Introduction

When it comes to treating pain, there are a lot of different choices. These include things like over-the-counter remedies like acetaminophen and ibuprofen, medications that are rubbed onto the skin, and prescription drugs known as opioids. Antidepressants and antiseizure medications are also sometimes used to help with pain. Managing acute (sudden and intense) and chronic (long lasting) pain can be challenging. Each person not only has a different response to pain, but they may also have a different response to pain medication. In short, what works for one person may not work for another. A person’s genetics may affect pain perception and how the body processes medications. Genetic tests have been developed to try to find out how a person might respond to drugs to treat pain. These genetic tests are investigational (unproven). There is not enough medical evidence in published studies to show whether these genetic tests will improve overall health results.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Service</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing for pain management</td>
<td>Genetic testing for pain management is considered investigational for all indications.</td>
</tr>
</tbody>
</table>

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

This policy is not intended to address testing that is limited to cytochrome P450 genotyping, which is addressed in a separate medical policy, (see Related Policies).

Commercially-available genetic tests for pain management consist 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 (methylenetetrahydrofolate 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

Coding
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0078U</td>
<td>Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder (new code effective 10/1/18)</td>
</tr>
<tr>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

N/A

**Evidence Review**

**Description**

While multiple pharmacologic therapies are available for the management of acute and chronic pain, there is a lot of variability in the person’s response to pain, 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.

**Background**

Pain is a universal human experience and an important contributor to outpatient and inpatient medical visits. The Institute of Medicine (IOM) reported in 2011 that common chronic pain conditions affect at least 116 million adults in the United States. Chronic pain may be due to cancer or chronic noncancer conditions. These noncancer conditions may include migraines, low back pain, or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, physical and occupational therapy, and complementary/alternative therapies. Nonetheless, the 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. These include non-opioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and opioid analgesics which target central nervous system pain perception. Adjuvant medications such as antiepileptic drugs (eg, gabapentin, pregabalin), antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors), and topical analgesics have also been used. The management of chronic pain has been driven, in part, by the World Health Organization’s analgesic ladder for pain management, which was developed for the management of cancer-related pain but has been applied to the management of other forms of pain. The ladder outlines a stepped approach to pain management, beginning with non-opioid analgesia and proceeding to a weak opioid (eg, codeine), with or without an adjuvant for persisting pain. If these fail to control pain, the next step is 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 variety of routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.
Pharmacologic Treatment

For acute pain management, particularly postoperative pain, systemic opioids and non-opioid analgesics remain the mainstay of therapy. However, there has been growing interest in using alternative, nonsystemic treatments in addition to or instead of systemic opioids. These options include neuraxial anesthesia, a type of regional anesthesia including epidural or intrathecal opioid injection. This type of anesthesia may be managed by 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 great deal of variability in pain response, particularly in the management of chronic pain. In addition, many opioids have a significant risk of adverse events (AEs), ranging from mild (eg, constipation) to severe (eg, respiratory depression) and are associated with a 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 in order to predict and avoid AEs.

Genetics of Pain Management

Genetic factors may influence many 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 look at single-nucleotide variants (SNVs) in single genes potentially related to pharmacokinetic or pharmacodynamic processes.

Broadly speaking, genes related to these clinical scenarios include 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 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>SHT2C (serotonin receptor gene)</td>
<td>Xq23</td>
<td>1 of 6 subtypes of serotonin receptor, which is involved in</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>Locus</td>
<td>Gene Product Function</td>
<td>Potential Role in Pain Management</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>5HT2A (serotonin receptor gene)</td>
<td>13q14–21</td>
<td>Another serotonin receptor subtype.</td>
<td>Polymorphisms (ie, 102T/C) have been associated with variation in pain threshold.</td>
</tr>
<tr>
<td><em>SLC6A4</em> (serotonin transporter gene)</td>
<td>17q11.2</td>
<td>Clears serotonin metabolites from the synaptic spaces in the CNS.</td>
<td></td>
</tr>
<tr>
<td><em>DRD1</em> (dopamine receptor gene)</td>
<td>5q35.2</td>
<td>G-protein-coupled receptors that have dopamine as their ligands</td>
<td></td>
</tr>
<tr>
<td><em>DRD2</em> (dopamine receptor gene)</td>
<td>11q23.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>DRD4</em> (dopamine receptor gene)</td>
<td>11p15.5</td>
<td></td>
<td><em>DRD4</em> VNTR have been associated with presence of pain-related disorders (fibromyalgia, TMJ syndrome, migraine).</td>
</tr>
<tr>
<td><em>DAT1</em> or <em>SLC6A3</em> (dopamine transporter gene)</td>
<td>5p15.33</td>
<td>Mediates dopamine reuptake from synaptic spaces in the CNS.</td>
<td></td>
</tr>
<tr>
<td><em>DBH</em> (dopamine beta-hydroxylase gene)</td>
<td>9q34.2</td>
<td>Catalyzes the hydroxylase of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons.</td>
<td></td>
</tr>
<tr>
<td><em>COMT</em> (catechol-O-methyltransferase gene)</td>
<td>22q11.21</td>
<td>Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine.</td>
<td>Val158Met polymorphism has been associated with alterations in emotional processing and executive function. Other polymorphisms have been associated with pain sensitivity.</td>
</tr>
<tr>
<td><em>MTHFR</em> (methylene-tetrahydrofolate reductase gene)</td>
<td>1p36.22</td>
<td>Converts folic acid to methylfolate, a precursor to the norepinephrine, dopamine, and serotonin neurotransmitters.</td>
<td>Multiple polymorphisms have been identified, which are associated with a wide variety of clinical disorders.</td>
</tr>
<tr>
<td>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>
</tbody>
</table>
| *OPRM1* (µ-opioid receptors) | 6q25.2  | G-protein coupled receptor that is the primary site of action for                                                                                                                                                                                                                | A118G polymorphism (rs1799971) has been associated with reduced...


