2.04.131	Pharmacogenetic Testing for Pain Management		
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Section:	2.0 Medicine	**Page:**	Page 1 of 26

Policy Statement

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

II. Genetic testing for acute pain management to assess the risk of developing opioid use disorder 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. 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*.

A commercially available genetic test (Averted™, AutoGenomics, Inc.) to assess the risk of developing opioid use disorder consists of a panel that detects single nucleotide polymorphisms (SNPs) involved in the brain reward pathway. SNPs include the following (see also Table 2):

- *5-HTR2A C>T* (serotonin 2A receptor)
- *COMT G>A* (catechol-o-methyltransferase)
- *DRD1 A>G* (dopamine D1 receptor)
- *DRD2 G>A* (dopamine D2 receptor)
- *DRD4 T>C* (dopamine D4 receptor)

- *DAT1 A>G* (dopamine transporter)
- *DBH C>T* (dopamine beta hydroxylase)
- *MTHFR C>T* (methylene tetrahydrofolate reductase)
- *OPRKI G>T* (kappa Opioid Receptor)
- *GABA C>A* (gamma-Aminobutyric Acid [GABA])
- *OPRM1 A>G* (mu Opioid Receptor)
- *MUOR G>A* (mu Opioid Receptor)
- *GAL T>C* (galanin)
- *DOR G>A* (delta Opioid Receptor)
- *ABCB1 C>T* (ATP binding cassette transporter I [ABCB1])

Coding
See the Codes table for details.

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 randomized trial, a single-blind randomized trial, a prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain, and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The hybrid 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 compared to usual care; however, these results were only exploratory in nature. The single-blind randomized trial similarly concluded that postoperative opioid prescription guided by genetic results may improve pain control and reduce opioid consumption compared to usual care. 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 and found 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.

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to assess the risk of developing opioid use disorder (OUD), the evidence includes nonrandomized studies. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. One nonrandomized study has demonstrated the clinical validity of a pharmacogenetic test to assess the risk of developing OUD. From this study the classifier demonstrated a sensitivity of 82.5% (95% CI: 76.1% to 87.8%) and specificity of 79.9% (95% CI: 73.7% to 85.2%), with no significant differences in performance based on gender, age, follow-up length, race, or ethnicity. The positive likelihood ratio was 3.98 (95% CI: 3.26 to 6.87) and the negative likelihood

ratio was 0.22 (95% CI: 0.17 to 0.33). However, the study had several limitations, including recall bias due to self-reported opioid use, selection bias due to the study's enrichment strategy, and a lack of diversity. One case-control study was identified that investigated the clinical utility of this technology. An ensemble machine learning model was run using the 15 genetic variants in the FDA-approved algorithm. The model correctly classified 52.83% (95% CI: 52.07% to 53.59%) of individuals and had a sensitivity of 50.72% and a specificity of 54.95%. While the sample was ancestrally diverse, the study population was mostly male and, compared to the general population, was older and had higher rates of OUD and pain. Also electronic health record data was used, which is susceptible to bias. Prospective studies investigating the clinical utility are needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Not applicable.

Related Policies

- Genetic Testing for Diagnosis and Management of Mental Health Conditions

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services 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 law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

SB 496

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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."

In December 2023, AvertD™ (AutoGenomics, Inc.) received approval from the FDA for their premarket approval application (PMA) (PMA Number: P230032; Product Code: QZH). The device "is a prescription, qualitative genotyping test used to detect and identify 15 genetic polymorphisms in genomic DNA isolated from buccal samples collected from individuals 18 years of age and older. The test may be used as part of a clinical evaluation and risk assessment to identify patients who may be at elevated risk for developing opioid use disorder (OUD). The test is indicated for use only in patients prior to receiving a first prescription of oral opioids for 4-30 days for acute pain, such as in patients scheduled to undergo a planned surgical procedure and who consent to having the test performed." Of note, in October 2022, the FDA voted strongly against AvertD in an Advisory Committee Meeting.[5,] The Advisory Committee panel described mitigation strategies to address the risks of the device, including:

- "Presentation of the device results along a continuum rather than as a binary result.
- Strong and plain language that makes clear the test is not intended to be used alone but instead with other tools to evaluate risk.
- Clear labeling that opioid sparing techniques should be used in all patients regardless of the results of the test.
- Additional studies to better understand test performance in subpopulations that were not included in the clinical study population."

