



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for pain management for all indications to be **investigational**.*

Policy Guidelines

This policy does not address testing limited to cytochrome p450 genotyping. This policy also does not address testing for congenital insensitivity to pain.

Commercially available genetic tests for pain management consist of panels of single-nucleotide variants (SNVs) or (less commonly) individual SNV testing. SNVs implicated in pain management include the following (see also Table 1):

- *5HT2C* (serotonin receptor gene)
- *5HT2A* (serotonin receptor gene)
- *SLC6A4* (serotonin transporter gene)
- *DRD1* (dopamine receptor gene)
- *DRD2* (dopamine receptor gene)
- *DRD4* (dopamine receptor gene)
- *DAT1* or *SLC6A3* (dopamine transporter gene)
- *DBH* (dopamine beta-hydroxylase gene)
- *COMT* (catechol O-methyltransferase gene)
- *MTHFR* (methylenetetrahydrofolate reductase gene)
- γ -aminobutyric acid (GABA) A receptor gene
- *OPRM1* (μ -opioid receptor gene)
- *OPRK1* (κ -opioid receptor gene)
- *UGT2B15* (uridine diphosphate glycosyltransferase 2 family, member 15)
- Cytochrome p450 genes: *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP3A4*, *CYP2B6*, *CYP1A2*.

Background/Overview

Pain is a universal human experience and an important contributor to outpatient and inpatient medical visits. The Institute of Medicine's (IOM) reported in 2011 that common chronic pain conditions affect at least 116 million adults in the United States. Chronic pain may be related to cancer, or be what is termed *chronic noncancer pain*, which may be secondary to a wide range of conditions, such as migraines, low back pain,

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

or fibromyalgia. Multiple therapeutic options exist to manage pain, including pharmacotherapies, behavioral modifications, and physical and occupational therapy, and complementary/alternative therapies. Nonetheless, IOM has reported 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.

PAIN MANAGEMENT

A variety of medication classes are available to manage pain: nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), opioid analgesics, which target central nervous system pain perception, and classes of adjuvants, including antiepileptic drugs (eg, gabapentin, pregabalin), antidepressants (eg, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors), and topical analgesics. The management of chronic pain has been driven, in part, by the World Health Organization's analgesic ladder for pain management, which was developed to manage cancer-related pain but has been applied to other forms of pain. The ladder outlines a stepped approach to pain management, beginning with nonopioid analgesia and proceeding to a weak opioid (eg, codeine), with or without an adjuvant for persisting pain, and subsequently to a strong opioid (eg, fentanyl, morphine), with or without an adjuvant for persisting or worsening pain. Various opioids are available in short- and long-acting preparations and administered through different routes, including oral, intramuscular, subcutaneous, sublingual, and transdermal.

Pharmacologic Treatment

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

While available pain management therapies are effective for many patients, there is a high degree of heterogeneity in pain response, particularly for chronic pain. In addition, many opioids are associated with significant risk of adverse events, ranging from mild (eg, constipation) to severe (eg, 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 in 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 SNVs in single genes potentially relevant to pharmacokinetic or pharmacodynamic processes.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

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 and currently available panels are summarized in Table 1.

Table 1: Genes Relevant to Pain Management

Gene	Locus	Gene Product Function	Potential Role in Pain Management
<i>5HT2C</i> (serotonin receptor gene)	Xq23	1 of 6 subtypes of serotonin receptor, which is involved in release of dopamine and norepinephrine	Variants (ie, 102T/C) associated with variation in pain threshold
<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>DRD4</i> VNTR associated with presence of pain-related disorders (fibromyalgia, TMJ syndrome, migraine)
<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-methyltransferase gene)	22q11.21	Responsible for enzymatic metabolism of catecholamine neurotransmitters dopamine, epinephrine, and norepinephrine	<ul style="list-style-type: none"> • Val158Met variant associated with alterations in emotional processing and executive function • Other variants have been associated with pain sensitivity
<i>MTHFR</i> (methylenetetrahydrofolate reductase gene)	1p36.22	Converts folic acid to methylfolate, a precursor to norepinephrine, dopamine, and serotonin neurotransmitters	Multiple variants identified, which are associated with a wide variety of clinical disorders
GABA A receptor gene	5q34	Ligand-gated chloride channel that responds to GABA, a major inhibitory neurotransmitter	1519T>C GABA A 6 gene variant associated with methamphetamine dependence
<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	A118G variant (rs1799971) associated with reduced pain sensitivity and opioid requirements
<i>OPRK1</i> (κ -opioid receptor gene)	8q11.23	Binds the natural ligand dynorphin and synthetic ligands	Variants associated with the risk for opioid addiction
<i>UGT2B15</i> (uridine)	4q13.2	Member of UDP family involved in the	Tamoxifen, diclofenac, naloxone,

