Pharmacogenetic Testing for Pain Management

Policy # 00468
Original Effective Date: 04/20/2015
Current Effective Date: 07/11/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for pain management for all indications to be investigational.*

Policy Guidelines
This policy does not address testing limited to cytochrome p450 genotyping. This policy also does not address testing for congenital insensitivity to pain.

Commercially available genetic tests for pain management consist of panels of single-nucleotide variants (SNVs) or (less commonly) individual SNV testing. SNVs implicated in pain management include the following (see also Table 1):

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol O-methyltransferase gene)
- MTHFR (methylene tetrahydrofolate reductase gene)
- γ-aminobutyric acid (GABA) A receptor gene
- OPRM1 (μ-opioid receptor gene)
- OPRK1 (κ-opioid receptor gene)
- UGT2B15 (uridine diphosphatase glucosyltransferase 2 family, member 15)
- Cytochrome p450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2.

Background/Overview
Pain is a universal human experience and an important contributor to outpatient and inpatient medical visits. The Institute of Medicine’s (IOM) reported in 2011 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 noncancer pain, which may be secondary to a wide range of conditions, such as migraines, low back pain,
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or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, and physical and occupational therapy, and complementary/alternative therapies. Nonetheless, IOM has reported 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.

PAIN MANAGEMENT
A variety of medication classes are available to manage pain: nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, which target central nervous system pain perception, and classes of adjuvants, including antiepileptic drugs (eg, 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 to manage cancer-related pain but has been applied to other forms of pain. The ladder outlines a stepped approach to pain management, beginning with nonopioid 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. Various opioids are available in short- and long-acting preparations and administered through different routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.

Pharmacologic Treatment
For acute pain management, particularly postoperative pain, systemic opioids and nonopioid 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 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 for chronic pain. In addition, many opioids are associated with significant risk of adverse events, 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 events.

Genetics of Pain Management
Genetic factors may contribute to a range of aspects in 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. Currently available genetic tests relevant to pain management assess SNVs in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes.

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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 proposed for use in the management of pain. Genes identified as being relevant to pain management and currently available panels are summarized in Table 1.

**Table 1: Genes Relevant to Pain Management**

<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 gene)</td>
<td>Xq23</td>
<td>1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine</td>
<td></td>
</tr>
<tr>
<td>5HT2A (serotonin receptor gene)</td>
<td>13q14-21</td>
<td>Another serotonin receptor subtype</td>
<td>Variants (ie, 102T/C) associated with variation in pain threshold</td>
</tr>
<tr>
<td>SLC6A4 (serotonin transporter gene)</td>
<td>17q11.2</td>
<td>clears serotonin metabolites from synaptic spaces in the CNS</td>
<td></td>
</tr>
<tr>
<td>DRD1 (dopamine receptor gene)</td>
<td>5q35.2</td>
<td>G-protein-coupled receptors that have dopamine as their ligands</td>
<td>DRD4 VNTR associated with presence of pain-related disorders (fibromyalgia, TMJ syndrome, migraine)</td>
</tr>
<tr>
<td>DRD2 (dopamine receptor gene)</td>
<td>11q23.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 (dopamine receptor gene)</td>
<td>11p15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT1 or SLC6A3 (dopamine transporter gene)</td>
<td>5p15.33</td>
<td>Mediates dopamine reuptake from synaptic spaces in the CNS</td>
<td></td>
</tr>
<tr>
<td>DBH (dopamine beta-hydroxylase gene)</td>
<td>9q34.2</td>
<td>Catalyzes the hydroxylation of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons</td>
<td></td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase gene)</td>
<td>22q11.21</td>
<td>Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine</td>
<td>Val158Met variant associated with alterations in emotional processing and executive function. Other variants have been associated with pain sensitivity and a wide variety of clinical disorders</td>
</tr>
<tr>
<td>MTHFR (methylenetetrahydrofolate reductase gene)</td>
<td>1p36.22</td>
<td>Converts folic acid to methyfolate, a precursor to norepinephrine and dopamine, and serotonin neurotransmitters</td>
<td>Multiple variants identified, which are associated with a wide variety of clinical disorders</td>
</tr>
<tr>
<td>GABA A receptor gene</td>
<td>5q34</td>
<td>Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter</td>
<td>1519T&gt;C GABA A 6 gene variant associated with methamphetamine dependence</td>
</tr>
<tr>
<td>OPRM1 (μ-opioid receptors gene)</td>
<td>6q25.2</td>
<td>G-protein coupled receptor that is primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone</td>
<td>A118G variant (rs1799971) associated with reduced pain sensitivity and opioid requirements</td>
</tr>
<tr>
<td>OPRK1 (k-opioid receptor gene)</td>
<td>8q11.23</td>
<td>Binds the natural ligand dynorphin and synthetic ligands</td>
<td>Variants associated with the risk for opioid addiction</td>
</tr>
<tr>
<td>UGT2B15 (uridine)</td>
<td>4q13.2</td>
<td>Member of UDP family involved in the</td>
<td>Tamoxifen, diclofenac, naloxone,</td>
</tr>
</tbody>
</table>
### Gene Summary Table

<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>Diphosphate glycosyltransferase 2 family, member 15</td>
<td></td>
<td>Glycosylation and elimination of potentially toxic compounds</td>
<td>Carbamazepine, and benzodiazepines inhibit UGT2B7 potentially leading to opioid hyperalgesia</td>
</tr>
<tr>
<td>Cytochrome p450 genes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>22q13.2</td>
<td>Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics</td>
<td>CYP2D6 is primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>10q23.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10q23.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>7q22.1</td>
<td></td>
<td>Involved in metabolism of up to 60% of clinically used drugs</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>19q13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>15q24.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; CYP: cytochrome; GABA: γ-aminobutyric acid; TMJ: temporomandibular joint; UG: uridine diphosphate glycosyltransferase; VNTR: varying number of tandem repeats.