Rationale

Background

Pain

According to an analysis of 2016 National Health Interview Survey (NHIS) data, an estimated 20.4% (50 million) of 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	Locusssd	Gene Product Function
***5HT2C* (serotonin receptor gene)**	Xq23	1 of 6 subtypes of serotonin receptor, which participates 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

Gene	Locusssd	Gene Product Function
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; CYP: cytochrome P450;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 to 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 following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals 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 one 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.[6,]

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 AIBioTech, which markets the PersonaGene Genetic Panel, offer panels of cytochrome P450 (CYP) genes. Panels that are restricted to *CYP* genes are discussed in evidence review 2.04.38 (Cytochrome P450 testing).

In addition to the available panel tests, several labs offer genetic testing for individual genes that are included in some of the panels, including the *MTFHR*, *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.

Gene	Potential Role in Pain Management
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 P450; 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 individual is recommended.[7,] A multimodal approach to pain management consists of using treatments (ie, nonpharmacologic and pharmacologic) from one 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.

Outcomes

Specific outcomes of interest for individuals 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.[8,] Table 4 summarizes provisional benchmarks for interpreting changes in chronic pain clinical trial outcome measures per IMMPACT.[9,]

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

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

Domain and Measure	Type of Improvement	Change
Physical functioning • **Multidimensional Pain Inventory Interference Scale** • **Brief Pain Inventory Interference Scale**	Clinically important Minimally important	≥0.6 point decrease1 point decrease
Emotional functioning • **Beck Depression Inventory** • **Profile of Mood States** ○ **Total Mood Disturbance** ○ **Specific Subscales**	Clinically important Clinically important Clinically important	≥5 point decrease ≥10 to 15 point decrease ≥2 to 12 point change
Global Rating of Improvement • **Patient Global Impression of Change**	Minimally important Moderately important Substantial	Minimally improved Much improved Very much improved

Regarding optimal timing of outcome assessment, this varies with pain setting.[10,] 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 (ie, 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 Studies

Hamilton et al (2022) conducted a randomized trial of genotype-guided postoperative pain control compared to usual care in 107 patients who underwent hip or knee arthroplasty.[11,] All patients underwent preoperative genetic testing using a 16-gene panel, then patients were randomized in a single-blind manner to genotype-guided opioid therapy or usual care (oxycodone, tramadol, celecoxib, acetaminophen). Self-reported pain scores and opioid usage were recorded for 10 days after surgery. Table 5 summarizes the key characteristics of the trial. The gene panel showed that 22.4% of patients had relevant genetic variations. Among the patients with genetic variants, patients in the genotype-guided group consumed 86.7 mg morphine equivalents during the 10-day study period versus 162.6 mg morphine equivalents (p=.126). Ten-day average pain levels in both groups were 3.1 versus 4.2, respectively (p=.026). Table 6 summarizes the key clinical outcomes of the 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.[12,] 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 Randomized Controlled Trial Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Hamilton et al (2022)[11],	US	1 orthopedic clinic	NR	Adults scheduled for primary hip or knee arthroplasty (N=107)	Genotype-guided arm (n=61)	Usual care (n=46)
Thomas et al (2021)[12],	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)

CYP: cytochrome P450 NR: not reported.

Table 6. Summary of Key Randomized Controlled Trial Results

Study	Opioid consumption	Composite pain intensity
Hamilton et al (2022)[11],	N=107	N=107
Genotype-guided (with genetic variants)	86.68 mg MME (0 to 264) [10-day mean (range)]	10-day mean: 3.08
Genotype-guided (no genetic variants)	106.07 mg MME (0 to 439.5) [10-day mean (range)]	10-day mean: 4.12
Usual care (with genetic variants)	162.58 mg MME (0 to 741) [10-day mean (range)]	10-day mean: 4.24
Usual care (no genetic variants)	124.44 mg MME (0 to 327.5) [10-day mean (range)]	10-day mean: 3.93
p value	.126 (patients with genetic variants)	.0257 (patients with genetic variants)
Thomas et al (2021)[12],	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]
Hamilton et al (2022)[11],		3. Not all patients chose to use opioids	3. Not all patients chose to use opioids	5. Unclear what difference in pain levels between groups was considered clinically significant	
Thomas et al (2021)[12],	4. CYP2D6 phenotype distributions were unequal between the groups; usual			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

