Protocol

Pharmacogenetic Testing for Pain Management

(204131)

Medical Benefit		**Effective Date**: 07/01/15	**Next Review Date**: 03/19
Preauthorization	Yes	**Review Dates**: 03/15, 03/16, 03/17, 03/18	

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.

Populations	Interventions	Comparators	Outcomes
Individuals: • With need for pharmacologic pain management	Interventions of interest are: • Pharmacogenetic testing to target therapy	Comparators of interest are: • Management without pharmacogenetic testing	Relevant outcomes include: • Test accuracy • Test validity • Other test performance measures • Morbid events • Health status measures • Medication use

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. 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.

Summary of Evidence

For individuals who have need for pharmacologic pain management who receive pharmacogenetic 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

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 Genotyping Protocol. 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 polymorphisms (SNPs) or (less commonly) individual SNP testing. SNPs that have been implicated in pain management include the following (see also Table 1):

- 5HT2C (serotonin receptor gene)
- 5HT2A (serotonin receptor gene)
- SLC6A4 (serotonin transporter gene)
- DRD1 (dopamine receptor gene)
- DRD2 (dopamine receptor gene)
- DRD4 (dopamine receptor gene)
- DAT1 or SLC6A3 (dopamine transporter gene)
- DBH (dopamine beta-hydroxylase gene)
- COMT (catechol-O-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 two family, member 15)
- Cytochrome P450 genes: CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP2B6, CYP1A2

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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 evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background

Pain is a universal human experience and an important contributor to 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.[1] Chronic pain may be related to cancer, or be what is termed *chronic non-cancer 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 (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 stepped approach to pain management, beginning with nonopioid analgesia and proceeding to a weak opioid (e.g., codeine), with or without an adjuvant for persisting pain, and subsequently to a strong opioid (e.g., fentanyl, morphine), with or without an adjuvant for persisting or worsening pain. 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 intra-operative 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 (e.g., constipation) to severe (e.g., respiratory depression), and are associated with risk of dependence, addiction, and abuse. Limitations in currently available pain management techniques have led to interest in the use of pharmacogenetics to improve the targeting of therapies and prediction and avoidance of 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

Gene	Locus	Gene Product Function	Potential Role in Pain Management
5HT2C (serotonin receptor gene)	Xq23	one of six subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine	
5HT2A (serotonin receptor gene)	13q14-21	Another serotonin receptor subtype	Variants (i.e., 102T/C) associated with variation in pain threshold
SLC6A4 (serotonin transporter gene)	17q11.2	Clears serotonin metabolites from synaptic spaces in the CNS	
DRD1 (dopamine receptor gene)	5q35.2	G-protein-coupled receptors that have dopamine as their ligands	

Gene	Locus	Gene Product Function	Potential Role in Pain Management
DRD2 (dopamine receptor gene)	11q23.2		
DRD4 (dopamine receptor gene)	11p15.5		DRD4 VNTR associated with presence of pain-related disorders (fibromyalgia, TMJ syndrome, migraine)
DAT1 or SLC6A3 (dopamine transporter gene)	5p15.33	Mediates dopamine reuptake from synaptic spaces in the CNS	
DBH (dopamine beta-hydroxylase gene)	9q34.2	Catalyzes the hydroxylase of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons	
COMT (catechol O-methyl-transferase 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 methylfolate, 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
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	A118G variant (rs1799971) associated with reduced pain sensitivity and opioid requirements
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 glycosyltrans-ferase 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	Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics	CYP2D6 is primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects
CYP2C19	10q23.33		
CYP2C9	10q23.33		
CYP3A4	7q22.1		Involved in metabolism of up to 60% of clinically used drugs
CYP2B6	19q13.2		
CYP1A2	15q24.1		

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 one 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."[2] 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.[3] 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 three other genes. Results are provided with a report that stratifies patients' pain sensitivity based on *COMT* haplotype.[3] In addition, Proove Biosciences offers panels designed to predict good and poor responders to opioid therapies and nonopioid pain therapies–the Proove® Opioid Response[4] panel and the Proove® Non Opioid Response,[5] 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.[6] The testing method is not specified on the company's website.
- Millennium PGT℠ (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.[7] 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.[8]
- 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 protocol and are discussed in the Cytochrome P450 Genotyping Protocol.

In addition to the available panel tests, several labs offer genetic testing for individual genes that are included in some of the panels, including the *MTFHR*, *CYP450*, and *OPRM1* genes (see Table 2).

Table 2: Genes Included in Commercially Available Genetic Panels for Pain Management

Gene	Proove Opioid Risk (Proove Biosciences)	Proove Pain Perception (Proove Biosciences)	GeneSightRx Analgesic (AssureRx Health)	Pain Medication DNA Insight (Pathway Genomics)	Millennium PGT (Millennium Health)	YouScript Analgesic (Genelex)
SLC6A4 (5-HTT; serotonin transporter)		X				
5HT2A (serotonin receptor)	X	X				
DRD1 (dopamine receptor)	X					
DRD2 (dopamine receptor)	X					
DRD4 (dopamine receptor)	X					
DAT1 (dopamine transporter)	X					
DA beta-hydroxylase	X	X				
COMT (catechol O-methyltransferase)	X	X			X	X
MTHFR	X	X		X	X	
GABA	X	X				
OPRK1 (κ-opioid receptor)	X					
OPRM1 (μ-opioid receptor)	X	X	X	X	X	X
VKORC1					X	
UGT2B15					X	
CYP genes						
CYP2D6			X	X	X	X
CYP2C19			X	X	X	
CYP3A4			X		X	X
CYP1A2			X			
CYP2C9			X	X	X	X
CYP2B6				X	X	X
CYP3A5					X	X

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

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 Amendments (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.

Related Protocols

Cytochrome P450 Genotyping

Genetic Testing for Mental Health Conditions

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

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

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

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