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

Gene	Locus	Gene Product Function	Potential Role in Pain Management
diphosphate glycosyltransferase 2 family, member 15)		glycosylation and elimination of potentially toxic compounds	carbamazepine, and benzodiazepines inhibit <i>UGT2B7</i> potentially leading to opioid hyperalgesia
Cytochrome p450 genes			
<i>CYP2D6</i>	22q13.2		<i>CYP2D6</i> is primary metabolizer for multiple oral opioids; metabolizer phenotype associated with variability in opioid effects
<i>CYP2C19</i>	10q23.33	Hepatic enzymes responsible for the metabolism of a wide variety of medications, including analgesics	
<i>CYP2C9</i>	10q23.33		
<i>CYP3A4</i>	7q22.1		Involved in metabolism of up to 60% of clinically used drugs
<i>CYP2B6</i>	19q13.2		
<i>CYP1A2</i>	15q24.1		

CNS: central nervous system; CYP: cytochrome; GABA: γ -aminobutyric acid; TMJ: temporomandibular joint; UG: uridine diphosphate glycosyltransferase; VNTR: varying number of tandem repeats.

Commercially Available Genetic Tests for Pain Management

Several test labs market panel tests 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. Specific variants included in the panels are shown in Table 2.

- GeneSight^{®†} Analgesic (Assurex Health, Mason, OH) is a genetic panel test intended to analyze “how patients’ genes can affect their metabolism and possible response to FDA [U.S. Food and Drug Administration]-approved opioids, NSAIDs and muscle relaxants commonly used to treat chronic pain.” Results are provided with a color-coded report based on efficacy and tolerability, which displays those medications that should be used as directed, used with caution, or used with increased caution and more frequent monitoring. The company’s website does not specify the testing methods. Publications describing other tests provided by the company specify that testing is conducted via SNV sequencing performed via multiplex polymerase chain reaction.
- Proove Biosciences (Irvine, CA) offers several genetic panels that address pain control. The Proove^{®†} Opioid Risk Panel includes 11 genes intended to predict opioid abuse and failure of opioid therapy. Genetic testing results are provided with an overall Dependence Risk Index. The company also markets the Proove Pain Perception panel, which is a test for SNVs in several genes related to pain perception, including *COMT* and at least 3 other genes. Results are provided with a report that stratifies patients’ pain sensitivity based on *COMT* haplotype. In addition, Proove Biosciences offers panels designed to predict good and poor responders to opioid therapies and nonopioid pain therapies—the Proove Opioid Response panel and the Proove Non Opioid Response, respectively. Genetic testing for these panels is conducted by sequencing of target regions with reverse-transcription polymerase chain reaction.
- Pain Medication DNA Insight^{™†} (Pathway Genomics, San Diego, CA) is a panel test intended to identify genetic variants that affect how an individual will respond to the analgesic effects of

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

certain types of pain medications. The results report includes the genotype/SNV for each gene included, along with a description of the toxicity risk, dose required, medication efficacy, or plasma concentration based on genotype results for a range of medications used for pain management, primarily opioids. The testing method is not specified on the company's website.

- Millennium PGT^{SM‡} (Pain Management) (Millennium Health, San Diego, CA) is a genetic panel test intended to help physicians select pain medication. The panel analyzes 11 genes related to pain management; results are provided with a proprietary Millennium Analysis of Patient Phenotype report that provides decision support for medications that may be affected by the patient's genotype.
- Molecular Testing Labs^{TM‡} Pain Management Panel (Molecular Testing Labs, Vancouver, WA) is a panel designed to evaluate the metabolism of pain relievers. The manufacturer's website states that the test evaluates "a number of relevant genes coding for the metabolism of a wide variety of pain relief drugs," but the specific genes tested are not readily described.
- Genelex (Seattle, WA) offers several pharmacogenomic panels, one of which (the YouScript^{®‡} Analgesic Panel) focuses on genes relevant to pain management.
- AltheaDx (San Diego) offers IDgenetix^{®‡} pain tests that analyze the genes and genetic variants involved in the metabolism of opioids, NSAIDs, and other pain drugs as well as variations in pharmacodynamic genes, such as the μ -opioid receptor gene (*OPRM1*).

