects) which
reported A118G genotype frequencies, included a group with opioid dependence and a control group, and had genotype samples which were in Hardy-Weinberg equilibrium. Similar to the Haerian et al meta-analysis, most studies (N=11) included evaluated the association between A118G genotype and heroin dependence, with 5 studies reporting associations with opioids in general. In pooled analysis, no difference in A118G SNP genotype frequencies between opioid-dependent and control groups was observed, with a pooled OR of 1.28 (95% CI 0.77 to 2.11; P=0.34). No difference in A118G SNP allelic frequencies between opioid-dependence and control groups was observed, with a pooled OR of 1.16 (95% CI 0.91 to 1.47; P=0.23).

Other earlier meta-analyses of OPRM1 A118G SNP and substance dependence similarly reported no significant association between A118G SNPs and dependence.38,39

Section Summary
The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that evaluate associations of many different genetic variants and response to analgesic medication, risk of adverse events, and addiction risk. For tests that are available in currently-available genetic panel tests, the largest body of evidence is related to the association of the OPRM1 A118G SNP with analgesic response and addiction risk. Studies evaluating OPRM1’s role in analgesic response are generally relatively small cross-sectional studies conducted in the postoperative setting and have had mixed findings, with some studies showing an association between OPRM1 genotype and analgesic dose and/or measures of pain intensity, and others showing no significant association. Results of several meta-analyses have not consistently demonstrated an association between OPRM1 polymorphisms and addiction risk.

For other genes, the body of evidence evaluating associations between polymorphism and analgesic response, adverse effects, or addiction risk is small.

Clinical Utility
Pharmacogenetic testing for pain management has potential role for clinical utility in several settings, including drug selection or avoidance or in dose optimization. For drug selection, pharmacogenetic testing could potentially be used to identify individuals not likely to respond to a particular drug, or to identify individuals at high risk of an adverse drug reaction. For dose optimization, pharmacogenetic testing could potentially be used to identify individuals who are likely to be sensitive or resistant to a particular drug, or to estimate dose and dosing frequency.

For a testing for a given gene or panel of genes to demonstrate clinical utility, evidence is needed that testing for genetic variants leads to changes in clinical management that improve outcomes, such as improved pain control, shorter time to pain control, reduced frequency of adverse events, or reduced rates of addiction. No published studies were identified that reported management changes or patient outcomes for patients managed with pharmacogenetic testing for pain management. Therefore, the clinical utility of such testing cannot be determined.

Ongoing and Unpublished Clinical Trials
A search of the online database ClinicalTrials.gov in December 2014 identified found several ongoing studies related to genetic testing for pain management that are currently enrolling subjects:
- Predisposition to Persistent Pain After Orthopaedic Surgery: Genetic Aspects (NCT01989351) – This is an observational study to assess the relationship between several genetic polymorphisms (ADBR2, OPRM1, COMT, and IL1Ra) and the presence of persistent pain 4 months after orthopedic surgery. Enrollment is planned for 130 subjects; the estimated study completion date is March 2015.

- Acute Pain Genomic Study (NCT01557751) – This is a genome-wide association study to evaluate the association of genetic markers and acute perioperative pain following total knee arthroplasty. Enrollment is planned for 400 subjects; the estimated study completion date is December 2015.

- A Prospective Trial to Identify Biomarkers Involved in the Transition From Acute to Persistent Chronic Low Back Pain (NCT02037763) – This is a prospective observational cohort study to evaluate genetic polymorphisms associated with the presence of persistent low back pain in patients presenting with an episode of acute low back pain. Enrollment is planned for 5000 subjects; the estimated study completion date is August 2018.

- Utility of Pharmacogenomics for Reducing Adverse Drug Effects (UPGRADE) (NCT02081872) – This is an observational cohort study to assess whether pharmacogenic testing is associated with changes in how physicians manage patient medication regimens and changes in rates of adverse drug reactions, hospitalizations, and emergency department visits. The enrollment target is not specified; the estimated study completion date is July 2017.

- Pharmacogenomics Analysis of Morphine Pharmacokinetics in Pediatric Tonsillectomy and Adenoidectomy (NCT00836264) – This is an observational cohort study to assess whether gene polymorphisms are associated with variability in response to morphine among pediatric patients who undergo outpatient tonsillectomy/adenoidectomy. Enrollment is planned for 1650 subjects; the estimated study completion date is December 2017, with follow up through June 2018.

**Summary of Evidence**

Panels of genetic tests for genes that have shown some association with the pharmacokinetics or pharmacodynamics of analgesic medications have been developed to aid in the management of pain. The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that evaluate associations of many different genetic variants and response to analgesic medication, risk of adverse events, and addiction risk. The largest body of evidence is to be related to the association of the OPRM1 A118G single nucleotide polymorphism (SNP) with analgesic response and addiction risk, which have not consistently demonstrated significant associations. For other genes included in commercially-available pain management panels, the body of evidence evaluating associations between polymorphism and analgesic response, adverse effects, or addiction risk is small. At present, the clinical utility of pharmacogenetic testing in pain management is poorly defined. No published studies were identified that report on ways that clinical management of pain and/or patient outcomes are associated with pharmacogenetic testing. Therefore, genetic testing panels for pain management are considered *investigational* for all indications.


**Subject:** Pharmacogenetic Testing for Pain Management  

**Section:** Medicine  

**Subsection:** Pathology/Laboratory  

**Effective Date:** July 15, 2015  

**Original Policy Date:** June 19, 2015  

**Page:** 20 of 24

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**Supplemental Information**

**Practice Guidelines and Position Statements**

**Clinical Pharmacogenetics Implementation Consortium**

In 2012, the Clinical Pharmacogenetics Implementation Consortium (CPIC) issued guidelines for the management of codeine therapy in the context of CYP2D6 genotype, which were updated in 2014 to reflect U.S. Food and Drug Administration (FDA) labeling about codeine in children status post tonsillectomy with or without adenoidectomy and to include other opioids metabolized by CYP2D6. These guidelines do not specifically recommend CYP2D6 genotyping in particular patients, although they do provide the following codeine therapy recommendations based on CYP2D6 phenotype:

**Table 5: CPIC Guideline for Codeine Therapy Based on CYP2D6 Phenotype (Adapted from Crews et al, 2014)**

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>Implications for Codeine Metabolism</th>
<th>Recommendations for Codeine Therapy</th>
<th>Classification of Recommendations ns for Codeine Therapy</th>
<th>Considerations for Alternative Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label recommended age or weight-specific dosing.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Poor metabolizer</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.</td>
</tr>
</tbody>
</table>
American Academy of Neurology

In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic noncancer pain. Regarding pharmacogenetic testing, the guidelines state that genotyping to determine whether response to opioid therapy can or should be more individualized is an emerging issue that will “require critical original research to determine effectiveness and appropriateness of use.”

U.S. Preventive Services Task Force Recommendations

Not applicable

Medicare National Coverage

There is no national coverage determination (NCD).

References


<table>
<thead>
<tr>
<th>Policy History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
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<tr>
<td>June 2015</td>
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</tbody>
</table>

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 19, 2015 and is effective July 15, 2015.

Signature on File

Deborah M. Smith, MD, MPH