Medical Policy
Pharmacogenetic Testing for Pain Management

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- Policy: Commercial
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Policy Number: 724
BCBSA Reference Number: 2.04.131
NCD/LCD: Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

Related Policies
- Cytochrome p450 Genotyping, #256
- Genetic Testing for Mental Health Conditions, #669

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for pain management is considered INVESTIGATIONAL for all indications.

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:

- 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)
- aminobutyric acid (GABA) A receptor gene
- OPRM1 (µ-opioid receptor gene)
- OPRK1 (k-opioid receptor gene)
- UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome p450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2.
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35072)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
<td>No</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
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</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

According to the policy statement above, the following CPT codes are considered investigational for the conditions listed for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Code Description</th>
</tr>
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<tbody>
<tr>
<td>81291</td>
<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
</tbody>
</table>
The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0032U</td>
<td>COMT (catechol-O-methyltransferase) (drug metabolism) gene analysis, c.472G&gt;A (rs4680) variant</td>
</tr>
</tbody>
</table>

**Description**

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, 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 single-nucleotide
variants (SNVs) in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes. 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)</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></td>
</tr>
<tr>
<td>DRD2 (dopamine receptor gene)</td>
<td>1q23.</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 betahydroxylase 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>DRD4 VNTR associated with presence of pain-related disorders (fibromyalgia, TMJ syndrome, migraine)</td>
</tr>
</tbody>
</table>
| COMT (catechol O-methyltransferase gene) | 22q11.21 | Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine | • Val158Met variant associated with alterations in emotional processing and executive function  
• Other variants have been associated with pain sensitivity |
| MTHFR (methylenetetrahydrofolate reductase gene) | 1p36.22 | Converts folic acid to methyfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters | Multiple variants identified, which are associated with a wide variety of clinical disorders |
| GABA A receptor gene | 5q34 | Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter | 1519T>C GABA A 6 gene variant associated with methamphetamine dependence  
A118G variant (rs1799971) associated with reduced pain sensitivity and opioid requirements |
| OPRM1 (μ-opioid receptors gene) | 6q25.2 | G-protein coupled receptor that is primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone | |
| OPRK1 (κ-opioid receptor gene) | 8q11.23 | Binds the natural ligand dynorphin and synthetic ligands | Variants associated with the risk for opioid addiction |
| UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15) | 4q13.2 | Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds | Tamoxifen, diclofenac, naloxone, carbamazepine, and benzodiazepines inhibit UGT2B7 potentially leading to opioid hyperalgesia |
| Cytochrome p450 genes | | | |


CYP2D6 22q13.2  
CYP2C19 10q23.33  
CYP2C9 10q23.33  
CYP3A4 7q22.1  
CYP2B6 19q13.2  
CYP1A2 15q24.1  

CYP2D6 is primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects  
Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics  
Involved in metabolism of up to 60% of clinically used drugs  

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 Response4 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 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 PGTSM (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 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 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>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>5HT2A (serotonin receptor)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>DRD1 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>DRD2 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>DRD4 (dopamine receptor)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>DAT1 (dopamine transporter)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>DA beta-hydroxylase</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase)</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>MTHFR</td>
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<td>GABA</td>
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<td>OPRK1 (κ-opioid receptor)</td>
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<tr>
<td>OPRM1 (μ-opioid receptor)</td>
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<td>VKORC1</td>
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<td>UGT2B15</td>
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<td>CYP genes</td>
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<td>CYP3A5</td>
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<td></td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</tbody>
</table>

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

**Summary**

While multiple pharmacologic therapies are available for the management of acute and chronic pain, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain, and in adverse events. This has prompted interest in better targeting pain therapies based on pharmacogenetic testing of genes relevant to analgesic pharmacokinetics or pharmacodynamics. A number of panel tests, having shown some association with the pharmacokinetics or pharmacodynamics of analgesic medications, have been developed to aid in pain management.

For individuals who have need for pharmacologic pain management who receive pharmacogenetics 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. However, methodologic limitations precluded assessment of the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>1/2018</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>7/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>1/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>7/2015</td>
<td>Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L34499) added.</td>
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</table>

**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**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.


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