### Commercially Available Genetic Tests for Pain Management

Several test labs market panel tests or individual tests designed to address 1 or more aspects of pain management, including but not limited to drug selection, drug dosing, or prediction of adverse events. Specific variants included in the panels are shown in Table 2.

- **GeneSight® Analgesic** (Assurex Health, Mason, OH) is a genetic panel test intended to analyze "how patients' genes can affect their metabolism and possible response to FDA [U.S. Food and Drug Administration]-approved opioids, NSAIDs and muscle relaxants commonly used to treat chronic pain." Results are provided with a color-coded report based on efficacy and tolerability, which displays those medications that 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 SNV sequencing performed via multiplex polymerase chain reaction.

- **Proove Biosciences** (Irvine, CA) offers several genetic panels that address pain control. The Proove® Opioid Risk Panel includes 11 genes intended to predict opioid abuse and failure of opioid therapy. Genetic testing results are provided with an overall Dependence Risk Index. The company also markets the Proove Pain Perception panel, which is a test for SNVs in several genes related to pain perception, including COMT and at least 3 other genes. Results are provided with a report that stratifies patients' pain sensitivity based on COMT haplotype. In addition, Proove Biosciences offers panels designed to predict good and poor responders to opioid therapies and nonopioid pain therapies—the Proove Opioid Response panel and the Proove Non Opioid Response, respectively. Genetic testing for these panels is conducted by sequencing of target regions with reverse-transcription polymerase chain reaction.

- **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
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certain types of pain medications. The results report includes the genotype/SNV 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 analyzes 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.

- Molecular Testing Labs™ Pain Management Panel (Molecular Testing Labs, Vancouver, WA) is a panel designed to evaluate the metabolism of pain relievers. The manufacturer’s website states that the test evaluates “a number of relevant genes coding for the metabolism of a wide variety of pain relief drugs,” but the specific genes tested are not readily described.

- Genelex (Seattle, WA) offers several pharmacogenomic panels, one of which (the YouScript℠ Analgesic Panel) focuses on genes relevant to pain management.

- AltheaDx (San Diego) offers IDgenetix℠ pain tests that analyze the genes and genetic variants involved in the metabolism of opioids, NSAIDs, and other pain drugs as well as variations in pharmacodynamic genes, such as the μ-opioid receptor gene (OPRM1).

Other laboratories, including CompanionDx (Houston, TX), ARUP Laboratories (Salt Lake City, UT), 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 evidence review and are discussed in evidence review 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 the MTFHR, CYP450, and OPRM1 genes (see Table 2).

Table 2: Genes Included in Commercially Available Genetic Panels for Pain Management

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proove Opioid Risk (Proove Biosciences)</th>
<th>Proove Pain Perception (Proove Biosciences)</th>
<th>GeneSightRx Analgesic (AssureRx Health)</th>
<th>Pain Medication DNA Insight (Pathway Genomics)</th>
<th>Millennium PGT (Millennium Health)</th>
<th>YouScript Analgesic (Genelex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC6A4 (5-HTT; serotonin transporter)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD1 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD2 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD4 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT1 (dopamine)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Gene</th>
<th>Proove Opioid Risk (Proove Biosciences)</th>
<th>Proove Pain Perception (Proove Biosciences)</th>
<th>GeneSightRx Analgesic (AssureRx Health)</th>
<th>Pain Medication DNA Insight (Pathway Genomics)</th>
<th>Millennium PGT (Millennium Health)</th>
<th>YouScript Analgesic (Genelex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA beta-hydroxylase</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTHFR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRK1 (k-opioid receptor)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 (μ-opioid receptor)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKORC1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT2B15</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP genes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C3</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A5</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CYP: cytochrome; GABA: γ-aminobutyric acid; 5-HHT: hereditary hemorrhagic telangiectasia type 5.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). 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 available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

No FDA-approved genetic tests for pain management were identified.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, 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). Following is a summary of the key literature.

GENETIC TESTING FOR THE MANAGEMENT OF ACUTE AND CHRONIC PAIN

Clinical Context and Test Purpose

The purpose of genetic testing for management of acute and chronic pain is to

- Select appropriate pain medications or avoid use of inappropriate pain medications
  - To identify individuals likely or unlikely 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.
- Optimize the dose selection or frequency by:
  - Identifying individuals who are likely to require higher or lower doses of a drug.

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for pain management has clinical validity? and (2) Does patient management change in a way that potentially improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with chronic and acute pain, including conditions such as cancer, migraines, low back pain, and fibromyalgia.

Interventions

Testing for individual genes is available for most, or all, or the genes listed in Table 2, as well as for a wider range of genes. Because of the large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes that broadly test potential response to 4 relevant medication classes: opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, and opioid dependency. Examples of commercially available genetic panels for pain management are listed in Table 3.

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proove Biosciences</td>
<td>Proove Opioid Risk</td>
<td>11</td>
</tr>
<tr>
<td>Proove Biosciences</td>
<td>Proove Pain Perception</td>
<td>1</td>
</tr>
<tr>
<td>AssureRx Health</td>
<td>GeneSightRx Analgesic</td>
<td>7</td>
</tr>
</tbody>
</table>

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Comparators
The comparator of interest is standard pain management without genetic testing.

Outcomes
Specific outcomes in each of these categories are listed in Table 4.

