2.04.131	Pharmacogenetic Testing for Pain Management		
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Section:	2.0 Medicine	**Page:**	Page 1 of 20

Policy Statement

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not address testing limited to cytochrome p450 genotyping, which is addressed in Blue Shield of California Medical Policy: Cytochrome P450 Genotype-Guided Treatment Strategy. 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)
- *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*.

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 evidence 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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence

Previous	Updated	Definition
	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

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.

Coding

The following tests have been codified in CPT. There is specific CPT coding for this testing:

- **81225**: CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
- **81226**: CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
- **81227**: CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
- **81291**: MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)

CPT 81401 has been revised and no longer includes CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4), hence is no longer applicable to this policy.

Effective January 1, 2022, there is a new code that represents MindX Blood Test™ - Pain, MindX Sciences™ Laboratory, MindX Sciences™ Inc. Per the manufacturer, this is a MAAA test that tracks pain intensity and predicts short and long-term risk for clinical worsening and clinical visits due to pain. It matches patients with possible medications and may be repeated to monitor response to treatment. It uses an algorithm reported as predictive risk score. This test may have been billed with 81599.

- **0290U**: Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score

There is no specific CPT code for pain management testing panels. If there are CPT codes for the component tests in the panel and there is no algorithmic analysis used, the individual CPT codes may be reported. The unlisted molecular pathology code 81479 would be reported once for the balance of the panel and for any variants listed in this policy without specific codes.

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.

Related Policies

- Cytochrome P450 Genotype-Guided Treatment Strategy
- Genetic Testing for Diagnosis and Management of Mental Health Conditions

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 resource[4] 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

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).[1,] 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.[2,] 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, 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 (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

Gene	Locus	Gene Product Function
***5HT2C* (serotonin receptor gene)**	Xq23	1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine
***5HT2A* (serotonin receptor gene)**	13q14-21	Another serotonin receptor subtype
***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
***DRD2* (dopamine receptor gene)**	11q23.2	
***DRD4* (dopamine receptor gene)**	11p15.5	
***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
***MTHFR* (methylenetetrahydrofolate 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 glycosyltransferase 2 family, member 15)**	4q13.2	Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds
Cytochrome p450 genes		Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics
CYP2D6	22q13.2	
CYP2C19	10q23.33	
CYP2C9	10q23.33	
CYP3A4	7q22.1	
CYP2B6	19q13.2	
CYP1A2	15q24.1	

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

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be

relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Testing-Guided Treatment for Managing Acute and Chronic Pain

Clinical Context and Therapy Purpose

The purpose of pharmacogenetic testing-guided treatment for the management of acute and chronic pain is to:

- Select appropriate pain medications or avoid the use of inappropriate pain medications, including:
  - To identify individuals likely or unlikely to respond to a specific medication.
  - To identify individuals at high-risk of adverse drug reactions.
  - To identify individuals at high-risk of opioid addiction or abuse.
- Optimize the dose selection or frequency by:
  - Identifying individuals who are likely to require higher or lower doses of a drug.

The question addressed in this evidence review is: Does a pharmacogenetic testing-guided treatment strategy for managing acute and chronic pain improve the net health outcome in individuals with acute and chronic pain?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with chronic and acute pain, including conditions such as cancer, migraine, low back pain, and fibromyalgia.

Interventions

Testing for individual genes is available for most, or all, of the genes listed in Table 2, as well as for a wider range of genes. Because of a large number of potential genes, panel testing is available from a number of genetic companies. These panels include a variable number of genes that broadly test potential response to relevant medication classes such as opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors, and tricyclic antidepressants. Several test labs market panel 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.

OmePainMeds (OmeCare) is a panel test that provides analysis and recommendations regarding how a patient's body is likely to respond to 13 pain relief medications. The results report includes information about the patient's genetic variables and detailed breakdowns of

each core aspect of the patient's genetic markers with recommendations. The product generally informs patients about how a patient's body metabolizes a pain medication, relative risks of taking the drug, and appropriate dosages.

Millennium PGT℠ (Pain Management) (Millennium Health) 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.

Genelex offers several pharmacogenomic panels, one of which (the YouScript® Analgesic Panel) focuses on genes relevant to pain management.[5]

AltheaDx 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, Kashi Labs, Inagene Diagnostics, Quest Diagnostics, ARUP Laboratories, and AlBioTech, which markets the PersonaGene Genetic Panel, offer panels of cytochrome P450 (CYP) genes. Panels that are restricted to *CYP* genes are discussed in Blue Shield of California Medical Policy: Cytochrome P450 Genotype-Guided Treatment Strategy.