<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>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>
<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 the 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></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 the 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 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 variants 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.” Results are provided with a color-coded report based on efficacy and tolerability, which displays which medications should be used as directed, used with caution, or used with increased caution and more frequent monitoring.
The company’s website does not specify the testing methods. Publications describing other tests provided by the company specify that testing is conducted via SNP sequencing performed via multiplex polymerase chain reaction.

- **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 3 other genes. Results are provided with a report which stratifies patients’ pain sensitivity based on COMT haplotype. In addition, Proove offers panels designed to predict good and poor responders to opioid therapies and non-opioid pain therapies. These are 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 includes the genotype/SNP for each gene examined, 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 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 AIBioTech (Richmond, VA), which markets the PersonaGene™ Genetic Panel, offer panels of CYP450 genes. Panels that are restricted to CYP450 genes are beyond the scope of this policy and are discussed in a separate medical policy (see Related Policies).

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>Commercially Available Test Panels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proove Opioid Risk Proove Biosciences</td>
</tr>
<tr>
<td>SLC6A4 (5-HTT; serotonin transporter)</td>
<td>X</td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td>X</td>
</tr>
<tr>
<td>DRD1 (dopamine receptor)</td>
<td>X</td>
</tr>
<tr>
<td>DRD2 (dopamine receptor)</td>
<td>X</td>
</tr>
<tr>
<td>DRD4 (dopamine receptor)</td>
<td>X</td>
</tr>
<tr>
<td>DAT1 (dopamine transporter)</td>
<td>X</td>
</tr>
<tr>
<td>DA beta-hydroxylase</td>
<td>X</td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase)</td>
<td>X</td>
</tr>
</tbody>
</table>
Gene | Commercially Available Test Panels
---|---
MTHFR | X | X | X
GABA | X |
OPRK1 (κ-opioid receptor) | X | X
OPRM1 (µ-opioid receptor) | X | X | X | X
VKORC1 | X |
UGT2B15 | X |
CYP genes
CYP2D6 | X | X | X | X | X
CYP2C19 | X | X | X
CYP3A4 | X | X | X
CYP1A2 | X |
CYP2C9 | X | X | X | X | X
CYP2B6 | X | X | X
CYP3A5 | X | X

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

**Summary of Evidence**

The evidence for pharmacogenetic testing for pain management includes:

- genome-wide association studies that 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
- systematic reviews
- 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 evaluate associations of many different genetic variants and response to analgesic medication, risk of AEs, and addiction risk. The largest body of evidence assesses 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 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.

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 codeine in pediatric patients. However, it 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. However, methodologic limitations precluded assessment of the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore the use of genetic testing for this indication is investigational.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3: Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02487888*</td>
<td>A Study of the Impact of genetic Testing on Clinical Decision Making and Patient Care</td>
<td>100,000</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT02081872*</td>
<td>Utility of PharmacoGenomics for Reducing Adverse Drug Effects</td>
<td>297,000</td>
<td>Jul 2017</td>
</tr>
<tr>
<td>NCT02037763</td>
<td>A Prospective Controlled Trial to Identify Biomarkers Involved in the Transition From Acute to Persistent Chronic Low Back Pain</td>
<td>5000</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>NCT02256943</td>
<td>Genetic Determinants of Amitriptyline Efficiency for Pain Treatment</td>
<td>48</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02256956</td>
<td>Genetic Determinants of Amitriptyline Efficiency for Pain Treatment - Part II</td>
<td>48</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT00836264</td>
<td>Pharmacogenomic Analysis of Morphine Pharmacokinetics and Response Variability Following Pediatric Tonsillectomy and Adenoidectomy: A Genome-Wide Association Approach</td>
<td>1650</td>
<td>Jun 2019 (suspended)</td>
</tr>
<tr>
<td>NCT02871934</td>
<td>Integrating Pharmacogenetics In Clinical Care</td>
<td>408</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
*a Denotes industry-sponsored or cosponsored trial.