Table 4. Outcomes of Interest for Individuals With Chronic or Acute Pain

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbid events</td>
<td>Opioid addiction, adverse events</td>
</tr>
<tr>
<td>Health status measures</td>
<td>Pain relief, functional status</td>
</tr>
<tr>
<td>Medication use</td>
<td>No. of unsuccessful medication trials, no. of medications needed, dose of medication, dose frequency</td>
</tr>
</tbody>
</table>

The potential beneficial outcomes of primary interest would be improvement in pain, functioning, and quality of life.

The potential harmful outcomes are those resulting from a false test result. False-positive or -negative test results can lead to initiation of unnecessary treatment and adverse effects from that treatment or undertreatment.

Timing
Genetic testing may be used for pain management planning before a procedure associated with acute pain or to evaluate an individual with difficulty managing chronic pain.

Setting
Patients with chronic and acute pain are likely to be managed by a wide variety of specialties such as chiropractors, general physicians, physiatrists (rehabilitation physicians) rheumatologists, orthopedic surgeons, oncologist, pain management specialist, physical therapists, and acupuncturists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity
No published studies were identified that specifically evaluated the analytic validity of the test as performed commercially. No information was identified in the published literature or on 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. In general, Sanger sequencing or next-generation sequencing methods would be expected to have high analytic validity.

**Section Summary: Analytic Validity**

No studies were identified that specifically addressed the analytic validity of commercially available tests.

**Clinical Validity**

Evidence on the clinical validity of genetic testing for pain management primarily consists of genome-wide association studies (GWAS) that correlate specific genetic variants 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 evidence review. However, some of the representative literature, with a focus on studies published within the last 10 years, in this area is discussed next.

**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 from reports of pain or indirectly from analgesic dose requirements. Studies that evaluate the association between SNVs 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: Multigene Studies**

Several studies have evaluated the association between multiple genes and SNVs and pain control. Klepstad et al (2011) reported results of a large gene association study that evaluated the impact of variability in multiple genes on opioid use 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 SNVs in multiple candidate genes, which had previously been associated with pain control:

- **OPRM1** (μ-opioid receptor gene; 9 SNVs);
- **OPRD1** (δ-opioid receptor gene; 3 SNVs);
- **OPRK1** (κ-opioid receptor gene; 1 SNV);
- **ARRB** (beta-arrestin gene; 7 SNVs);
- **GNAZ** (G nucleotide-binding protein 1 gene; 1 SNV);
- **HINT** (histidine trinucleotide binding protein 1 gene; 5 SNVs);
- **Stat6** (signal transducer and activator of receptor 6 gene; 3 SNVs);
- **ABCB1** (p-glycoprotein transporter gene; 8 SNVs);
- **COMT** (catechol O-methyltransferase gene; 6 SNVs);

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- **ADRA21** (alpha 2A adrenergic receptor gene; 3 SNVs);
- **MC1R** (melanocortin 1 receptor gene; 1 SNV);
- **TACR1** (neurokinin 1 receptor gene; 10 SNVs);
- **GCH1** (GTP cyclohydrolase 1 gene; 3 SNVs);
- **DRD2** (dopamine receptor D2 gene; 11 SNVs);
- **DRD3** (dopamine receptor D3 gene; 8 SNVs);
- **HTR3A, -3B, -2A, -3C, -3D, -3E, 1, and 4 genes** (serotonin receptors; 36 SNVs);
- **HRH1** (histamine receptor H1 gene; 4 SNVs);
- **CNR1** (cannabinoid receptor 1 gene; 3 SNVs.

Patients' primary opioids were morphine (n=830), oxycodone (n=446), fentanyl (n=699), or other opioids (n=234). Patients were randomized to 2 groups, with two-thirds serving as a development sample and one-third serving as a validation sample. The authors used appropriate measures to control for type I error related to multiple comparisons. Ten SNVs 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 SNVs 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) did not permit determining the relative genetic influence of pain perception and opioid efficacy.

In another study in the same patient cohort as the Klepstad study, Scarpi et al (2014) reported on genetic differences between patients (total N=2294 patients) with (n=577) and without cancer-induced bone pain (n=1624) and, among patients with cancer-induced bone pain, genetic differences in opioid response. No SNV haplotypes were associated with the presence of cancer-induced bone pain or opioid response after correction for multiple comparisons.

In another relatively large study, Lotsch et al (2009) evaluated the effect of SNVs in multiple candidate genes on pain control among 352 patients treated in outpatient tertiary care centers. The authors assessed the following SNVs:

- **OPRM1** (μ-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 variant was the only factor significantly associated with opioid dose (p=0.004). In linear regression, the **OPRM1** 118A>G variant was
the only candidate gene significantly associated with 24-hour pain score ($p=0.041$). No genetic associations were found with opioid-related adverse events, including nausea/vomiting, constipation, fatigue, or laboratory abnormalities.

Blanco et al (2016) reported on the association between SNVs in the $UGT2B7$, $CYP3A4$, and $OPRM1$ variants and transdermal buprenorphine pain control in a cohort of 107 patients with critical limb ischemia awaiting revascularization. The $UGT2B7$ and $OPRM1$ variants were not associated with response to buprenorphine pain control, as measured on a visual analog scale. In contrast, carriers of the $CYP3A4$ AA genotype had significantly better pain response ($p=0.003$).

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

The largest body of research assessing the association between SNVs in a specific gene and pain management appears to be for $OPRM1$ genotype, most often for the A118G SNV (rs1799971). While multiple studies have suggested a link between $OPRM1$ genotype and dose/intensity of required analgesia, the association is inconsistent across studies. Further, the wide variety of patient population (women in labor, patients undergoing surgery, patients with cancer), genetic variant, and outcome measures (dose, frequency, timing, pain control) used makes it difficult to understand collectively the association between a genetic variant and an analgesic requirement. These studies are summarized in Table 5.

