
Medical Policy



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***Current Policy Effective Date: 7/1/26**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Pharmacogenetic Pain Management

Description

Pharmacogenetic testing is a type of genetic test that in some instances can predict how a person responds to specific medications. Thus, this type of testing is proposed for informing the selection or dosing of some medications for certain individuals.

Medical Policy Statement

Genetic testing for pain management is experimental/investigational for all indications. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Genetic testing for acute pain management to assess the risk of developing opioid use disorder is experimental/investigational for all indications. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Investigational codes

81225

81226

81227

81291

81401

81479

This policy does not address testing for congenital insensitivity to pain.

* 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.

***Established codes may be considered investigational for the purpose of this policy.

Background

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. It has been proposed that testing for genetic variants affecting pharmacokinetics or pharmacodynamics of analgesics might assist in selecting dosing analgesic drugs.

Due to the growing interest in genetic testing and pain management, the number of potential genes and proprietary pain management panel tests, the list of panels and manufacturers may not be all inclusive in this policy.

PAIN

During 2021, an estimated 20.9% (51.6 million) of U.S adults experienced chronic pain and 6.9% (17.1 million) had high-impact chronic pain (i.e., chronic pain that limits daily activities).(1) Chronic pain may be related to cancer, or be what is termed *chronic non-cancer pain*, which may be secondary to a wide range of conditions, such as migraines, low back pain, or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, physical and occupational therapy, and complementary/alternative therapies. Nonetheless, Institute of Medicine (rebranded 2015: National Academy of Medicine) reports that many individuals receive inadequate pain prevention, assessment, and treatment. Given that pain is an individual and subjective experience, assessing and predicting response to pain interventions, including pain medications, is challenging.

Pharmacologic Treatment

A variety of medication classes are available to manage pain: nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, which target central nervous system (CNS) pain perception, and a variety of 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 for the management of cancer-related pain but has been applied to the management of other forms of pain. The ladder outlines a stepped approach to pain management, beginning with non-opioid 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. A wide variety of opioids are available in short- and long-acting preparations and administered through variety of routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.

For acute pain management, particularly postoperative pain, systemic opioids and non-opioid analgesics remain a mainstay of therapy. However, there has been growing interest in using an alternative, non-systemic treatments in addition to or as an alternative to systemic opioids. These options include neuraxial anesthesia, including intra-operative epidural or intrathecal opioid injection, which can provide pain relief for up to 24 hours postoperatively, and postoperative indwelling epidural anesthesia with opioids and local anesthetics, which may be controlled with a patient-controlled anesthesia (PCA) pump. Postoperative peripheral nerve blocks may also be used.

While available pharmacologic therapies are effective for many individuals, there is a high degree of heterogeneity in pain response, particularly in the management of chronic pain. In addition, many opioids are associated with a significant risk of adverse events (AEs), ranging from mild (e.g., constipation) to severe (e.g., respiratory depression) and are associated with risk of dependence, addiction, and abuse. Limitations in currently available pain management techniques have led to interest in the use of pharmacogenetics to improve the targeting of therapies and prediction and avoidance of adverse events.

Genetics of Pain Management

Genetic factors may contribute to a range of aspects 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 have been proposed for use in the management of pain. Genes identified as being relevant to pain management and currently available panels are summarized in Table 1.

Table 1. Genes Relevant to Pain Management

Gene	Locus	Gene Product Function
<i>5HT2C</i> (serotonin receptor gene)	Xq23	1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine
<i>5HT2A</i> (serotonin receptor gene)	13q14-21	Another serotonin receptor subtype
<i>SLC6A4</i> (serotonin transporter gene)	17q11.2	Clears serotonin metabolites from synaptic spaces in the CNS
<i>DRD1</i> (dopamine receptor gene)	5q35.2	G-protein-coupled receptors that have dopamine as their ligands
<i>DRD2</i> (dopamine receptor gene)	11q23.2	
<i>DRD4</i> (dopamine receptor gene)	11p15.5	
<i>DAT1</i> or <i>SLC6A3</i> (dopamine transporter gene)	5p15.33	Mediates dopamine reuptake from synaptic spaces in the CNS
<i>DBH</i> (dopamine beta-hydroxylase gene)	9q34.2	Catalyzes the hydroxylase of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons

