Pharmacogenetic Testing for Pain Management

Policy #: 00468
Original Effective Date: 04/20/2015
Current Effective Date: 08/09/2021

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.

Note: Genetic Testing for Diagnosis and Management of Mental Health Conditions is addressed separately in medical policy 00402.

Note: Cytochrome P450 Genotype-Guided Treatment Strategy is addressed separately in medical policy 00169.

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)
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- **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**.

### Background/Overview

**Pain**

According to an analysis of 2016 National Health Interview Survey (NHIS) data, an estimated 20.4% (50 million) U.S. adults experience chronic pain and 8% (19.6 million) have high-impact chronic pain (ie, pain that frequently limits life or work activities). 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, physical and occupational therapy, and complementary/alternative therapies. Nonetheless, the Institute of Medicine 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.

### Pharmacologic Treatment

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 stepwise 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...
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administered through different routes, including oral, intravenous, 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 pharmacologic 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 a significant risk of adverse events, ranging from mild (eg, constipation) to severe (eg, respiratory depression), and a risk of dependence, addiction, and abuse. Limitations in currently available pain management techniques have led to an 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 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. Currently available genetic tests relevant to pain management assess single-nucleotide variants 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 are summarized in Table 1.
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Table 1. Genes Relevant to Pain Management

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Gene Product Function</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>
</tr>
<tr>
<td>5HT2A (serotonin receptor gene)</td>
<td>13q14-21</td>
<td>Another serotonin receptor subtype</td>
</tr>
<tr>
<td>SLC6A4 (serotonin transporter gene)</td>
<td>17q11.2</td>
<td>Clears serotonin metabolites from synaptic spaces in the CNS</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>
</tr>
<tr>
<td>DRD2 (dopamine receptor gene)</td>
<td>11q23.2</td>
<td></td>
</tr>
<tr>
<td>DRD4 (dopamine receptor gene)</td>
<td>11p15.5</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>
</tr>
<tr>
<td>DBH (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>
</tr>
<tr>
<td>COMT (catechol O-methyl-transferase gene)</td>
<td>22q11.21</td>
<td>Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine</td>
</tr>
<tr>
<td>MTHFR (methylenetetrahydrofolate reductase gene)</td>
<td>1p36.22</td>
<td>Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters</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>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Gene</th>
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<th>Gene Product Function</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>OPRK1 (κ-opioid receptor gene)</td>
<td>8q11.23</td>
<td>Binds the natural ligand dynorphin and synthetic ligands</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>
</tr>
<tr>
<td>Cytochrome p450 genes</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>
</tr>
<tr>
<td>CYP2C19</td>
<td>10q23.33</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10q23.33</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>7q22.1</td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>19q13.2</td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>15q24.1</td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; GABA: γ-aminobutyric acid; UDP: uridine diphosphate glycosyltransferase.

**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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Pathway Genomics Pain Medication DNA Insight panel, the Millennium PGT (Pain Management) panel, and You Script Analgesic panel are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments.
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for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

No genetic tests approved by the FDA for pain management were identified.

Of note, in February 2020, the FDA expressed "concerns with firms offering genetic tests making claims about how to use the genetic test results to manage medication treatment that are not supported by recommendations in the FDA-approved drug labeling or other scientific evidence". Due to these concerns, the FDA announced a collaboration between the FDA’s Center for Devices and Radiological Health and Center for Drug Evaluation and Research intended to provide the agency’s view of the state of the current science in pharmacogenetics. This collaborative effort includes a web resource that describes "some of the gene-drug interactions for which the FDA believes there is sufficient scientific evidence to support the described associations between certain genetic variants, or genetic variant-inferred phenotypes, and altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events."

**Rationale/Source**

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. Testing for genetic variants that are relevant to pharmacokinetics or pharmacodynamics of analgesics may assist in selecting and dosing drugs affected by these genetic variants.

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects
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on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach finding a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Practice Guidelines and Position Statements

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 stated that genotyping to determine whether the 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.”

Clinical Pharmacogenomics Implementation Consortium
The Clinical Pharmacogenomics Implementation Consortium (2020) published a guideline for CYP2C9 and NSAIDs, which was developed to provide interpretation of CYP2C9 genotype tests so that the results could potentially guide dosing and/or appropriate NSAID use. The guideline notes that CYP2C9 genotyping information may provide an opportunity "to prescribe NSAIDs for acute or chronic pain conditions at genetically-informed doses to limit long-term drug exposure and secondary adverse events for patients who may be at increased risk.” However, the authors also acknowledge that "while traditional pharmacogenetic studies have provided evidence associating common CYP2C9 genetic variation with NSAID pharmacokinetics, there is sparse prospective evidence showing that genetically-guided NSAID prescribing improves clinical outcomes." In 2014, the Consortium also published therapeutic recommendations for codeine based on CYP2D6 phenotype. These recommendations state that codeine should be avoided in poor metabolizers due to lack of efficacy and in ultra rapid metabolizers due to toxicity potential.

U.S. Preventive Services Task Force Recommendations
Not applicable.
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Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. 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>NCT03498014</td>
<td>Comparison of Standard Opioid Prescription Versus Prescription Guided by Pharmacogenetic Analysis in Patients With Non-cancerous Chronic Pain.</td>
<td>80</td>
<td>Sep 2022</td>
</tr>
<tr>
<td>NCT03772535</td>
<td>Using Pharmacogenetics to Structure Individual Pain Management Protocols for Joint Replacement Patients</td>
<td>50</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>NCT01140724</td>
<td>Predicting Perioperative Opioid Adverse Effects and Personalizing Analgesia in Children</td>
<td>1200</td>
<td>Apr 2021</td>
</tr>
<tr>
<td><strong>Unpublished</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02081872a</td>
<td>Utility of PharmacoGenomics for Reducing Adverse Drug Effects</td>
<td>279,000</td>
<td>Jul 2017 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
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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.
07/03/2019  Medical Policy Committee review
07/18/2019  Medical Policy Implementation Committee approval. No change to coverage.
07/02/2020  Medical Policy Committee review
07/08/2020  Medical Policy Implementation Committee approval. No change to coverage.
07/01/2021  Medical Policy Committee review
07/14/2021  Medical Policy Implementation Committee approval. No change to coverage.
12/20/2021  Coding Update

Next Scheduled Review Date:  07/2022
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Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
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<tbody>
<tr>
<td>CPT</td>
<td>0029U, 0031U, 0032U, 0078U, 81225, 81226, 81227, 81291, 81401, 81479</td>
</tr>
<tr>
<td></td>
<td>Add code effective 01/01/2022: 0290U</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.