**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 review (see evidence review 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 next.

**CYP450 and Metabolism of Opioids**

Jannatto et al (2009) 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 comparisons not reported).

**CYP450 and Metabolism of Tramadol**

Lassen et al (2015) reported on results for a systematic review of the pharmacogenetics of tramadol, which included $CYP2D6$ and other genes encoding other CYP450 enzymes and enzymes involved in tramadol metabolism. Reviewers included 54 articles, including 43 cohort and case-control studies, 3 case reports, 6
in vitro studies, and 2 animal studies. The review was primarily descriptive, with the conclusion that \textit{CYP2D6} is the major genetic factor in tramadol metabolism, while other genetic factors have a limited associated body of research.

Kirschheiner et al (2008) evaluated the association between \textit{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 \textit{CYP2D6} genotype). The maximum plasma concentration of tramadol's active metabolite was significantly higher for UM subjects than for EM subjects (mean difference, 14 ng/mL; 95% confidence interval [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 (2006) reported on an association between \textit{CYP2D6*10 C188T} variants and postoperative tramadol consumption in 71 patients following gastrectomy.

\textit{CYP450 and Metabolism of Codeine}

Kirschheiner et al (2007) evaluated the association between \textit{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 \textit{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/h/L vs 11 µg/h/L; \(p=0.02\)). UMs were more likely to report sedation than EMs (91% vs 50%; \(p=0.03\)).

Baber et al (2015) reported on the genetic variability of pain control in a cohort of 98 women prescribed codeine for pain after a cesarean section. In this study, \textit{CYP2D6} genotype was not associated with postoperative pain score or codeine dose. However, \textit{UGT2B7} and \textit{OPRM1} variants, coding for other enzymes involved in codeine metabolism, were associated with codeine dose requirements. In multivariable analysis, the presence of the \textit{UGT2B7} rs7439366 variant and the \textit{OPRM1} rs1799971 were significantly predictive of mean codeine input (regression coefficient, -0.30 [95% CI, -0.086 to -0.021] and 0.34 [95% CI, 0.032 to 0.10], respectively).
# Table 5: Summary of Clinical Validity Studies of OPRM1 Genotype and Pain Management