<i>COMT</i> (catechol O-methyl-transferase gene)	22q11.21	Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine
<i>MTHFR</i> (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
<i>OPRM1</i> (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
<i>OPRK1</i> (κ-opioid receptor gene)	8q11.23	Binds the natural ligand dynorphin and synthetic ligands
<i>UGT2B15</i> (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
<i>CYP2D6</i>	22q13.2	
<i>CYP2C19</i>	10q23.33	
<i>CYP2C9</i>	10q23.33	
<i>CYP3A4</i>	7q22.1	
<i>CYP2B6</i>	19q13.2	
<i>CYP1A2</i>	15q24.1	

CNS: central nervous system; CYP: cytochrome P450; GABA: γ-aminobutyric acid; UDP: uridine diphosphate glycosyltransferase.

Opioid Use Disorder Risk

Opioid use disorder (OUD) is a chronic disorder in which individuals have a pattern of opioid misuse. Currently, the standard of care for OUD risk prediction includes structured clinician interviews. Pharmacogenetic testing has recently become commercially available in the United States to assess the risk of developing opioid use disorders in individuals with a need for pharmacologic management of acute pain.

Summary of Evidence

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a systematic review, 2 hybrid implementation-effectiveness randomized trials, 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 cytochrome P450 (CYP) 2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The systematic review found a difference in opioid consumption but not pain intensity (possibly due to heterogeneity of the included trials). 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. Another hybrid randomized trial found that no difference in pain intensity with genetic test-guided opioid selection versus usual care in patients with chronic pain. 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, 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 opioid use disorder. 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. No evidence was identified that investigated the clinical utility of the technology. 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.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to 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. The following is a summary of the key literature to date.

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 use of inappropriate pain medications, including:
 - To identify individuals likely or not likely 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 relevant population of interest are individuals with chronic and acute pain, including conditions such as cancer, migraines, low back pain, and fibromyalgia.

Testing for individual genes is available for most, or all, or the genes listed in Table 2, as well as for a wider range of genes. Because of the 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 PGTSM (Pain Management) (Millennium Health) is a genetic panel test intended to help physicians' select pain medication. The panel includes analysis of 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*).

GeneSight Analgesic test includes 22 opioids and non-opioid pain medications, which represent 98% of all medications prescribed for low back pain. Opioids, NSAIDs, muscle relaxants and opioid-dependency medications are covered.

The Pain Management pharmacogenetic panel by Molecular Testing Labs tests 13 commonly prescribed pain medications in an attempt to determine how well a medication will relieve an individual's pain and whether that individual is at high risk for experiencing adverse side effects. Testing is also promoted to reveal any genetic abnormalities that could elevate an individual's pain perception.

Pathway Genomics indicates that the Pain Medication DNA Insight® test can help to determine how certain drugs are metabolized, which medications should be used with caution, may cause adverse side effects, and may require higher or lower dosages.

Proove Genomics offers 3 proprietary panels for pain management. The Proove Pain Sensitivity panel was designed to objectively assess patient pain thresholds and the role of central pain perception to guide patient care. The Proove Opioid Risk panel is intended to objectively assess patient risk for opioid use disorder to appropriately prescribe opioids and protect those patients at-risk. Finally, the Proove NSAID Risk panel is proposed to objectively assess patient risk for NSAID-mediated side effects to guide use of NSAID therapy.