Other laboratories, including CompanionDx (Houston, TX), ARUP Laboratories (Salt Lake City, UT), and AlBioTech (Richmond, VA), which markets the PersonaGene^{TM‡} Genetic Panel, offer panels of *CYP450* genes. Panels that are restricted to *CYP450* genes are beyond the scope of this evidence review and are discussed in evidence review 2.04.38 (cytochrome p450 testing).

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

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

Gene	Proove Opioid Risk (Proove Biosciences)	Proove Pain Perception (Proove Biosciences)	GeneSightRx Analgesic (AssureRx Health)	Pain Medication DNA Insight (Pathway Genomics)	Millennium PGT (Millennium Health)	YouScript Analgesic (Genelex)
<i>SLC6A4</i> (5-HTT; serotonin transporter)		X				
<i>5HT2A</i> (serotonin receptor)	X	X				
<i>DRD1</i> (dopamine receptor)	X					
<i>DRD2</i> (dopamine receptor)	X					
<i>DRD4</i> (dopamine receptor)	X					
<i>DAT1</i> (dopamine)	X					

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Gene	Proove Opioid Risk (Proove Biosciences)	Proove Pain Perception (Proove Biosciences)	GeneSightRx Analgesic (AssureRx Health)	Pain Medication DNA Insight (Pathway Genomics)	Millennium PGT (Millennium Health)	YouScript Analgesic (Genelex)
transporter)						
DA beta-hydroxylase	X	X				
COMT (catechol O-methyltransferase)	X	X			X	X
MTHFR	X	X		X	X	
GABA	X	X				
OPRK1 (κ-opioid receptor)	X					
OPRM1 (μ-opioid receptor)	X	X	X	X	X	X
VKORC1					X	
UGT2B15					X	
CYP genes						
CYP2D6			X	X	X	X
CYP2C19			X	X	X	
CYP3A4			X		X	X
CYP1A2			X			
CYP2C9			X	X	X	X
CYP2B6				X	X	X
CYP3A5					X	X

CYP: cytochrome; GABA: γ-aminobutyric acid; 5-HHT: hereditary hemorrhagic telangiectasia type 5.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 Proove Narcotic Risk and Pain Perception panel, the GeneSight Analgesic panel, the Pathway Genomics Pain Medication DNA Insight panel, and the Millennium PGT (Pain Management) 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. FDA has chosen not to require any regulatory review of this test.

No FDA-approved genetic tests for pain management were identified.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.

GENETIC TESTING FOR THE MANAGEMENT OF ACUTE AND CHRONIC PAIN

Clinical Context and Test Purpose

The purpose of genetic testing for management of acute and chronic pain is to

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

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for pain management has clinical validity? and (2) Does patient management change in a way that potentially improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

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 4 relevant medication classes: opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, and opioid dependency. Examples of commercially available genetic panels for pain management are listed in Table 3.

Table 3: Commercially Available Genetic Panels for Pain Management

Manufacturer	Panel Name	No. of Genes Tested
Proove Biosciences	Proove Opioid Risk	11
Proove Biosciences	Proove Pain Perception	1
AssureRx Health	GeneSightRx Analgesic	7

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Manufacturer	Panel Name	No. of Genes Tested
Pathway Genomics	Pain Medication DNA Insight	3
Millennium Health	Millennium PGT	14
Genelex	YouScript Analgesic	7
AltheaDx	IDgenetix	9

Comparators

The comparator of interest is standard pain management without genetic testing.

Outcomes

Specific outcomes in each of these categories are listed in Table 4.

Table 4. 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 potential beneficial outcomes of primary interest would be improvement 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 initiation of unnecessary treatment and adverse effects from that treatment or under-treatment.

Timing

Genetic testing may be used for pain management planning before a procedure associated with acute pain or to evaluate an individual with difficulty managing chronic pain.