<table>
<thead>
<tr>
<th>Study</th>
<th>SNV</th>
<th>Population</th>
<th>Primary Outcomes</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camorcia et al (2012)</td>
<td>OPRM1 A118G SNV</td>
<td>57 women undergoing epidural anesthesia for labor</td>
<td>ED50 for epidural sufentanil dose (estimated from up-down sequence and probit regression)</td>
<td>Median effective dose of epidural sufentanil in nulliparous women in spontaneous labor lower in women carrying the variant G118 allele of OPRM1</td>
</tr>
<tr>
<td>Chou et al (2006)</td>
<td>OPRM1 A118G SNV</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, 1st 48 h postoperatively)</td>
<td>No. of morphine demands significantly higher for heterozygotes (GA) and homozygotes (GG) carrying G allele vs WT homozygotes (AA):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total morphine dose</td>
<td>o 1st 24 h: morphine demands 36.1 for GG vs 24.3 for AA (p=0.033) and vs 22.2 for AG (p=0.021)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>o 1st 48 h: 57.8 for GG vs 39 for AA (p=0.026) and vs 35.3 for AG (p=0.012)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Total morphine dose significantly higher for GA and GG vs AA:</td>
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<tr>
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<td></td>
<td>o 1st 24 h: morphine dose 22.3 mg for GG vs 16 mg for AA (p=0.018) and vs 14.8 mg for GA (p=0.010)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>o 1st 48 h: morphine dose 40.5 mg for GG vs 25.3 mg for AA (p=0.003) and vs 25.6 mg for GA (p=0.008)</td>
</tr>
<tr>
<td>Fukuda et al (2009)</td>
<td>Multiple OPRM1 SNVs</td>
<td>280 patients undergoing mandibular sagittal split ramus osteotomy</td>
<td>Pain perception latency</td>
<td>For the A118 G SNV (rs1799971):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Perioperative fentanyl dose</td>
<td>No significant differences in perioperative fentanyl dose or pain intensity on VAS at 3 and 34 h postop (WT AA homozygote vs heterozygotes and homozygotes carrying G allele)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pain intensity on 100-mm VAS at 3 and 24 h postop</td>
<td>For IVS3+ A8449G SNV (representing the complete linkage disequilibrium block; rs8334179):</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>o 24-h postop fentanyl dose higher for AA: 2.5 μg/kg for AA vs 1.55 μg/kg for AG/GG (p=0.01)</td>
</tr>
<tr>
<td>Ginosar et al (2013)</td>
<td>OPRM1 A118G SNV</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></td>
<td></td>
<td>Pain intensity at first request for additional analgesia on VAS</td>
<td>o Time to analgesia request: 110.1 min for AA vs 108.3 min for GA and GG (p=0.836)</td>
</tr>
<tr>
<td></td>
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<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 GG (p=0.470)</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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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Authors</th>
<th>OPRM1 SNVs</th>
<th>Patients</th>
<th>Procedures</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Ginosar et al (2009) | OPRM1 A118G SNV | 99 patients recovering alfentanil PCA for extracorporeal shock wave lithotripsy | • PCA bolus requests  
• Alfentanil dose  
• Alfentanil plasma concentration  
• Verbal analog pain scores | • Compared with WT AA genotype, heterozygotes (GA) and homozygotes (GG) carrying G allele had:  
  o Higher alfentanil dose over 20 min (75.4 μg/kg vs 51.4 μg/kg, p<0.004)  
  o Higher no. of boluses attempted over 25 min (7.2 vs 3.4, p<0.015)  
  o Higher mean plasma alfentanil concentration (177 ng/mL vs 139 ng/mL, p=0.034)  
• Higher mean VAS pain score (3.2 vs 2.1, p=0.047) |
| Hayashida et al (2008) | Multiple OPRM1 SNVs | 138 patients undergoing major abdominal surgery receiving continuous postop epidural opioid analgesia with rescue systemic opioids and/or NSAIDs | • Postop opioid equivalent dose requirement  
• NRS pain score | • A118G SNV genotype significantly associated with opioid requirement (p=0.009)  
• None of the SNVs evaluated associated with NRS pain score |
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<table>
<thead>
<tr>
<th>Authors</th>
<th>Gene</th>
<th>Study Details</th>
<th>Pain Management Outcomes</th>
</tr>
</thead>
</table>
| Kim et al (2013) | OPRM1 A118G SNV | 196 patients undergoing laparoscopic or total abdominal hysterectomy managed postop with intravenous PCA with fentanyl | *OPRM1 A118G variant not associated with 48-h cumulative postop fentanyl dose*
|                  |      |                                                                                | - 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  |
| Kolesnikov et al (2011) | OPRM1 A118G SNV and COMT | 102 patients undergoing lower abdominal surgery managed postop with intravenous PCA with morphine | *OPRM1 A118G and COMT G1947A variants alone not associated with 48-h fentanyl consumption*
|                  |      |                                                                                | - Joint OPRM1 and COMT variants significantly associated with 48-h morphine consumption:  
|                  |      |                                                                                | - For OPRM1 G carriers and COMT G carriers: total morphine dose, 51.9 mg  
|                  |      |                                                                                | - For OPRM1 WT homozygotes: total morphine dose, 66.2 (p<0.05)  |
| Landau et al (2008) | OPRM1 A118G SNV | 147 nulliparous women receiving combined spinal-epidural anesthesia with fentanyl for labor | *OPRM1 304 A/G variant associated with fentanyl dose requirement (median ED50 ratio for 304A homozygosity vs 304A/G heterozygotes and 304 G/G homozygotes):*
|                  |      |                                                                                | - For sequential allocation: median ED50 ratio, 1.51 (95% CI, 1.18 to 2.01; p=0.009)  
|                  |      |                                                                                | - For random allocation: median ED50 ratio, 2.14 (95% CI, 1.30 to 5.17; p=0.002)  |
| Zhang et al (2010) | OPRM1 A118G SNV | 177 women undergoing total abdominal hysterectomy or myomectomy managed postop with intravenous PCA with fentanyl | *OPRM1 A118G variants not associated with initial VAS scores or first 24-h mean VAS scores*
|                  |      |                                                                                | - OPRM1 A118G variants 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  
|                  |      |                                                                                | - For A/G heterozygotes: mean 24-h fentanyl consumption, 391 µg  
|                  |      |                                                                                | - For G/G homozygotes: mean 24-h fentanyl consumption, 485 µg  |
| Cajanus et al (2014) | OPRM1 A118G SNV | 1000 women undergoing breast cancer surgery managed with intravenous oxycodone | *OPRM1 A118G variants associated with oxycodone dose required for adequate postop analgesia*
|                  |      |                                                                                | - Presence of 2 minor (G) alleles at rs558025 significantly associated with intraoperative remifentanil requirement  
|                  |      |                                                                                | - Other OPRM SNVs evaluated not associated with medication dose or side effects  |
| Liu et al (2014) | Multiple OPRM1 SNVs | 178 women undergoing elective endometrial polypectomy or hysteroscopic cervical canal ring resection managed intraoperatively with remifentanil | *Presence of 2 minor (G) alleles at rs558025 significantly associated with intraoperative remifentanil requirement*
|                  |      |                                                                                | - Other OPRM SNVs evaluated not associated with medication dose or side effects  

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CYP450 and Metabolism of Oxycodone
Zwisler et al (2010) reported the results of a case-control study that found no difference in total oxycodone consumption between CYP2D6 EMs (14.7 mg) and PMs (13 mg; p=0.42) following surgery (primarily thyroid or hysterectomy) in 270 patients.

CYP450 and Metabolism of Fentanyl
Liao et al (2013) evaluated the association between CYP3A4 variants and interactions with OPRM1 A118G variants and postoperative fentanyl requirements among 97 patients undergoing radical gastrectomy. Patients with the CYP3A4*18B/*18B genotype used less fentanyl via patient-controlled analgesia in the 48 hours after surgery (16.3 μg/kg) compared with patients in the *1/*1 group (22.5 μg/kg; p=0.032). Although OPRM A118G variants were not significantly associated with cumulative fentanyl dose at 24 or 48 hours postsurgery, 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 events (nausea, vomiting, dizziness) did not differ significantly across CYP3A4 groups.

Zhang et al (2011) reported no association between CYP3A5*3 variants and 24-hour postoperative 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 SNVs, the association between multiple other genes and responses to analgesics has been reported. A summary of studies evaluating the associations between some of these other genes and pain management outcomes are shown in Table 6.