Other laboratories, including CompanionDx, ARUP Laboratories, and AIBioTech, which markets the PersonaGene Genetic Panel, offer panels of CYP450 genes. Panels that are restricted to CYP450 genes are beyond the scope of this policy. (see related policies)

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

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

Gene	Potential Role in Pain Management
<i>COMT</i>	Val158Met variant associated with alterations in emotional processing and executive function. Other variants have been associated with pain sensitivity
<i>MTHFR</i>	Multiple variants identified, which are associated with a wide variety of clinical disorders
<i>GABA</i>	1519T>C GABA A 6 gene variant associated with methamphetamine dependence
<i>OPRK1</i> (κ-opioid receptor)	Variants associated with the risk for opioid addiction
<i>OPRM1</i> (μ-opioid receptor)	A118Gvariant (rs1799971) associated with reduced pain sensitivity and opioid requirements
<i>VKORC1</i>	
<i>UGT2B15</i>	Tamoxifen, diclofenac, naloxone, carbamazepine, and benzodiazepines inhibit UGT2B7 potentially leading to opioid hyperalgesia
<i>CYP</i> genes	Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics
• <i>CYP2D6</i>	<i>CYP2D6</i> is the primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects
• <i>CYP2C19</i>	
• <i>CYP3A4</i>	Involved in metabolism of up to 60% of clinically used drugs
• <i>CYP1A2</i>	
• <i>CYP2C9</i>	
• <i>CYP2B6</i>	
• <i>CYP3A5</i>	

CYP: cytochrome P450; GABA: g-aminobutyric acid.

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 subject is recommended.(7) 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.

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	No. of unsuccessful medication trials, no. of medications needed, dose of medication, 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.

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		
Multidimensional Pain Inventory	Clinically important	≥0.6-point decrease
Interference Scale		
Brief Pain Inventory Interference Scale	Minimally important	1 point decrease
Emotional functioning		
Beck Depression Inventory	Clinically important	≥5 point decrease
Profile of Mood States		
Total Mood Disturbance	Clinically important	≥10-to-15-point decrease
Specific Subscales	Clinically important	≥2-to-12-point change
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.(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 timepoints 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).

Review of Evidence

Systematic Review

Jethwa et al (2025) conducted a systematic review and meta-analysis of 6 RCTs (N=619) that compared pharmacogenomic testing to usual care in patients with pain requiring opioids.(11) The analysis included 2 of the trials summarized below (Hamilton et al [2022] and Thomas et al [2021]) in addition to 4 smaller trials. Most of the trials had a low risk of bias, but one study had a high risk of bias and was excluded from the meta-analysis. Three studies were included in the random effects analysis comparison of pain intensity, which found no difference between groups (standardized mean difference, -0.31; 95% confidence interval [CI], -0.89 to 0.27; $I^2=81\%$; $p=.3$). There was a significant difference in opioid consumption between groups (SMD, -0.38; 95% CI, -0.67 to -0.08; $I^2=22\%$; $p=.01$), which was based on a pooled analysis of 2 studies.

Randomized Studies

Smith et al (2025) conducted a open-label, multicenter RCT that compared pharmacogenomic-guided pain control and standard care in patients with chronic pain (Pharmacogenomics Applied to Chronic Pain Treatment in Primary Care, PGx-ACT).(12) All patients had pain lasting more than 3 months and were taking tramadol, codeine, or hydrocodone. Patients underwent pharmacogenomic testing, but providers were not required to change the analgesic regimen based on the testing results. The primary outcome was change in pain intensity at 3 months among CYP2D6 intermediate or poor metabolizers whose therapy changed to align with their test results ($n=49$), and those who received standard care despite being CYP2D6 intermediate or poor metabolizers ($n=57$). Pain intensity was a patient-reported composite of current, worst, and average pain over the past 7 days. There was no difference in pain intensity at 3 months ($p=.74$) between the patients who did and did not have their treatment changed based on pharmacogenomic test results. Other secondary measures were also not significant, including physical function and opioid exposure.

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.(13) 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.(14) 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 post-surgery 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
Smith et al (2025)	NR	1 outpatient clinic	2021-2022	Adults with chronic pain who were taking codeine, tramadol, or hydrocodone (N=253)	Change of therapy after CYP2D6 poor or intermediate metabolizer status was identified (n=49)	No change of therapy after CYP2D6 poor or intermediate metabolizer status was identified (n=57)
Hamilton et al (2022)	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)	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 RCT Results