Setting

Patients with chronic and acute pain are likely to be managed by a wide variety of specialties such as chiropractors, general physicians, physiatrists (rehabilitation physicians) rheumatologists, orthopedic surgeons, oncologist, pain management specialist, physical therapists, and acupuncturists. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Analytic Validity

No published studies were identified that specifically evaluated the analytic validity of the test as performed commercially. No information was identified in the published literature or on manufacturers' websites concerning the genetic testing methods used for analysis. As a result, it is not possible to determine the

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

analytic validity of the testing process. In general, Sanger sequencing or next-generation sequencing methods would be expected to have high analytic validity.

Section Summary: Analytic Validity

No studies were identified that specifically addressed the analytic validity of commercially available tests.

Clinical Validity

Evidence on the clinical validity of genetic testing for pain management primarily consists of genome-wide association studies (GWAS) that correlate specific genetic variants with pain medication requirements or measures of pain control and case-control and cohort studies that report differences in pain medication requirements or measures of pain control for different genotypes. A comprehensive review of the GWAS and case control studies for all of these genes is beyond the scope of this evidence review. However, some of the representative literature, with a focus on studies published within the last 10 years, in this area is discussed next.

Genetic Variants and Analgesic Requirements

A variety of studies have evaluated the association of various genes with pain sensitivity or efficacy of pain medication, either elicited directly from reports of pain or indirectly from analgesic dose requirements. Studies that evaluate the association between SNVs and analgesic dose requirements may provide a more objective outcome measurement of pain control; although this design makes it difficult to separate the effects of genotype on pain sensitivity from those of genotype on pain medication efficacy, these types of studies most directly translate to the clinical use of dose optimization.

Genetic Variants and Analgesic Requirements: Multigene Studies

Several studies have evaluated the association between multiple genes and SNVs and pain control. Klepstad et al (2011) reported results of a large gene association study that evaluated the impact of variability in multiple genes on opioid use among 2294 cancer pain patients. Patients were enrolled from 17 European centers and were considered eligible if they had malignant disease and were using an opioid for moderate or severe pain (step III or higher on the World Health Organization treatment ladder for cancer pain). The authors assessed a large number of SNVs in multiple candidate genes, which had previously been associated with pain control:

- *OPRM1* (μ -opioid receptor gene; 9 SNVs);
- *OPRD1* (δ -opioid receptor gene; 3 SNVs);
- *OPRK1* (κ -opioid receptor gene; 1 SNV);
- *ARRB* (beta-arrestin gene; 7 SNVs);
- *GNAZ* (G nucleotide-binding protein 1 gene; 1 SNV);
- *HIN1* (histidine trinucleotide binding protein 1 gene; 5 SNVs);
- *Stat6* (signal transducer and activator of receptor 6 gene; 3 SNVs);
- *ABCB1* (p-glycoprotein transporter gene; 8 SNVs);
- *COMT* (catechol O-methyltransferase gene; 6 SNVs);

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

- *ADRA21* (alpha 2A adrenergic receptor gene; 3 SNVs);
- *MC1R* (melanocortin 1 receptor gene; 1 SNV);
- *TACR1* (neurokinin 1 receptor gene; 10 SNVs);
- *GCH1* (GTP cyclohydrolase 1 gene; 3 SNVs);
- *DRD2* (dopamine receptor D2 gene; 11 SNVs);
- *DRD3* (dopamine receptor D3 gene; 8 SNVs);
- *HTR3A, -3B, -2A, -3C, -3D, -3E, 1, and 4* genes (serotonin receptors; 36 SNVs);
- *HRH1* (histamine receptor H1 gene; 4 SNVs);
- *CNR1* (cannabinoid receptor 1 gene; 3 SNVs).

Patients' primary opioids were morphine (n=830), oxycodone (n=446), fentanyl (n=699), or other opioids (n=234). Patients were randomized to 2 groups, with two-thirds serving as a development sample and one-third serving as a validation sample. The authors used appropriate measures to control for type I error related to multiple comparisons. Ten SNVs investigated had a minor allele frequency of less than 0.05 and/or were not in Hardy–Weinberg equilibrium and were excluded from further analyses. For the primary outcome of opioid dosage, no SNVs were consistently associated with dosage in both the development and validation samples. The authors note that their study design (cross-sectional evaluation of cancer patients already managed with opioids) did not permit determining the relative genetic influence of pain perception and opioid efficacy.