Genetic Variants and Medication-Related Adverse Events
Some studies have evaluated the association between genetic variants and medication-related adverse events, which translate to a clinical use of dose optimization (to avoid an unwanted effect) OR to drug selection (appropriate drug) or avoidance (to identify individuals at high risk of adverse events).
Genetic Variants and Medication-Related Adverse Events: CYP2D6 and Respiratory Depression/Central Nervous System Depression

There has been particular interest in evaluating the role of CYP2D6 in the metabolism of codeine and other narcotics in children, particularly after tonsillectomy or 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 (2009) reported the results of a case-control study evaluating the association between maternal CYP2D6 variants 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 UM (in combination with a UGT2B7*2/*2 genotype), compared with 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).
<table>
<thead>
<tr>
<th>Study</th>
<th>Gene(s)</th>
<th>Population</th>
<th>Primary Outcomes</th>
<th>Main Results</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoki et al (2010)</td>
<td>5HT2A</td>
<td>135 patients after open abdominal surgery, managed with continuous epidural anesthesia with opioids</td>
<td>Index of analgesic requirement (expressed as equivalent dose of systemic pentazocine)</td>
<td>• Total rescue analgesic plus antipyretic frequency higher for 102T/T vs T/C genotype (1.34 vs 0.84; p=0.011)</td>
<td></td>
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</tbody>
</table>
|                       |              |                                                                            | 5-point NRS pain score                                                             | For female subjects:  
  • Total rescue analgesic plus antipyretic frequency higher for 102T/T vs C/C genotype (1.75 vs 0.63; p=0.009)                                                                                           |  |
|                       |              |                                                                            |                                                                                   | • Total rescue analgesic frequency higher for 102T/T vs T/C genotype (1.63 vs 0.53; p=0.003)                                                                                                                |  |
|                       |              |                                                                            |                                                                                   | • Total systemic pentazocine equivalent dose higher for 102T/T vs T/C (27.7 vs 9; p=0.016) and vs C/C (27.7 vs 8.18; p=0.044)                                                                               |  |
|                       |              |                                                                            |                                                                                   | • No significant association between genotype and NRS pain scores                                                                                                                                       |  |
| Aoki et al (2013)     | DRD4         | 355 patients undergoing mandibular sagittal split ramus osteotomy          | Intraoperative fentanyl dose and postop PCA fentanyl dose                           | 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)                                                                      |  |
|                       |              |                                                                            | Spontaneous pain intensity on 100-mm VAS                                            | 3-h VAS scores did not significantly differ among VNTR groups                                                                                                                                       |  |
| Jensen et al (2009)   | COMT         | 43 healthy subjects subjected to thermal pain after short-acting opioid administration | Pain intensity on VAS after 5 blocks of 30-s heat administration                    | • At all 5 points, presence of met allele associated with higher pain scores:  
  • For met homozygotes vs val homozygotes: p=0.010 (difference in normalized pain score at time 5 estimated from chart: Δ0.5)  
  • For met homozygotes vs val-met heterozygotes: p=0.042 (difference in normalized pain score at time 5 estimated from chart: Δ0.25)  
  • Analgesia 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 variant associated with morphine requirements (p=0.025):  
  • For Val/Val genotype (n=44): mean 24-h morphine requirement, 155 mg/24 h  
  • For Val/Met genotype (n=86): mean 24-h morphine requirement, 117 mg/24 h  
  • For Met/Met genotype (n=67): mean 24-h morphine requirement, 95 mg/24 h  
  • Other symptoms, including pain scores and adverse effects, did not differ significantly across groups                                                                                                                                |  |
| Kim et al (2006)      | Multiple genes | 221 adults undergoing 3rd molar extraction including at least 1 impacted 3rd molar | Pain intensity on VAS before and after ketorolac administration                     |  
  
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COMT

- COMTs 740663 showed significant association with maximum postop pain (p<0.039):
  - For A/A homozygotes: mean, 25.0 (95% CI, 15.5 to 34.6)
  - For A/G heterozygotes: mean, 9.8 (95% CI, 4.9 to 14.7)
  - For G/G homozygotes: mean, 1.7 (95% CI, 0.9 to 2.4)

SLC8A2

- SLC8A2 299654 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 min)
  - For A/G heterozygotes: mean, 9.5 min (95% CI, 7.8 to 11.2 min)
  - For GG homozygotes: mean, 11.3 min (95% CI, 7.3 to 15.3 min)

SLC6A4

- SLC6A4 2996713 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 min)
  - For T/C heterozygotes: mean, 124.4 min (95% CI, 115.4 to 133.5 min)
  - For C/C homozygotes: mean, 117.6 min (95% CI, 105.2 to 130.0 min)

Kim et al (2013) 1

- Multiple 196 patients undergoing laparoscopic or total abdominal hysterectomy.
  - Managed postop with intravenous PCA with fentanyl.
  - • 48-h cumulative postop fentanyl dose

OPRM1

- OPRM1 A118G variant 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, 1013.9 µg

CYP3A4

- CYP3A4 1188 variant not associated with 48-h fentanyl consumption:
  - For A/G heterozygotes: mean, 52.6 (95% CI, 44.5 to 60.6)
  - For A/A homozygotes: mean, 62.8 (95% CI, 56.4 to 67.2)
  - For G/G homozygotes: mean, 63.9 (95% CI, 57.5 to 64.5)

ACB1

- ACB1 36676G>A/T and 34315C>T variants not associated with 48-h fentanyl consumption:
  - For T/T homozygotes: mean, 117.6 min (95% CI, 105.2 to 130.0 min)
  - For T/C heterozygotes: mean, 124.4 min (95% CI, 115.4 to 133.5 min)
  - For C/C homozygotes: mean, 117.6 min (95% CI, 105.2 to 130.0 min)

Koak et al (2009) 2

- S-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

Biases: biphasic index; BPI: Brief Pain Inventory; CI: confidence interval; EDS: median effective dose; S-HTT: S-HTT; hereditary hemorrhagic telangiectasia type 5; S-HTTLPR: serotonin transporter linked polymorphic region; NRS: numeric rating scale; PCA: patient-controlled analgesia; postop: postoperative; SNP: single-nucleotide variant; VAS: visual analog scale; VNTR: varying number of tandem repeats.