**Practice Guidelines and Position Statements**

*Clinical Pharmacogenetics Implementation Consortium*

In 2012, the Clinical Pharmacogenetics Implementation Consortium issued guidelines for the management of codeine therapy in the context of CYP2D6 genotype. These were updated in 2014 to reflect a U.S. Food and Drug Administration (FDA) warning about using codeine in children status post tonsillectomy, with or without adenoidectomy. It also discussed the use of other opioids metabolized by CYP2D6.54,55 These guidelines do not specifically recommend CYP2D6 genotyping in particular patients, although they do provide the following codeine therapy recommendations based on CYP2D6 phenotype (see Table 4).

**Table 4: CPIC Guideline for Codeine Therapy Based on CYP2D6 Phenotype (Adapted from Crews et al, 2014)55**

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

CPIC: Clinical Pharmacogenetics Implementation Consortium.
American Academy of Neurology

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

Medicare National Coverage

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

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). 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. 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.

References

1. Institute of Medicine, Committee on Advancing Pain Research Care and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press; 2011.

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


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/10/15</td>
<td>New Policy. Policy created with literature review through December 2, 2014. Pharmacogenetic testing for pain management is considered investigational for all indications.</td>
</tr>
<tr>
<td>09/18/15</td>
<td>Coding update. ICD-10-CM codes removed; these are non-specific and informational only.</td>
</tr>
<tr>
<td>01/12/16</td>
<td>Replace Policy. Policy updated with literature review through October 13, 2015; references 10, 12, 18, 30-31, and 50 added. Policy statement unchanged.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Update Related Policies. Remove 12.04.38 as it was deleted and replaced with</td>
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<td>Coding update, added CPT code 0078U.</td>
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**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filling a grievance, the Civil Rights Coordinator is available to help you.


Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.
Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):
ويحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طبلك أو المطلوبة التي تزيد الحصول عليها من خلال معلومات Premera Blue Cross. قد تكون هناك تفاصيل معلومات نتائج اجراء في هذا الإشعار. قد تحتاج للاطلاع في توزيع ميزة للعامة على تطبيقات الصحة والمغذية في دفع الكاب. إذا كنت الحصول على هذه المعلومات والمعلومات المتعلقة دون تكلفة إلقاء. تأكد من اخذ 800-722-1471 (TTY: 800-842-5357).

Oromo (Oromo):

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci dati chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.
Chiamare 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

037338 (07-2016)
Premera Blue Cross

1. Health plans may cover the health care expenses that you incur. If you have questions about your plan, please call the number on the back of your member ID card or visit premerablue.com.

2. If you have pre-existing conditions, this coverage may not be effective until a specific date. Please contact Premera Blue Cross at 800-722-1471 to confirm this date.

3. If you change your mind about the coverage, you can disenroll at any time. The disenrollment date is the date you file an application to disenroll. The date will be determined by Premera Blue Cross.

4. For more information, please visit premerablue.com or call 800-722-1471.

Premera Blue Cross

1. Зашитній захист включає обслуговування у бюджетних закладах.

2. Якщо у вас існували попередні умови, ця покриття може не бути ефективним до特定 дати. Будь ласка, зв'яжіться з Premera Blue Cross на 800-722-1471 для підтвердження цієї дати.

3. Якщо ви зміните свої думки про обслуговування, ви можете скасувати це на будь-коли. Дата скасування є датою, коли ви подадете документи на скасування. Дата буде визначена Premera Blue Cross.

4. Для більшої інформації, будь ласка, відвідайте premerablue.com або зв'яжіться з нами по телефону 800-722-1471.

Premera Blue Cross

1. Наша компанія може покрити витрати на обслуговування в бюджетних закладах.

2. Якщо у вас існували попередні умови, ця покриття може не бути ефективним до специфічної дати. Будь ласка, зв'яжіться з Premera Blue Cross на 800-722-1471 для підтвердження цієї дати.

3. Якщо ви зміните свої думки про обслуговування, ви можете скасувати це на будь-коли. Дата скасування є датою, коли ви подадете документи на скасування. Дата буде визначена Premera Blue Cross.

4. Для більшої інформації, будь ласка, відвідайте premerablue.com або зв'яжіться з нами по телефону 800-722-1471.

Premera Blue Cross

1. Ваши страхові оплати можуть покрити обслуговування у бюджетних закладах.

2. Якщо у вас існували попередні умови, ця покриття може не бути ефективним до специфічної дати. Будь ласка, зв'яжіться з Premera Blue Cross на 800-722-1471 для підтвердження цієї дати.

3. Якщо ви зміните свої думки про обслуговування, ви можете скасувати це на будь-коли. Дата скасування є датою, коли ви подадете документи на скасування. Дата буде визначена Premera Blue Cross.

4. Для більшої інформації, будь ласка, відвідайте premerablue.com або зв'яжіться з нами по телефону 800-722-1471.