**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.

**RELATED PROTOCOLS**

Cytochrome P450 Genotype-Guided Treatment Strategy

Genetic Testing for Diagnosis and Management of Mental Health Conditions

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With need for</td>
<td>• Pharmacogenetic testing to target</td>
<td>• Management without pharmacogenetic</td>
<td>• Symptoms</td>
</tr>
<tr>
<td>pharmacologic pain</td>
<td>therapy</td>
<td>testing</td>
<td>• Health status measures</td>
</tr>
<tr>
<td>management</td>
<td></td>
<td></td>
<td>• Medication use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment–related morbidity</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 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.

**SUMMARY OF EVIDENCE**

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a hybrid implementation-effectiveness, open-label, randomized trial, 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 cytochrome (CYP) P450 2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The randomized trial concluded that preemptive CYP2D6-guided opioid selection is feasible in an elective surgery setting and that this approach may decrease postoperative opioid utilization with similar pain control as compared to usual care; however, these results were only exploratory in nature. 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 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 that the technology results in an improvement in the net health outcome.

**POLICY**

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

**POLICY GUIDELINES**

This policy does not address testing limited to cytochrome p450 genotyping, which is addressed in the Cytochrome P450 Genotype-Guided Treatment Strategy Protocol. This protocol 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 that implicated in pain management include the following (see also Table 1):

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol-O-methyltransferase gene)
- MTHFR (methylene tetrahydrofolate reductase gene)
- γ-aminobutyric acid (GABA) A receptor gene
- OPRM1 (µ-opioid receptor gene)
- OPRK1 (K-opioid receptor gene)
- UGT2B15 (uridine diphosphate glycosyltransferase two family, member 15)
- Cytochrome P450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

**GENETICS NOMENCLATURE UPDATE**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical pro-
Pharmacogenetic Testing for Pain Management

Protocol review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BACKGROUND

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 (i.e., 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 (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 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 (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. Various opioids are available in short- and long-acting preparations and 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, non-systemic 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 (e.g., constipation) to severe (e.g., 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 (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 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>
</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>DRD3 (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 hydroxylation of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons</td>
</tr>
<tr>
<td>COMT (catechol O-methyltransferase gene)</td>
<td>22q11.21</td>
<td>Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine</td>
</tr>
</tbody>
</table>
### Gene | Locus | Gene Product Function
--- | --- | ---
*MTHFR* (methylene tetrahydrofolate reductase gene) | 1p36.22 | Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters
*GABA A receptor gene* | 5q34 | Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter
*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
*UGT2B15* (uridine diphosphate-glucuronosyltransferase 2 family, member 15) | 4q13.2 | Member of UDP family involved in the glucosylation and elimination of potentially toxic compounds

**Cytochrome p450 genes**
- CYP2D6
- CYP2C19
- CYP2C9
- CYP3A4
- CYP2B6
- CYP1A2

Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics

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### REGULATORY STATUS

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 (CLIA). The OmeCare OmePainMeds panel, the Millennium PGT (Pain Management) panel, and YouScript Analgesic panel are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

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”.3 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 resource4 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.”

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