FEP Medical Policy Manual

FEP 2.04.131 Pharmacogenetic Testing for Pain Management

Effective Policy Date: **April 1, 2021**

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

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 in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes.

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

Table 1. Genes Relevant to Pain Management

Gene	Locus	Gene Product Function
5HT2C (serotonin receptor gene)	Xq23	1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine
5HT2A (serotonin receptor gene)	13q14-21	Another serotonin receptor subtype
SLC6A4 (serotonin transporter gene)	17q11.2	Clears serotonin metabolites from synaptic spaces in the CNS
DRD1 (dopamine receptor gene)	5q35.2	G-protein-coupled receptors that have dopamine as their ligands
DRD2 (dopamine receptor gene)	11q23.2	
DRD4 (dopamine receptor gene)	11p15.5	
DAT1 or *SLC6A3* (dopamine transporter gene)	5p15.33	Mediates dopamine reuptake from synaptic spaces in the CNS
DBH (dopamine beta-hydroxylase gene)	9q34.2	Catalyzes the hydroxylase of dopamine to norepinephrine; active primarily in adrenal medulla and postganglionic synaptic neurons
COMT (catechol *O*-methyl-transferase gene)	22q11.21	Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine
MTHFR (methylenetetrahydrofolate reductase gene)	1p36.22	Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters
GABA A receptor gene	5q34	Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter
OPRM1(μ-opioid receptors gene)	6q25.2	G-protein coupled receptor that is primary site of action for commonly used opioids, including morphine, heroin, fentanyl, and methadone
OPRK1 (κ-opioid receptor gene)	8q11.23	Binds the natural ligand dynorphin and synthetic ligands
UGT2B15 (uridine diphosphate glycosyltransferase 2 family, member 15)	4q13.2	Member of UDP family involved in the glycosylation and elimination of potentially toxic compounds
Cytochrome p450 genes		Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics
CYP2D6	22q13.2	
CYP2C19	10q23.33	
CYP2C9	10q23.33	
CYP3A4	7q22.1	
CYP2B6	19q13.2	
CYP1A2	15q24.1	

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

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).

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*.

BENEFIT APPLICATION

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

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. The Pathway Genomics Pain Medication DNA Insight panel, the Millennium PGT (Pain Management) panel, and YouScript Analgesic panel are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

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

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

RATIONALE

Summary of Evidence

For individuals who have a need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes a prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. Relevant outcomes are symptoms, health status measures, medication use, and treatment-related morbidity. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach finding a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Academy of Neurology

In 2014, the American Academy of Neurology published a position paper on the use of opioids for chronic noncancer pain.[13.] Regarding pharmacogenetic testing, the guidelines stated that genotyping to determine whether the response to opioid therapy can or should be more individualized is an emerging issue that will "require critical original research to determine effectiveness and appropriateness of use."

Clinical Pharmacogenomics Implementation Consortium

The Clinical Pharmacogenomics Implementation Consortium (2020) published a guideline for 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.[14.] The guideline notes that CYP2C9 genotyping information may provide an opportunity "to prescribe NSAIDs for acute or chronic pain conditions at genetically-informed doses to limit long-term drug exposure and secondary adverse events for patients who may be at increased risk." However, the authors also acknowledge that "while traditional pharmacogenetic studies have provided evidence associating common CYP2C9 genetic variation with NSAID pharmacokinetics, there is sparse prospective evidence showing that genetically-guided NSAID prescribing improves clinical outcomes." In 2014, the Consortium also published therapeutic recommendations for codeine based on CYP2D6 phenotype.[15.] These recommendations state that codeine should be avoided in poor metabolizers due to lack of efficacy and in ultra rapid metabolizers due to toxicity potential.

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.

REFERENCES

1. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. Sep 14 2018; 67(36): 1001-1006. PMID 30212442
2. Institute of Medicine, Committee on Advancing Pain Research Care and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press; 2011.
3. U.S Food and Drug Administration. FDA announces collaborative review of scientific evidence to support associations between genetic information and specific medications. February 20, 2020. https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic. Accessed September 21, 2020
4. U.S. Food and Drug Administration. Table of pharmacogenetics associations. February 25, 2020. https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Accessed September 21, 2020
5. Carma Nabavi PG. Personal Communication. 2014.
6. Genelex. Genelex announces new genetic testing options. n.d.; https://youscript.com/genelex-announces-new-genetic-testing-options/. Accessed September 21, 2020
7. U.S. Department of Health and Human Services. Pain management best practices. May 2019. https://www.hhs.gov/sites/default/files/pain-mgmt-best-practices-draft-final-report-05062019.pdf. Accessed September 21, 2020
8. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. Jan 2005; 113(1-2): 9-19. PMID 15621359
9. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. Feb 2008; 9(2): 105-21. PMID 18055266
10. Gewandter JS, Dworkin RH, Turk DC, et al. Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. Pain. Jul 2015; 156(7): 1184-97. PMID 25887465
11. Senagore AJ, Champagne BJ, Dosokey E, et al. Pharmacogenetics-guided analgesics in major abdominal surgery: Further benefits within an enhanced recovery protocol. Am J Surg. Mar 2017; 213(3): 467-472. PMID 27955884
12. Smith DM, Weitzel KW, Elsey AR, et al. CYP2D6-guided opioid therapy improves pain control in CYP2D6 intermediate and poor metabolizers: a pragmatic clinical trial. Genet Med. Aug 2019; 21(8): 1842-1850. PMID 30670877
13. Franklin GM. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. Neurology. Sep 30 2014; 83(14): 1277-84. PMID 25267983
14. Theken KN, Lee CR, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs. Clin Pharmacol Ther. Aug 2020; 108(2): 191-200. PMID 32189324
15. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clin Pharmacol Ther. Apr 2014; 95(4): 376-82. PMID 24458010

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.