In another study in the same patient cohort as the Klepstad study, Scarpi et al (2014) reported on genetic differences between patients (total N=2294 patients) with (n=577) and without cancer-induced bone pain (n=1624) and, among patients with cancer-induced bone pain, genetic differences in opioid response. No SNV haplotypes were associated with the presence of cancer-induced bone pain or opioid response after correction for multiple comparisons.

In another relatively large study, Lotsch et al (2009) evaluated the effect of SNVs in multiple candidate genes on pain control among 352 patients treated in outpatient tertiary care centers. The authors assessed the following SNVs:

- *OPRM1* (μ -opioid receptor) 118A>G;
- *COMT* (catechol O-methyltransferase) 472G>A;
- *ABCB1* (p-glycoprotein transporter) 1236C>T, 2677G>T(A), and 3435C>T;
- *MC1R* (melanocortin 1 receptor) 29insA, 451C>T, 478C>T, and 880G>C;
- Nonfunctional *CYP2D6* alleles: *3, *4, * rs735686416, *7, *8, *9;
- Functionally impaired *CYP2D6**41 allele.

Patients were managed with multiple opioids, most commonly oral tilidine (n=81 [15.6%]), oral tramadol (n=81 [15.6%]), and intravenous or subcutaneous morphine (n=74 [14.3%]). Opioid doses were converted to oral morphine equivalents. In linear regression, the *ABCB1* 3435C>T variant was the only factor significantly associated with opioid dose (p=0.004). In linear regression, the *OPRM1* 118A>G variant was

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

the only candidate gene significantly associated with 24-hour pain score ($p=0.041$). No genetic associations were found with opioid-related adverse events, including nausea/vomiting, constipation, fatigue, or laboratory abnormalities.

Blanco et al (2016) reported on the association between SNVs in the *UGT2B7*, *CYP3A4*, and *OPRM1* variants and transdermal buprenorphine pain control in a cohort of 107 patients with critical limb ischemia awaiting revascularization. The *UGT2B7* and *OPRM1* variants were not associated with response to buprenorphine pain control, as measured on a visual analog scale. In contrast, carriers of the *CYP3A4* AA genotype had significantly better pain response ($p=0.003$).

Genetic Variants and Analgesic Requirements: *OPRM1* Genotype

The largest body of research assessing the association between SNVs in a specific gene and pain management appears to be for *OPRM1* genotype, most often for the A118G SNV (rs1799971). While multiple studies have suggested a link between *OPRM1* genotype and dose/intensity of required analgesia, the association is inconsistent across studies. Further, the wide variety of patient population (women in labor, patients undergoing surgery, patients with cancer), genetic variant, and outcome measures (dose, frequency, timing, pain control) used makes it difficult to understand collectively the association between a genetic variant and an analgesic requirement. These studies are summarized in Table 5.

Genetic Variants and Analgesic Requirements: *CYP450* Genotype

A full review of the association between *CYP450* genotypes and medications used for pain is beyond the scope of this review (see evidence review 2.04.38 [cytochrome p450 genotyping]). However, a summary of recent studies focusing on *CYP2D6* metabolism status and pain management, primarily in the use of opioid medications, is outlined next.

CYP450 and Metabolism of Opioids

Jannatto et al (2009) evaluated the association between steady-state concentrations of the opioids methadone, oxycodone, hydrocodone, and tramadol and *CYP2D6* genotype among 61 patients being treated for chronic pain. Most patients (54%) were extensive metabolizers (EM), while 41% were intermediate metabolizers (IM), and 5% were poor metabolizers (PM). No statistically significant associations were seen with *CYP2D6* metabolizer status and opioid steady-state concentration. For *CYP2D6* EMs, 21% had complete pain relief, 58% had partial pain relief, and 21% had no relief, whereas for *CYP2D6* IMs, 20% had complete pain relief, 68% had partial pain relief, and 12% had no pain relief, while all *CYP2D6* PMs had partial pain relief (statistical comparisons not reported).

CYP450 and Metabolism of Tramadol

Lassen et al (2015) reported on results for a systematic review of the pharmacogenetics of tramadol, which included *CYP2D6* and other genes encoding other *CYP450* enzymes and enzymes involved in tramadol metabolism. Reviewers included 54 articles, including 43 cohort and case-control studies, 3 case reports, 6

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

in vitro studies, and 2 animal studies. The review was primarily descriptive, with the conclusion that *CYP2D6* is the major genetic factor in tramadol metabolism, while other genetic factors have a limited associated body of research.