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*, *CYP*, and *OPRM1* genes (Table 2).

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

Gene	Potential Role in Pain Management
COMT	Val158Met variant associated with alterations in emotional processing and executive function. Other variants have been associated with pain sensitivity
MTHFR	Multiple variants identified, which are associated with a wide variety of clinical disorders
GABA	1519T>C GABA A 6 gene variant associated with methamphetamine dependence
OPRK1 (κ-opioid receptor)	Variants associated with the risk for opioid addiction
OPRM1 (μ-opioid receptor)	*A118G* variant (rs1799971) associated with reduced pain sensitivity and opioid requirements
VKORC1	
UGT2B15	Tamoxifen, diclofenac, naloxone, carbamazepine, and benzodiazepines inhibit UGT2B7 potentially leading to opioid hyperalgesia
***CYP* genes:**	Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics
CYP2D6	*CYP2D6* is the primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects
CYP2C19	
CYP3A4	Involved in the metabolism of up to 60% of clinically used drugs
CYP1A2	
CYP2C9	
CYP2B6	
CYP3A5	

CYP: cytochrome; GABA: g-aminobutyric acid; UGT: uridine diphosphate glycosyltransferase.

Comparators

The following practice is currently being used to treat chronic and acute pain: standard pain management without genetic testing. For chronic pain management, a multimodal, multidisciplinary approach that is individualized to the patient is recommended.[6] A multimodal approach to pain management consists of using treatments (i.e., nonpharmacologic and pharmacologic) from 1 or more clinical disciplines incorporated into an overall treatment plan. This allows for different avenues to address the pain condition, often enabling a synergistic

approach that impacts various aspects of pain, including functionality. The efficacy of such a coordinated, integrated approach has been documented to reduce pain severity, improve mood and overall quality of life, and increase function. Patients with pain are likely to be managed by a wide variety of specialties such as chiropractors, primary care physicians, physiatrists (rehabilitation physicians), neurologists, rheumatologists, orthopedic surgeons, oncologists, pain management specialists, physical therapists, and acupuncturists. Most patients are likely to be tested in an outpatient setting.

Outcomes

Specific outcomes of interest for patients with acute or chronic pain are listed in Table 3. The potential beneficial outcomes of primary interest would be improvements in pain, functioning, and quality of life. The potential harmful outcomes are those resulting from a false test result. False-positive or -negative test results can lead to the initiation of unnecessary treatment and associated adverse events or under-treatment.

Table 3. Outcomes of Interest for Individuals with Chronic or Acute Pain

Outcomes	Details
Morbid events	Opioid addiction, adverse events
Health status measures	Pain relief, functional status
Medication use	The number of unsuccessful medication trials and medications needed, including the dose of medication and dose frequency

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends that chronic pain trials should consider assessing outcomes representing 6 core domains: pain, physical functioning, emotional functioning, participant ratings of improvement and satisfaction with treatment, symptoms and adverse events, and participant disposition.[7] Table 4 summarizes provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures per IMMPACT.[8]

Table 4. Benchmarks for Interpreting Changes in Chronic Pain Outcome Measures.

Outcome Domain and Measure	Type of Improvement	Change
Pain intensity	Minimally important	10 to 20% decrease
• **0 to 10 numeric rating scale**	Moderately important	≥30% decrease
	Substantial	≥50% decrease
Physical functioning	Clinically important	≥0.6 point decrease
• **Multidimensional Pain Inventory Interference Scale**	Minimally important	1 point decrease
• **Brief Pain Inventory Interference Scale**		
Emotional functioning	Clinically important	≥5 point decrease
• **Beck Depression Inventory**	Clinically important	≥10 to 15 point decrease
• **Profile of Mood States**	Clinically important	≥2 to 12 point change
o **Total Mood Disturbance**		
o **Specific Subscales**		
Global Rating of Improvement	Minimally important	Minimally improved
• **Patient Global Impression of Change**	Moderately important	Much improved
	Substantial	Very much improved

Regarding optimal timing of outcome assessment, this varies with pain setting.[9] Per IMMPACT, recommended assessment timing includes at 3, 6, and 12 months in patients with chronic low back pain, 3 to 4 months after rash onset in postherpetic neuralgia, 3 and 6 months in patients with painful chemotherapy-induced peripheral neuropathy, and at various time points in the chronic post-surgical pain setting (i.e., 24 to 48 hours after surgery; 3, 6, and 12 months; or surgery-specific times based on the natural history of acute to chronic pain transition).