**Genetic Variants and Medication-Related Adverse Events: CYP2D6 and Other Adverse Events**

The effect of CYP450 genotype on outcomes other than respiratory depression has also been evaluated. Prows et al (2014) conducted a prospective study to evaluate factors, including CYP2D6 genotype, associated with codeine-related adverse drug events in children following tonsillectomy. The study enrolled 249 children ages 5 to 19 years scheduled to undergo tonsillectomy. Symptoms were recorded in a symptom diary. Of 134 children 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 adverse drug reaction risk (p=0.044).

Candiotti et al (2005) evaluated the association between 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 (45.5%) of 11 UMs, compared with 1 (8.3%) of 12 PMs, 5 (16.7%) of 30 IMs, and 26 (14.7%) of 176 EMs (p=0.007 for UMs vs all other groups). However, nausea was not associated with genotype.
Genetic Variants and Medication-Related Adverse Events: OPRM1 and Fentanyl-Associated Nausea and Vomiting

The association between other genes and analgesic-related adverse events has also been reported. Zhang et al (2011) evaluated the association between the OPRM1 A118G variant and fentanyl-associated postoperative nausea and vomiting among 165 women undergoing elective total abdominal hysterectomy or myomectomy who received intravenous patient-controlled fentanyl - postoperatively. The study found no statistically significant differences between genotype groups in terms of frequencies or scores of nausea and vomiting. Tsai et al (2010) evaluated the association between the OPRM1 A118G variant and pruritus related to epidural morphine used as postoperative analgesia among 212 women who received epidural morphine for post-Caesarian section analgesia. Pruritus was evaluated using the Itching Severity Scale (ISS; score range, 0-4), with significant pruritus considered to be an ISS score of 2 to 4. Among the 25 patients with the OPRM1 GG genotype, 3 (12%) had pruritus with ISS grade 2 to 4, while among the 187 patients with the OPRM1 AA or AG genotype, 59 (31.6%) had significant pruritus (p=0.031). While this suggests that OPRM1 genotype is associated with morphine-related pruritus, the study did 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 2 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 next. 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) variant and opioid dependence. Reviewers included 18 studies overall. There were 13 studies including 9385 subjects (n=4601 with opioid dependence, n=4784 controls), which reported OPRM1 genotypes for cases and controls. In pooled analysis of all included studies, the presence of the A allele (vs 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 the risk of addiction to all opioids (excluding African-American subjects), the presence of the AA or AG genotype (vs the GG genotype) was significantly associated with opioid dependence (pooled OR=0.78; 95% CI, 0.63 to 0.97). Reviewers concluded that OPRM1 variants 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 SNV allelic and genotypic frequencies and opioid dependence. Reviewers 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 that were in Hardy-
Weinberg equilibrium. Similar to the Haerian meta-analysis, most studies (n=11) included evaluated the
association between A118G genotype and heroin dependence, with 5 studies reporting on associations with
opioids in general. In pooled analysis, no difference in A118G SNV genotype frequencies between opioid-
dependent and control groups was observed, with a pooled odds ratio of 1.28 (95% CI, 0.77 to 2.11; p=0.34). No difference in A118G SNV allelic frequencies between opioid-dependence and control groups
was observed, with a pooled odds ratio of 1.16 (95% CI, 0.91 to 1.47; p=0.23).

Other earlier meta-analyses (2006, 2007) of the OPRM1 A118G SNV and substance dependence similarly
reported no significant association between A118G SNVs and dependence.

**Genetic Variants and Addiction Risk: Dopamine Pharmacogenetics and Addiction**

In 2015, Patriquin et al reported on results of a systematic review of studies evaluating the role of
dopaminergic gene variation in the pharmacotherapy of alcohol, opioid, and cocaine use disorders. The
systematic review included a qualitative analysis of 9 studies that evaluated various genes, including DRD2,
ANKK1, DAT1, DBH, and DRD4. Four studies included addressed the treatment of opioid addiction (and/or
cocaine addiction in 3 studies), and are most relevant to the scope of this evidence review. One study,
evaluating 68 patients in a randomized controlled trial of disulfiram therapy for cocaine or opioid use,
reported that the DRD2 GT/TT genotype was associated with decreases in positive urine samples for
cocaine among disulfiram-treated patients (67%-48%), and carriers of at least 1 minor DRD2 or ANKK1 allele responded better to disulfiram. In a study of 321 patients treated with methadone for opioid
dependence, DRD2, ANKK1, ABCB1, CYP2B6, and OPRM1 genotypes were together associated with
methadone dose requirements. The 2 other studies reported associations between dopamine β-hydroxylase
level and treatment effects.

**Section Summary: Clinical Validity**

The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a
large number of studies that have evaluated associations among many different genetic variants and drug
responses, risk of adverse events, and addiction risk. For genes in currently available panel tests, the
largest body of evidence is related to the association between the OPRM1 A118G SNV and 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 reported mixed findings, with
some studies showing associations between OPRM1 genotype and analgesic dose and/or measures of
pain intensity, and others showing no significant associations. Results of several meta-analyses have not
consistently demonstrated an association between OPRM1 variants and addiction risk.

For other genes, the body of evidence evaluating associations between variant and analgesic response,
adverse events, or addiction risk is small and inconclusive.
Clinical Utility

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs.

Pharmacogenetic testing for pain management has a potential role for clinical utility in several settings, including drug selection or avoidance or in dose optimization. For drug selection, pharmacogenetic testing could 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 be used to identify individuals who are likely to be sensitive or resistant to a particular drug, or to estimate dose and dosing frequency.