Study	Opioid consumption	Composite pain intensity
Smith et al (2025)		
Change in therapy	-1.7 ± 13 MME	-0.10 ± 0.63
No change in therapy	-0.94 ± 13 MME	-0.21 ± 0.75
p value	NR	.74
Hamilton et al (2022)	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)	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
Smith et al (2025)	4. Only patients taking tramadol, codeine, or hydrocodone were included				
Hamilton et al (2022)		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)	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 priori power calculation; clinical outcomes were exploratory	1. Clinical outcomes evaluated at 2 weeks post-surgery only

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
Smith et al (2025)		1. Open-label trial design; no blinding			3. Trial was likely underpowered due to the assumptions of the power calculation	
Hamilton et al (2022)		2. Only patients were blinded				
Thomas et al (2021)		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 compared to a historical control 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.(15) The authors compared the findings with a historical cohort of 47 patients who underwent similar surgeries but were managed with standard enhanced recovery protocol. Results showed that the overall benefit of analgesia score were statistically significantly lower in patients in whom the analgesic protocol was initiated based on results of genotype testing versus the historical control on postoperative day one and day five (all $p < 0.05$). 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 three clinics without assessment of CYP2D6 inhibitors.(16) 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 (see 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)	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)	Historical group managed with standard enhanced recovery protocol undergoing similar operational procedures (n=47)	5 d

Smith et al (2019)	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=235)	Treatment based on standard of care. (n=135)	3 mo
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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	OBAS ^a	OBAS Pain Subscore	Postoperative Opioid Use, mg ^b
Senagore et al (2017)			
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)
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	0.01	0.04	0.018
Smith et al (2019)	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	0.016	0.019	

CYP: cytochrome P450; 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 limitation tables (see 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 et al (2017) reported that 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 of Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Senagore et al (2017)		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)			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 limitations 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 Outcome's 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. Clinically significant difference not prespecified; 6. Clinically 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)	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 clinically important difference	3. Confidence intervals and/or p values not reported
Smith et al (2019)	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 limitations 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. A systematic review found reduced opioid consumption with genetic test-guided therapy compared to usual care, but no difference in pain intensity (possibly due to substantial heterogeneity among studies).

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-naïve individuals at elevated risk of developing opioid use disorder (OUD).

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.

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-HTT2A 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

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 (i.e., 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.

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.

Review of Evidence

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).(17,5) 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.(18) 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.(19) 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) ; FDA SSSED (2023)	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); FDA SSSED (2023)	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 (i.e., 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 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.(20) 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. Most (90.46%) of the study population was 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)	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

OUD: opioid use disorder. 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)	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 (i.e., 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

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Neurology

The American Academy of Neurology (2014) published a position paper on the use of opioids for chronic noncancer pain.(21) Regarding pharmacogenetic testing, the guidelines state that genotyping to determine whether response to opioid therapy can or should be more individualized is an emerging issue that will “require critical original research to determine effectiveness and appropriateness of use.”

Clinical Pharmacogenomics Implementation Consortium

The Clinical Pharmacogenomics Implementation Consortium (2020) published a guideline for CYP2C9 and NSAIDs, which was developed to provide interpretation of CYP2C9 genotype tests so that the results could potentially guide dosing and/or appropriate NSAID use.(22) 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-methyltransferase (*COMT*) genotypes and select opioid therapy.(23) 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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently 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			
NCT05452694	Pharmacogenetics and Pharmacokinetics of Oxycodone to Personalize Postoperative Pain Management Following Lumbar Spinal Fusion and Decompression Surgery in Adults	235	Jul 2027
NCT05525923	Pharmacogenetics and Pharmacokinetics of Oxycodone to Personalize Postoperative Pain Management Following Thoracic Surgery in Adults	200	Mar 2028
NCT05259865	The Utility of Genetic Testing in Predicting Drug Response in Chronic Pain	400	Dec 2027 suspended
NCT01140724	Predicting Perioperative Opioid Adverse Effects and Personalizing Analgesia in Children	1200	Dec 2025
Unpublished			
NCT05548660	Pharmacogenetic-guided Choice of Post-surgery Analgesics	112	Feb 2025
NCT04445792	A Depression and Opioid Pragmatic Trial in Pharmacogenetics	4284	May 2024