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
	care group had more intermediate and poor metabolizers				

CYP: cytochrome P450; 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]
Hamilton et al (2022)[11],		2. Only patients were blinded				
Thomas et al (2021)[12],		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.[13,] 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.[14,] 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)[13,]	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)[14,]	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 P450.
[a] NeuroIDgenetix 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)[13,]	**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)

Study			
p	.01	.04	.018
Smith et al (2019)[14,]	**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 that the 2 groups were similar in terms of patient 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)[13,]		1. Not clearly defined. It is unclear if the intensity of the protocols was similar across the 2 groups	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
Smith et al (2019)[14,]			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)[13],	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)[14],	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.

Section Summary: Testing-Guided Treatment for Managing Acute and Chronic Pain

Both randomized and nonrandomized studies have demonstrated that opioid prescribing guided by genetic results may improve pain control and reduce opioid consumption compared to usual care, however limited samples sizes, exploratory nature of results, and methodological limitations preclude assessment on the effects of pharmacogenetic testing alone on pain management.

Pharmacogenetic Testing to Assess Risk of Developing Opioid Use Disorder

Clinical Context and Test Purpose

The purpose of pharmacogenetic testing in the management of acute pain is to identify treatment-naive individuals at elevated risk of developing opioid use disorder (OUD).

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

Populations

The relevant population of interest are individuals with acute pain, including for pain management after a procedure (e.g., surgery) or event (e.g., accident). The intended use population does not include those with chronic pain conditions.

Interventions

The test being considered is pharmacogenetic testing with the AvertD test (AutoGenomics, Inc.) to assess the risk of developing OUD. Genes included in the panel are listed in Table 13.

Table 13. Genes Included in AvertD Genetic Panel for Risk of Developing Opioid Use Disorder

Allelic Variants	Gene NAme	rs Number
5-HTR2A C>T	Serotonin 2A Receptor	rs7997012
COMT G>A	Catechol-O-Methyltransferase	rs4680
DRD1 A>G	Dopamine D1 Receptor	rs4532
DRD2 G>A	Dopamine D2 Receptor	rs1800497
DRD4 T>C	Dopamine D4 Receptor	rs3758653
DAT1 A>G	Dopamine Transporter	rs6347
DBH C>T	Dopamine Beta Hydroxylase	rs1611115
MTHFR C>T	Methylene Tetrahydrofolate Reductase	rs1801133
OPRK1 G>T	Kappa Opioid Receptor	rs1051660
GABA C>A	Gamma-Aminobutyric Acid (GABA)	rs211014
OPRM1 A>G	Mu Opioid Receptor	rs1799971
MUOR G>A	Mu Opioid Receptor	rs9479757
GAL T>C	Galanin	rs948854
DOR G>A	Delta Opioid Receptor	rs2236861
ABCB1 C>T	ATP Binding Cassette Transporter 1	rs1045642

Comparators

The following practice is currently being used to treat acute pain: standard pain management without genetic testing. For pain management, a multimodal, multidisciplinary approach that is individualized to the individual is recommended.[7,] A multimodal approach to pain management consists of using treatments (ie, nonpharmacologic and pharmacologic) from one 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.

Outcomes

The potential beneficial outcomes of primary interest would be improvements in pain, functioning, and quality of life. Benefits of a true-negative result would include improvements in pain, functioning, and quality of life. Benefits of a true-positive result would be the avoidance of treatment-related morbidity. Risks of a false-positive result include preventing an individual from receiving opioid therapy that could relieve pain and may have significant psychological implications and potentially lead to stigmatization of the individual. Risks of a false-negative include not appropriately identify individuals at elevated risk of OUD and result in exposure to opioids leading to adverse events, as

well as individuals participating in risky behavior due to a false sense of security of not being at risk of developing OUD.