Study Selection Criteria

Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with or without the test. Because these are intervention studies, the preferred evidence is from RCTs.

- We sought RCTs that reported the outcomes of pharmacogenetics testing to diagnose, assess the risk of developing, or to manage pain.
- We sought evidence on outcomes, with emphasis on efficacy outcomes, as the main purpose of genetic testing in pain conditions is to achieve clinically meaningful improvement compared with standard of care.
- We also included studies that reported only on adverse events, although for medications where adverse events tend to be mild, efficacy outcomes are of greater importance.
- The specific patient indications, interventions, comparators, and outcome measures of interest for each indication are described in the clinical context section.

Review of Evidence

Randomized Study

Thomas et al (2021) completed a hybrid implementation-effectiveness randomized trial of CYP2D6-guided postoperative pain management versus usual care in 260 adults undergoing joint arthroplasty.[10] In this open-label trial, the authors evaluated the feasibility of clinically implementing CYP2D6-guided post-surgical pain management via the collection of feasibility metrics and pain control through measures of opioid consumption and pain intensity. Table 5 summarizes the key characteristics of the trial. In the genotype-guided arm, 20% had a high-risk phenotype (intermediate, poor, or ultrarapid metabolizer). Of these, 72% were administered an alternative opioid versus 0% of usual care participants (p<.001). Effectiveness outcomes were collected 2 weeks postsurgery and results of the exploratory analysis revealed reduced opioid consumption and similar pain intensity between the 2 groups. Table 6 summarizes the key clinical outcomes of the study.

Table 5. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Thomas et al (2021)[10]	US	2 orthopedic clinics at the University of Florida	2018-2019	Adults scheduled for primary unilateral total hip or knee arthroplasty (N=260)	CYP2D6 genotype-guided arm (n=173)	Usual care (n=87)

RCT: randomized controlled trial.

Table 6. Summary of Key RCT Results

Study	Opioid consumption	Composite pain intensity
Thomas et al (2021)[10]	N=194	N=211
Genotype-guided	200 mg MME (104 to 280 mg) [median (IQR range)]	mean ± SD: 2.6 ± 0.8
Usual care	230 mg MME (133 to 350 mg) [median (IQR range)]	mean ± SD: 2.5 ± 0.7
p value	.047	.638

IQR; interquartile range; MME: morphine milligram equivalents; SD: standard deviation.

Tables 7 and 8 display notable limitations identified in each study. Although Thomas et al (2021) reported a reduction in opioid consumption and similar pain control between the genotype-guided and usual care groups at 2 weeks postsurgical intervention, the evaluation of the clinical outcomes was exploratory in nature.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Thomas et al (2021)[10.]	4. CYP2D6 phenotype distributions were unequal between the groups; usual care group had more intermediate and poor metabolizers			1. Assessment of MME was not the focus of the a priori power calculation; clinical outcomes were exploratory	1. Clinical outcomes evaluated at 2 weeks post-surgery only

CYP: cytochrome; MME: morphine milligram equivalents.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Thomas et al (2021)[10.]		1. Open-label trial design; no blinding		1. Reliance on subject-reported opioid consumption restricts MME analysis to those who successfully completed the 2-week survey		

MME: morphine milligram equivalents.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Studies

One prospective cohort study using historical controls and 1 prospective non-randomized pragmatic trial have assessed genotype-guided management of pain; these studies are summarized in Tables 9 and 10 and discussed next.

Senagore et al (2017) reported on the results of a prospective cohort study of 63 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery.[11] The authors compared the findings with a historical cohort of 47 patients who underwent similar surgeries but were managed with a standard enhanced recovery protocol. Results showed that the overall benefit of analgesia score was statistically significantly lower in patients in whom the analgesia protocol was initiated based on results of genotype testing versus the historical control on postoperative days 1 and day 5 (all p<.05). The need for narcotic-equivalent analgesics was also statistically significantly lower in the genotype-tested group versus historical controls.