Kirschheiner et al (2008) evaluated the association between *CYP2D6* genotype and tramadol pharmacokinetics and pharmacodynamics among 25 healthy volunteers given tramadol (11 considered ultrarapid metabolizers [UM], 11 EMs, and 5 PMs based on *CYP2D6* genotype). The maximum plasma concentration of tramadol's active metabolite was significantly higher for UM subjects than for EM subjects (mean difference, 14 ng/mL; 95% confidence interval [CI], 2 to 26 ng/mL; $p=0.005$). The mean increase in pain tolerance from baseline to 4 hours after tramadol intake was 1 second, 20 seconds, and 36 seconds in the PM, EM, and UM groups, respectively. UMs demonstrated a stronger miosis after tramadol (maximum decrease in pupillary diameter after tramadol: 1 mm, 1.4 mm, and 2.2 mm for PM, EM, and UM groups, respectively). The authors conclude that UMs were more sensitive to the effects of tramadol.

In an earlier case-control study, Wang et al (2006) reported on an association between *CYP2D6*10 C188T* variants and postoperative tramadol consumption in 71 patients following gastrectomy.

CYP450 and Metabolism of Codeine

Kirschheiner et al (2007) evaluated the association between *CYP2D6* genotype and codeine metabolism among 25 healthy volunteers given a single 30-mg dose of codeine (11 UMs, 11 EMs, and 5 PMs based on *CYP2D6* genotype). The area under the curve (AUC) for plasma concentration of morphine (the active metabolite of codeine) versus time was significantly greater for UMs (16 $\mu\text{g}/\text{h}/\text{L}$ vs 11 $\mu\text{g}/\text{h}/\text{L}$; $p=0.02$). UMs were more likely to report sedation than EMs (91% vs 50%; $p=0.03$).

Baber et al (2015) reported on the genetic variability of pain control in a cohort of 98 women prescribed codeine for pain after a cesarean section. In this study, *CYP2D6* genotype was not associated with postoperative pain score or codeine dose. However, *UGT2B7* and *OPRM1* variants, coding for other enzymes involved in codeine metabolism, were associated with codeine dose requirements. In multivariable analysis, the presence of the *UGT2B7* rs7439366 variant and the *OPRM1* rs1799971 were significantly predictive of mean codeine input (regression coefficient, -0.30 [95% CI, -0.086 to -0.021] and 0.34 [95% CI, 0.032 to 0.10], respectively).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Table 5: Summary of Clinical Validity Studies of *OPRM1* Genotype and Pain Management