Study Selection Criteria

For the evaluation of clinical validity of the pharmacogenetic test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard such as a clinical evaluation using the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Nonrandomized Studies

Donaldson et al (2021) conducted a multicenter, observational cohort study of adults exposed to prescription oral opioids for 4-30 days to evaluate the performance of an OUD classifier derived from machine learning (ML) (N=385).[15,5,] Participants who were 18 years or older were enrolled from 10 sites across the United States. Genotyping was performed using a qualitative SNP microarray on DNA from buccal samples collected after enrollment. The classifier demonstrated 82.5% sensitivity (95% CI: 76.1% to 87.8%) and 79.9% specificity (95% CI: 73.7% to 85.2%), with no significant differences in performance based on gender, age, follow-up length, race, or ethnicity. There was a positive likelihood ratio of 3.98 (95% CI: 3.26 to 6.87) and a negative likelihood ratio of 0.22 (95% CI: 0.17 to 0.33). This suggests that a positive result with AvertD is 18 times more likely (3.98/0.22) to occur in a patient who will develop OUD than it would in a patient who will not develop OUD. The authors concluded that the machine-learning (ML) classifier could provide additional objective information to help healthcare providers and patients make more informed decisions regarding the use of oral opioids. There were several limitations of the study. Participants were evaluated who had experienced a 4-30 day exposure to prescription oral opioids 1 to 51 years prior to study enrollment.

Opioid use was self-reported which could have introduced recall bias. There was a lack of diversity in this sample with the race of 92.2% of participants being White. The study evaluated participants' history of comorbidities, including alcohol use disorder, anxiety, bipolar disorder, cannabis use disorder, depression, schizophrenia, and substance use disorder other than opioids, alcohol, or cannabis. A higher percentage of subjects who were OUD-positive had a comorbidity compared to those who were OUD-negative (67.00% versus 22.59%) at any time. Several study sites had at least one prescribers who holds a waiver to prescribe buprenorphine. This was part of the study's enrichment strategy to ensure an adequate number of OUD-positive patients were enrolled, because patients at these sites are more likely to be OUD-positive. This could have led to selection bias. Study relevance limitations and design and conduct limitations are described in Tables 14 and 15.
Donaldson et al (2017) conducted a study on the genetic risk of opioid addiction.[16,] However, the genetic panel evaluated in this study was not the same as the panel in the commercially available test.

Hatoum et al (2021) published a study demonstrating that ancestry may confound genetic machine learning models used in candidate-gene prediction of opioid use disorder.[17,] They demonstrated that when ancestry was accounted for, their machine learning models did not predict OUD greater than chance. The authors conclude that researchers and clinicians should be skeptical of machine learning-derived genetic algorithms for polygenic traits such as addiction.

Table 14. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Donaldson et al (2021)[15]; FDA SSED (2023)[5]	5. Lack of diversity; a majority of enrolled participants were White; 6. Varying levels of documentation of preceding procedure or event and varying levels of opioid prescription		2. No comparator	1. Study does not directly assess a key health outcome	2. Follow-up duration not well defined

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; 5, Enrolled populations do not reflect relevant diversity; 6. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest; 4. Other.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose, 4. Other.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests); 6. Other.
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined); 2. Other.

Table 15. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Donaldson et al (2021)[15]	3. Selection bias due to enrichment strategy involving study sites with access to buprenorphine		5. Test performed after exposure to opioids	1. Not registered	2. High number of samples excluded in order to balance the risk pools for analysis.	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience); 3. Other.
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests; 2. Other.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described; 5. Other.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data; 4. Other.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported; 3. Other.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

One nonrandomized study was identified that studied the clinical utility of pharmacogenetic testing to assess the risk of developing OUD.

Nonrandomized Studies

Davis et al (2025) conducted a case-control study to assess the clinical utility of the candidate genetic variants included in the FDA-approved algorithm used to identify individuals at risk of OUD.[18,] The study used electronic health record data of individuals from the Million Veteran Program (MVP) with opioid exposure from 1992 to 2022 (N=452,664). Of these individuals 33,669 had OUD. 90.46% of the study population were male and the sample was ancestrally diverse. The performance of the 15 genetic variants for identifying OUD risk was assessed using logistic regression and machine learning models. In the logistic regression, the 15 candidate genes accounted for 0.40% of variation in OUD risk. The ensemble machine learning model correctly classified 52.83% (95% CI: 52.07% to 53.59%) of individuals and had a sensitivity of 50.72% and a specificity of 54.95%. The authors noted several limitations of the study. Electronic health record diagnosis codes were used, which can be susceptible to bias. The study population was also mostly male and, compared to the general population, was older and had higher rates of OUD and pain. The authors concluded these results do not demonstrate the clinical utility of this test. Study relevance limitations and design and conduct limitations are described in Tables 16 and 17.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Davis et al (2025)[18,]	5. Lack of diversity; a majority of study population was male; was older and had higher rates of OUD and pain compared to the general population 6. Study population does not represent intended use as only a subset of the population was identified as having short-term opioid exposure (4 to 30 days) (n=125,514)		2. No comparator	1. Study does not directly assess a key health outcome	2. Follow-up duration not defined