Smith et al (2019) reported a prospective non-randomized pragmatic trial of 375 patients who either underwent a CYP2D6-guided approach to opioid prescribing for pain control at 4 primary care clinics or standard of care pain management at 3 clinics without assessment of CYP2D6.[12] Based on genotyping alone, 10% of the CYP2D6-guided group were considered intermediate or poor metabolizers (IM/PM). The percentage of patients who were considered IM or PM increased to 35% after drug interactions were considered. In the CYP2D6-guided IM/PM group, there was a more frequent change to a nonopioid therapy. The reduction in pain was statistically significant, though modest, compared to the standard of care group (Table 10).

Table 9. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-Up
Senagore et al (2017)[11]	Prospective cohort	U.S.	2015-2016	Patients undergoing open or laparoscopic colorectal and major ventral hernia surgery (N=110)	Pharmacogenetic testing-guided[a] standard enhanced recovery protocol (n=63)	A historical group managed with standard enhanced recovery protocol undergoing similar operational procedures (n=47)	5 d
Smith et al (2019)[12]	Prospective, non-randomized, pragmatic trial	U.S.	2015-2017	Patients from 7 primary care clinics who had uncontrolled pain or for whom a change in medication was being considered; mean pain was 6.55 out of 10 (N=375)	CYP2D6-guided care (n=239)	Treatment based on the standard of care (n=136)	3 mo

CYP: cytochrome.
[a] NeurolDgenetix pain panel analyzes 9 genes, including *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, ABCB1, COMT,* and *OPRM1*.

Table 10. Summary of Key Nonrandomized Trials

Study			
Senagore et al (2017)[11]	**OBAS[a]**	**OBAS Pain Subscore**	**Postoperative Opioid Use, mg[b]**
n	97	96	96
Pharmacogenetic testing-guided standard enhanced recovery protocol group	Day 1: 3.8 Day 5: 3.0	Day 1: 1.8 Day 5: 1.2	104.5 (122.1)
A historical control group who underwent similar operations managed with a standard enhanced recovery protocol	Day 1: 5.4 Day 5: 4.5	Day 1: 2.3 Day 5: 2.0	222.1 (221.1)
p	.01	.04	.018
Smith et al (2019)[12]	**Change in composite pain intensity [mean (SEM)] from baseline[c]**	**Change in composite pain intensity [mean (SEM)] from baseline[c]**	
	IM/PM prescribed tramadol or codeine	IM/PM prescribed tramadol, codeine, or hydrocodone	
CYP2D6-guided opioid prescribing approach	-1.01 (1.59); (n=29)	-0.84 (1.51); (n=51)	
Standard of care	-0.40 (1.20); (n=16)	-0.12 (1.32); (n=19)	
p	.016	.019	

IM: intermediate metabolizer; PM; poor metabolizer; OBAS: Overall Benefit of Analgesia Score; SEM: standard error of the mean.
[a] The primary outcome measure was OBAS, which assesses the combined impact on analgesia, patient satisfaction, and the impact of drug-associated side effects. The lower the score, the better is overall analgesia.
[b] Measured in narcotic equivalent analgesics.
[c] Only includes participants with complete follow-up.

The purpose of the limitations tables (Tables 11 and 12) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. Although Senagore reported the 2 groups were similar in terms of patients' characteristics, details of disease status and other known prognostic factors were lacking in the published paper. The authors did not report how the historical cohort was selected nor did they describe efforts to control for known confounders using statistical adjustments. These methodologic limitations do not permit conclusions from this study. In the non-randomized study by Smith et al (2019), there were different baseline characteristics between the 2 groups, and possible differences in pain management between the clinics were not controlled. Most importantly for the present evidence review, the effect of gene variants was not distinguished from the drug inhibitors.

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Senagore et al (2017)[11]		1. Not clearly defined. It is unclear if the intensity of the protocols was similar	1. Not clearly defined	5. Clinically significant difference was not prespecified 6. Clinically significant difference not supported	1. Insufficient duration for benefit 2. Insufficient duration for harms

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
		across the 2 groups			
Smith et al (2019)[12]			1. Not clearly defined	4. Medications were assessed by the electronic health record and did not include possible changes in over-the-counter medications 5. Clinically significant difference was not prespecified	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms..

