BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.131 Pharmacogenetic Testing for Pain Management

Annual Effective Policy Date: April 1, 2026

Original Policy Date: June 2015

Related Policies:

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

Pharmacogenetic Testing for Pain Management

Description

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.

Genetic factors may contribute to a range of aspects of pain and pain control, including predisposition to conditions that lead to pain, pain perception, and the development of comorbid conditions that may affect pain perception. Currently available genetic tests relevant to pain management assess single-nucleotide variants (SNVs) in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes.

Genes related to these clinical scenarios include, broadly speaking, those involved in neurotransmitter uptake, clearance, and reception; opioid reception; and hepatic drug metabolism. Panels of genetic tests have been developed and proposed for use in the management of pain. Genes identified as being relevant to pain management are summarized in Table 1.

Table 1. Genes Relevant to Pain Management

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

Gene	Locus	Gene Product Function
COMT (catechol *O*-methyl-transferase gene)	22q11.21	Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine
MTHFR (methylenetetrahydrofolate reductase gene)	1p36.22	Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters
GABA A receptor gene	5q34	Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter
OPRM1 (μ-opioid receptors gene)	6q25.2	G-protein coupled receptor that is primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone
OPRK1 (κ-opioid receptor gene)	8q11.23	Binds the natural ligand dynorphin and synthetic ligands
UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)	4q13.2	Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds
Cytochrome p450 genes		Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics
CYP2D6	22q13.2	
CYP2C19	10q23.33	
CYP2C9	10q23.33	
CYP3A4	7q22.1	
CYP2B6	19q13.2	
CYP1A2	15q24.1	

CNS: central nervous system; CYP: cytochrome P450; GABA: g-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.

OBJECTIVE

The objective of this evidence review is to determine whether the use of genetic testing to manage patients with acute or chronic pain improves the net health outcome.

POLICY STATEMENT

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

Genetic testing for acute pain management to assess the risk of developing opioid use disorder is considered **not medically necessary** for all indications (see Policy Guidelines section).

POLICY GUIDELINES

This policy does not address testing limited to cytochrome p450 genotyping, which is addressed in evidence review 2.04.38. 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 (AvertD™, 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])

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

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

CYP2C19	
CYP3A4	Involved in the metabolism of up to 60% of clinically used drugs
CYP1A2	
CYP2C9	
CYP2B6	
CYP3A5	

CYP: cytochrome P450; GABA: g-aminobutyric acid; UGT: uridine diphosphate glycosyltransferase.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

No genetic tests approved by the FDA for pain management were identified.

Of note, in February 2020, the FDA expressed "concerns with firms offering genetic tests making claims about how to use the genetic test results to manage medication treatment that are not supported by recommendations in the FDA-approved drug labeling or other scientific evidence".[3,] Due to these concerns, the FDA announced a collaboration between the FDA"s Center for Devices and Radiological Health and Center for Drug Evaluation and Research intended to provide the agency"s view of the state of the current science in pharmacogenetics. This collaborative effort includes a web resource[4,] that describes "some of the gene-drug interactions for which the FDA believes there is sufficient scientific evidence to support the described associations between certain genetic variants, or genetic variant-inferred phenotypes, and altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events."

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

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). One 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 (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% confidence interval [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 Food and Drug Administration (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.

SUPPLEMENTAL INFORMATION

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.[21,] 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.[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*-methyl-transferase (*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.

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
June 2015	New policy	Policy created with literature review through December 2, 2014. Pharmacogenetic testing for pain management is considered investigational for all indications.
March 2019	Replace policy	Policy updated with literature review through September 4, 2018; no references added. Policy statement unchanged.
March 2020	Replace policy	Policy updated with literature review through October 15, 2019; reference added. Policy statement unchanged.
March 2021	Replace policy	Policy updated with literature review through September 21, 2020; references added. Policy statement unchanged.
March 2022	Replace policy	Policy updated with literature review through September 14, 2021; references added. Policy statement unchanged.
March 2023	Replace policy	Policy updated with literature review through September 23, 2022; reference added. Policy statement unchanged.
December 2024	Replace policy	Policy updated with literature review through September 14, 2022; reference added. Policy statement unchanged.
March 2025	Replace policy	Policy updated with literature review through January 9, 2025; references added. New indication added for individuals with need for pharmacologic management of acute pain who receive pharmacogenetic testing to assess risk of developing opioid use disorder, with a not medically necessary policy statement for FEP. Other policy statement unchanged.
March 2026	Replace policy	Policy updated with literature review through December 8, 2025; reference added. Policy statements unchanged.