Gammal et al (2016) reported on the feasibility of implementing a pre-emptive genetic test for \textit{CYP2D6} metabolizer status into their electronic clinical decision support system to guide prescribing of codeine with the goal of preventing its use after tonsillectomy or adenoidectomy and in \textit{CYP2D6} UM and PM (high-risk) genotypes. The authors did not report on any clinical outcomes, and did they report any outcomes pre or post implementation of the clinical decision support system for genetic testing for \textit{CYP2D6}. Results were reported for a subset of 621 patients with sickle cell disease who had a \textit{CYP2D6} genotype result. Of these, 7.1\% were UMs or possible UMs, and 1.4\% were PMs. None of the patients with an UM or PM genotype were prescribed codeine. The authors acknowledged the need for future studies to demonstrate the impact of their genetic testing algorithm on clinical end points such as adverse effects and pain control.

Senagore et al (2017) reported on results of a prospective cohort study of 50 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery. Prior to surgery, all patients underwent genetic testing using the NeuroIDgenetix pain panel that that analyzes 9 genes, including \textit{CYP1A2}, \textit{CYP2C9}, \textit{CYP2C19}, \textit{CYP2D6}, \textit{CYP3A4}, \textit{CYP3A5}, \textit{ABCB1}, \textit{COMT}, and \textit{OPRM1}. Results of the panel were reported along with a list of medications classified as “Use as Directed” or “Use with Caution and/or Increased Monitoring.” Investigators used these results to guide selection of analgesics using a standard 1-to-10 VAS pain score in accordance with the results of genetic panel results. The primary outcome measure was Overall Benefit of Analgesia Score (OBAS), which assesses the combined impact on analgesia, patient satisfaction, and the impact of drug-associated side effects. The lower the score, the better is overall analgesia. The authors compared the findings with a historical cohort of 47 patients who underwent similar surgeries but were managed with standard enhanced recovery protocol. Results showed that OBASs were significantly lower in patients managed via genotype testing than those given no testing on postoperative day 1 (3.8 vs 5.4; 1.8 vs 2.3) and day 5 (3.0 vs 4.5; 1.2 vs 2.0), all respectively (all \(p<0.05\)). Need for narcotic-equivalent analgesics in the genotype tested group was lower in the group of genotype-tested patients (104.5 mg, SD=122.1) than in the historical controls (222.1 mg, SD=221.1;\(p<0.05\)). Although the authors reported that the 2 groups were similar in terms of patients characteristics, details of disease status and other known prognostic factors were lacking in the published paper. The authors did not report how the historical cohort was selected nor did they describe efforts to control for known confounders using statistical adjustments. Furthermore, no attempt was made to assess
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the magnitude of any specific genetic variant combinations on drug efficacy or potency in our study population. This study was funded by the test manufacturer. Thus, multiple methodologic limitations do not permit conclusions from this study.

**Chain of Evidence**
It is not possible to construct an indirect chain of evidence for clinical utility due to the lack of clinical validity.

**Section Summary: Clinical Utility**
Because of the lack of established clinical validity, it is not possible to establish the clinical utility of genetic testing for pain management through a chain of evidence. Several studies have reported on a number of genes and responses to antiepileptic drugs or antiepileptic drug adverse events. How this information should be used to tailor medication management is not yet well-defined. Two studies were identified. The first reported on the use of preemptive genetic testing for CYP2D6 metabolizer status to guide prescribing codeine to pediatric patients but the study did not report on the impact of the genetic testing algorithm on clinical end points such as adverse effects and pain control. The second study reported on the impact of genetic panel testing to guide the selection of analgesics and reported significant improvement in total scores of a composite end point that measures analgesia, patient satisfaction, and the impact of drug-associated side effects compared to a historical control. However, methodologic limitations of that study preclude assessment of the effects on outcomes.

**SUMMARY OF EVIDENCE**
For individuals who have need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes genome-wide association studies, which correlate specific genetic variants with pain medication requirements or measures of pain control, case-control and cohort studies that report differences in pain medication requirements or measures of pain control for different genotypes, as well as systematic reviews and meta-analysis. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, health status measures, and medication use. The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that have evaluated associations between many different genetic variants and response to analgesic medication, risk of adverse events, and addiction risk. The largest body of evidence assesses the association between the OPRM1 A118G single-nucleotide variant and analgesic response and addiction risk, which has not consistently demonstrated significant associations. For other genes included in commercially available pain management panel tests, the evidence evaluating associations between variant and analgesic response, adverse events, or addiction risk is small. At present, the clinical utility of pharmacogenetic testing in pain management is poorly defined. Two studies were identified that reported on ways clinical management of pain can be modified based on genetic testing. The first study reported the use of preemptive genetic test for CYP2D6 metabolizer status to guide prescribing of codeine in pediatric patients but did not report the impact of the genetic testing algorithm on clinical end points such as adverse effects and pain control. The second study reported on the impact of a genetic panel test to guide selection of analgesics and reported significant improvement in total scores of a composite end point that measured analgesia, patient satisfaction, and the impact of drug-associated side effects compared to a historical control.
control. However, methodologic limitations precluded assessment of the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

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04/02/2015 Medical Policy Committee review
04/20/2015 Medical Policy Implementation Committee approval. New policy.
04/07/2016 Medical Policy Committee review
04/20/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017 Medical Policy Committee review
07/19/2017 Medical Policy Implementation Committee approval. No change to coverage.
07/05/2018 Medical Policy Committee review
07/11/2018 Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
Next Scheduled Review Date: 07/2019

Coding

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