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). The RightMed Test (OneOme LLC) panel, OmeCare OmePainMeds panel, the Millennium PGT (Pain Management) panel, and YouScript Analgesic panel are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In 2020, the FDA released a “Table of Pharmacogenetic Associations.” The FDA release indicated that although a particular gene-drug combination is listed, it does not mean the FDA advocates using a pharmacogenetic test before prescribing the corresponding medication, unless the test is a companion diagnostic. The gene-medication combinations used for pain management that were determined to have data which supports therapeutic management recommendations were as follows:

- HLA-B
 - carbamazepine
- CYP2C9
 - celecoxib,
 - codeine,
 - flurbiprofen,
 - piroxicam; and for
- CYP2D6
 - tramadol.

Data supporting potential impact on safety or response included carbamazepine (HLA-A).

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, which 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."

Government Regulations

National:

No CMS National Coverage Determination (NCD) was identified. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Local:

Local Coverage Determination (LCD): MoIDX: Pharmacogenomics Testing (L38435);
Effective: 7/26/20; Revision date: 10/2/25

Coverage Indications, Limitations, and/or Medical Necessity

PGx testing is considered reasonable and necessary in limited circumstances as described below:

- As an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to specific medications under consideration for use, or is already using a specified medication
- PGx tests must demonstrate analytical validity, clinical validity, and clinical utility that has been demonstrated through a required technical assessment of the test.
 - PGx Tests are considered germline tests and must adhere to other relevant germline testing policies published by this contractor.
- Medications are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the FDA (PGx information required for safe drug administration) or Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines (category A and B).
- The result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug.

PGx testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Unless the record reflects that the treating clinician has already considered non-genetic factors to make a preliminary drug selection, PGx testing is not considered reasonable and necessary.

Local Coverage Article: **Billing and Coding: MoIDX: Pharmacogenomics Testing (A58395)**; Effective date: July 26, 2020; Revised February 5, 2026

Only 1 test may be performed per date of service; the test should be the most likely to identify the necessary alleles/variants for the drug/drugs in question. This applies to both single gene tests and multigene panels.

Relevant gene/drug associations from CPIC and FDA sources.

Gene	CPT code(s)	Generic Name	Brand Name	Trade Name(s)	Intended use for Drug(s)	Guidance
CYP2C9	81227	celecoxib, flurbiprofen, lornoxicam, meloxicam, piroxicam, tenoxicam	celecoxib, flurbiprofen, lornoxicam, meloxicam, piroxicam, tenoxicam	Celebrex, Ansaid, Ocufen, Chlortenoxicam, Xefo, Mobic, Vivlodex, Anjeso, Qmiiz ODT, Feldene, Mobiflex	Non-steroidal anti-inflammatory (NSAID)	CPIC/FDA
CYP2D6	81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U	codeine, oliceridine, tramadol	codeine, oliceridine, tramadol	Olinvyk, Ultram	Opioid	CPIC/FDA
CYP2D6	81226, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, 0076U	lofexidine	lofexidine	Lucemyra	Opioid withdrawal	FDA

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing for Cytochrome P450 Polymorphisms
Genetic Testing for Specified Conditions Using Testing Panels

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 6, 2026 the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/16	2/16/16	3/16/16	Joint policy established
5/1/17	2/21/17	2/21/17	Routine update of noncovered service
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		• FDA approved gene:med combinations added • Updated LCD added • Title changed from “Genetic testing for pharmacogenetic testing for pain management”
7/1/22	4/19/22		• Routine maintenance
7/1/23	4/18/23		• Routine maintenance (slp) • Vendor managed: N/A
7/1/24	4/16/24		• Routine maintenance (slp) • Vendor managed: N/A
7/1/25	4/15/25		• Routine maintenance (slp) • Vendor managed: N/A • AdvertD added as EI • GT for evaluation of potential use disorders added as EI
7/1/26	4/21/26		• Routine maintenance (slp/fr) • Vendor managed: N/A • Policy reformatted

Next Review Date: 2nd Qtr, 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR PHARMACOGENETIC PAIN MANAGEMENT

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not Covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.