Preauthorization is required.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With need for pharmacologic pain management</td>
<td>Interventions of interest are: • Use of pharmacogenetic testing</td>
<td>Comparators of interest are: • Management without pharmacogenetic testing</td>
<td>Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Morbid events • Health status measures • Medication use</td>
</tr>
</tbody>
</table>

Description

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 (AEs). This has prompted interest in better targeting pain therapies through the use of pharmacogenetic testing of genes relevant to analgesic pharmacokinetics or pharmacodynamics. A number of 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.

Summary of Evidence

The evidence for use of pharmacogenetic testing in patients with need for pharmacologic pain management includes genome-wide association studies that correlate specific genetic polymorphisms with pain medication requirements or measures of pain control as well as case-control and cohort studies that report differences in pain medication requirements or measures of pain control for different genotypes. 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 evaluate associations of many different genetic variants and response to analgesic medication, risk of AEs, and addiction risk. The largest body of evidence is related to the association of the OPRM1 A118G single nucleotide polymorphism 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, AEs, 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genetic testing for pain management is considered **investigational** for all indications (See Policy Guidelines).

Policy Guidelines

This Protocol is not intended to address testing that is limited to cytochrome P450 genotyping, for information on this topic please refer to the Cytochrome P450 Genotyping Protocol.

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 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-methyl-transferase 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 diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome P450 genes: **CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2**

This Protocol does not address testing for congenital insensitivity to pain.

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
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 noncancer 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: nonopioid 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 (e.g., 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 nonopioid analgesia and proceeding to a weak opioid (e.g., codeine), with or without an adjuvant for persisting pain and subsequently to a strong opioid (e.g., 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 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 in the management of chronic pain. In addition, many opioids are associated with significant risk of adverse events (AEs), ranging from mild (e.g., constipation) to severe (e.g., 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 AEs.

Genetics of Pain Management

Genetic factors may contribute to a 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.
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 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>Polymorphisms (i.e., 102T/C) have been associated with variation in pain threshold</td>
</tr>
<tr>
<td>5HT2A (serotonin receptor gene)</td>
<td>13q14-21</td>
<td>Another serotonin receptor subtype</td>
<td></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></td>
<td></td>
</tr>
<tr>
<td>DRD2 (dopamine receptor gene)</td>
<td>11q23.2</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>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>22q11.2</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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other polymorphisms have been associated with pain sensitivity</td>
</tr>
<tr>
<td>MTHFR (methylene tetrahydrofolate reductase gene)</td>
<td>1p36.22</td>
<td>Converts folic acid to methylfolate, precursor to 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>GABA A receptor gene</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 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 polymorphism (rs1799971) has been associated with reduced pain sensitivity and opioid requirements</td>
</tr>
</tbody>
</table>

- 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.
## GeneLocusGene Product FunctionPotential Role in Pain Management

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Function</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRK1 (κ-opioid receptor gene)</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>
</tbody>
</table>

### Cytochrome p450 genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Function</th>
<th></th>
</tr>
</thead>
<tbody>
<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 has been associated with variability in opioid effects</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>10q23.33</td>
<td>Involved in metabolism of up to 60% of clinically used drugs</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10q23.33</td>
<td>Involved in metabolism of up to 60% of clinically used drugs</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>7q22.1</td>
<td>Involved in metabolism of up to 60% of clinically used drugs</td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>19q13.2</td>
<td>Involved in metabolism of up to 60% of clinically used drugs</td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>15q24.1</td>
<td>Involved in metabolism of up to 60% of clinically used drugs</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 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 AEs. 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 [U.S. Food and Drug Administration]-approved opioids, NSAIDs and muscle relaxants commonly used to treat chronic pain.”

- **Proove Biosciences** (Irvine, CA) offers several genetic panels that address pain control. The Proove® Opioid Risk Panel is a panel of 11 genes that is intended to predict opioid abuse and failure of opioid therapy. Genetic testing results are provided along with an overall “Dependence Risk Index.” The company also markets the Proove® Pain Perception panel, which is a panel test for SNPs in several genes related to pain perception, including COMT and at least three other genes. Results are provided with a report which stratifies patients’ pain sensitivity based on COMT haplotype. In addition, Proove offers to 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 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 PGTSM (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.

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 apparent.

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

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 Protocol and are discussed in the Cytochrome P450 Genotyping Protocol.

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 (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>5HT2C (serotonin receptor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD1 (dopamine receptor)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRD2 (dopamine receptor)</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>DRD4 (dopamine receptor)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT1 (dopamine transporter)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA beta-hydroxylase</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase)</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTHFR</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>GABA</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRK1 (κ-opioid receptor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPRM1 (μ-opioid receptor)</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>VKORC1</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGT2B15</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP genes</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>
Gene Pharmacogenetic Testing 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>
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<th>Millennium PGT (Millennium Health)</th>
<th>YouScript Analgesic (Genelex)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>CYP3A5</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

**Regulatory Status**

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 Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

No 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 LDTs.

**Related Protocols**

Cytochrome P450 Genotyping

Genetic Testing for Mental Health Conditions

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


46. Haerian BS, Haerian MS. OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis. Pharmacogenomics. May 2013; 14(7):813-824. PMID 23651028