Table 12. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Senagore et al (2017)[11]	1. Participants not randomly allocated 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician		1. High loss to follow-up or missing data; 13 (20%) of 63 patients excluded from analysis	1. Power calculations not reported 2. Power not calculated for primary outcome 3. Power not based on a clinically important difference	3. Confidence intervals and/or p values not reported
Smith et al (2019)[12]	1. Participants not randomly allocated 4. Inadequate control for selection bias	1. Not blinded to treatment assignment 2. Not blinded outcome assessment 3. Outcome assessed by treating physician				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physicians.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective

publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important differences.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

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 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 CYP2D6-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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic noncancer pain.[13] 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 cytochrome P450 (CYP) 2C9 and nonsteroidal anti-inflammatory drugs (NSAIDs), which was developed to provide interpretation of CYP2C9 genotype tests so that the results could potentially guide dosing and/or appropriate NSAID use.[14] 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 2021, the Consortium published an updated guideline for CYP2D6, μ-opioid receptor gene 1 (OPRM1), and catechol *O*-methyl-transferase (COMT) genotypes and select opioid therapy.[15] These recommendations state that codeine and tramadol should be avoided in CYP2D6 poor metabolizers due to diminished efficacy and in ultra-rapid metabolizers due to toxicity potential. In both situations, if opioid use is warranted, a non-codeine opioid should be considered. Regarding hydrocodone, there is insufficient evidence and confidence to provide a recommendation to guide clinical practice for CYP2D6 ultra-rapid metabolizers. For CYP2D6 poor metabolizers, the use of hydrocodone label age- or weight-specific dosing is recommended; however, if no response is observed and opioid use is warranted, a non-codeine and non-tramadol opioid option is warranted. There is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone or methadone based on CYP2D6 genotype. Additionally, there are no therapeutic recommendations for dosing opioids based on either OPRM1 or COMT genotype.

U.S. Preventive Services Task Force Recommendations
Not applicable.

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 13.

Table 13. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04685304	Pharmacogenomics Applied to Chronic Pain Treatment in Primary Care	400	Dec 2022
NCT04445792	A Depression and Opioid Pragmatic Trial in Pharmacogenetics	4509	Feb 2023
NCT03498014	Comparison of Standard Opioid Prescription Versus Prescription Guided by Pharmacogenetic Analysis in Patients With Non-cancerous Chronic Pain	80	Dec 2023
NCT03772535	Using Pharmacogenetics to Structure Individual Pain Management Protocols for Joint Replacement Patients	50	Dec 202 1
NCT01140724	Predicting Perioperative Opioid Adverse Effects and Personalizing Analgesia in Children	1200	Aug 2023
Unpublished			
NCT02081872[a]	Utility of PharmacoGenomics for Reducing Adverse Drug Effects	279,000	Jul 2017 (unknown)

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

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15. Crews KR, Monte AA, Huddart R, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6, OPRM1, and COMT Genotypes and Select Opioid Therapy. Clin Pharmacol Ther. Oct 2021; 110(4): 888-896. PMID 33387367
16. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.131 (November 2021).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	0033U	HTR2A (5-hydroxytryptamine receptor 2A), HTR2C (5-hydroxytryptamine receptor 2C) (e.g., citalopram metabolism) gene analysis, common variants (i.e., HTR2A rs7997012 [c.614-2211T>C], HTR2C rs3813929 [c.-759C>T] and rs1414334 [c.551-3008C>G])
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/multiplication) (List separately in addition to code for primary procedure)
	0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (i.e., 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
	0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score ***(Code effective 1/1/2022)***
	81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
	81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)

Type	Code	Description
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
	81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, common variants (e.g., 677T, 1298C)
	81401	Molecular Pathology Procedure Level 2
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
04/30/2015	BCBSA Medical Policy adoption
09/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
05/01/2018	Coding update
07/01/2018	Policy revision without position change
10/01/2018	Coding update
01/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Annual review. No change to policy statement. Literature review updated. Coding update
01/01/2022	Annual review. No change to policy statement. Policy guidelines and literature updated.
03/01/2022	Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Pharmacogenetic Testing for Pain Management 2.04.131 **Policy Statement:** Genetic testing for pain management is considered **investigational** for all indications (see Policy Guidelines section).	**Pharmacogenetic Testing for Pain Management 2.04.131** **Policy Statement:** Genetic testing for pain management is considered **investigational** for all indications (see Policy Guidelines section).