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; 5, Enrolled populations do not reflect relevant diversity; 6. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest; 4. Other.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose, 4. Other.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests); 6. Other.
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined); 2. Other.

Table 17. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Davis et al (2025)[18,]	2. Selection not random		5. Test performed after exposure to opioids	1. Not registered		1. Confidence intervals not reported for sensitivity and specificity measures

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience); 3. Other.
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests; 2. Other.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described; 5. Other.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data; 4. Other.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported; 3. Other.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Pharmacogenetic Testing to Assess Risk of Developing Opioid Use Disorder

One nonrandomized study has demonstrated the clinical validity of a pharmacogenetic test to assess the risk of developing OUD. From this study the classifier demonstrated a sensitivity of 82.5% (95% CI: 76.1% to 87.8%) and specificity of 79.9% (95% CI: 73.7% to 85.2%), with no significant differences in performance based on gender, age, follow-up length, race, or ethnicity. The positive likelihood ratio was 3.98 (95% CI: 3.26 to 6.87) and the negative likelihood ratio was 0.22 (95% CI: 0.17 to 0.33). However, the study had several limitations, including recall bias due to self-reported opioid use, selection bias due to the study's enrichment strategy, and a lack of diversity. One case-control study was identified that investigated the clinical utility of this technology. An ensemble machine learning model was run using the 15 genetic variants in the FDA-approved algorithm. The model correctly classified 52.83% (95% CI: 52.07% to 53.59%) of individuals and had a sensitivity of 50.72% and a specificity of 54.95%. While the sample was ancestrally diverse, the study population was mostly male and, compared to the general population, was older and had higher rates of OUD and pain. Also electronic health record data was used, which is susceptible to bias. More prospective studies with diverse sample populations are needed to assess the clinical utility of this test.

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.[19] 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.[20] 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.[21] 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 labeled 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 can be used. 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 18.

Table 18. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05548660	Pharmacogenetic-guided Choice of Post-surgery Analgesics	112 (actual)	Oct 2024
NCT05452694	Pharmacogenetics and Pharmacokinetics of Oxycodone to Personalize Postoperative Pain Management Following Lumbar Spinal Fusion and Decompression Surgery in Adults	200	Sept 2024
NCT05525923	Pharmacogenetics and Pharmacokinetics of Oxycodone to Personalize Postoperative Pain Management Following Thoracic Surgery in Adults	200	Oct 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05259865	The Utility of Genetic Testing in Predicting Drug Response in Chronic Pain	400	Dec 2027 (suspended)
NCT04685304	Pharmacogenomics Applied to Chronic Pain Treatment in Primary Care	315	Feb 2024
NCT04445792	A Depression and Opioid Pragmatic Trial in Pharmacogenetics	4111 (actual)	May 2024
NCT01140724	Predicting Perioperative Opioid Adverse Effects and Personalizing Analgesia in Children	1200	Dec 2025
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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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant
	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.,

Type	Code	Description
		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
	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)
	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.

Effective Date	Action
03/01/2022	Coding update
11/01/2022	Coding update
01/01/2023	Annual review. No change to policy statement. Literature review updated.
01/01/2024	Annual review. No change to policy statement. Policy guidelines and Literature review updated.
10/01/2025	Policy reactivated. Previously archived from 02/01/2024 to 09/30/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare 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 of California, are: (a) consistent with Blue Shield of California 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 member; 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 or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.

- When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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: 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Pharmacogenetic Testing for Pain Management 2.04.131** **Policy Statement:** I. Genetic testing for pain management is considered **investigational** for all indications (see Policy Guidelines section). II. Genetic testing for acute pain management to assess the risk of developing opioid use disorder is considered **investigational** for all indications (see Policy Guidelines section).