Study	SNV	Population	Primary Outcomes	Main Results
Camorcia et al (2012)	<i>OPRM1</i> A118G SNV	57 women undergoing epidural anesthesia for labor	<ul style="list-style-type: none"> ED50 for epidural sufentanil dose (estimated from up-down sequence and probit regression) 	<ul style="list-style-type: none"> Median effective dose of epidural sufentanil in nulliparous women in spontaneous labor lower in women carrying the variant G118 allele of <i>OPRM1</i> Estimated ED50 for <i>OPRM1</i> WT homozygotes (A118) vs heterozygotes and homozygotes carrying G allele (G118): <ul style="list-style-type: none"> A118: ED50, 25.3 µg (95% CI, 23.2 to 26.4 µg) G118: ED50, 20.2 µg (95% CI, 14.2 to 23.6; p=0.033)
Chou et al (2006)	<i>OPRM1</i> A118G SNV	120 patients undergoing total knee arthroplasty treated with morphine PCA who required rescue morphine	<ul style="list-style-type: none"> No. of morphine PCA demands (1st 24 h, 2nd 24 h, 1st 48 h postoperatively) Total morphine dose 	<ul style="list-style-type: none"> No. of morphine demands significantly higher for heterozygotes (GA) and homozygotes (GG) carrying G allele vs WT homozygotes (AA): <ul style="list-style-type: none"> 1st 24 h: morphine demands 36.1 for GG vs 24.3 for AA (p=0.033) and vs 22.2 for AG (p=0.021) 1st 48 h: 57.8 for GG vs 39 for AA (p=0.026) and vs 35.3 for AG (p=0.012) Total morphine dose significantly higher for GA and GG vs AA: <ul style="list-style-type: none"> 1st 24 h: morphine dose 22.3 mg for GG vs 16 mg for AA (p=0.018) and vs 14.8 mg for GA (p=0.010) 1st 48 h: morphine dose 40.5 mg for GG vs 25.3 mg for AA (p=0.003) and vs 25.6 mg for GA (p=0.008)
Fukuda et al (2009)	Multiple <i>OPRM1</i> SNVs	280 patients undergoing mandibular sagittal split ramus osteotomy	<ul style="list-style-type: none"> Pain perception latency Perioperative fentanyl dose Pain intensity on 100-mm VAS at 3 and 24 h postop 	<ul style="list-style-type: none"> For the A118 G SNV (rs1799971): <ul style="list-style-type: none"> No significant differences in perioperative fentanyl dose or pain intensity on VAS at 3 and 34 h postop (WT AA homozygote vs heterozygotes and homozygotes carrying G allele) For IVS3+ A8449G SNV (representing the complete linkage disequilibrium block; rs9384179): <ul style="list-style-type: none"> 24-h postop fentanyl dose higher for AA: 2.5 µg/kg for AA vs 1.55 µg/kg for AG/GG (p<0.01)
Ginosar et al (2013)	<i>OPRM1</i> A118G SNV	125 nulliparous women receiving combined spinal epidural-fentanyl anesthesia for labor	<ul style="list-style-type: none"> Time to first request for additional analgesia Pain intensity at first request for additional analgesia on VAS Intensity of anesthetic-related pruritus on VAS 	<ul style="list-style-type: none"> No difference in time to request for additional analgesia or VAS at request for analgesia for AA homozygotes vs heterozygotes (GA) and homozygotes (GG) carrying G allele: <ul style="list-style-type: none"> Time to analgesia request: 110.1 min for AA vs 108.3 min for GA and GG (p=0.836) VAS (0-100) at analgesia request: 57.6 for AA vs 55.0 for GA and GG (p=0.470) No difference in presence or intensity of pruritus based on genotype

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Ginosar et al (2009)	<i>OPRM1</i> A118G SNV	99 patients receiving alfentanil PCA for extracorporeal shock wave lithotripsy	<ul style="list-style-type: none"> • PCA bolus requests <ul style="list-style-type: none"> • Alfentanil dose • Alfentanil plasma concentration • Verbal analog pain scores 	<ul style="list-style-type: none"> • Compared with WT AA genotype, heterozygotes (GA) and homozygotes (GG) carrying G allele had: <ul style="list-style-type: none"> ○ Higher alfentanil dose over 20 min (75.4 µg/kg vs 51.4 µg/kg, p=0.004) ○ Higher no. of boluses attempted over 25 min (7.2 vs 3.4, p=0.015) <ul style="list-style-type: none"> ○ Higher mean plasma alfentanil concentration (177 ng/mL vs 139 ng/mL, p=0.034) • Higher mean VAS pain score (3.2 vs 2.1, p=0.047)
Hayashida et al (2008)	Multiple <i>OPRM1</i> SNVs	138 patients undergoing major abdominal surgery receiving continuous postop epidural opioid analgesia with rescue systemic opioids and/or NSAIDs	<ul style="list-style-type: none"> • Postop opioid equivalent dose requirement • NRS pain score 	<ul style="list-style-type: none"> • A118G SNV genotype significantly associated with opioid requirement (p=0.009) • None of the SNVs evaluated associated with NRS pain score

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Kim et al (2013)	<i>OPRM1</i> A118G SNV	196 patients undergoing laparoscopic or total abdominal hysterectomy managed postop with intravenous PCA with fentanyl	<ul style="list-style-type: none"> • 48-h cumulative postop fentanyl dose 	<ul style="list-style-type: none"> • <i>OPRM1</i> A118G variant not associated with 48-h fentanyl consumption: <ul style="list-style-type: none"> ○ For A/A homozygotes: mean cumulative fentanyl dose, 1044.9 µg ○ For A/G heterozygotes: mean cumulative fentanyl dose, 1019.8 µg ○ For G/G homozygotes: mean cumulative fentanyl dose, 1013.5 µg
Kolesnikov et al (2011)	<i>OPRM1</i> A118G SNV and <i>COMT</i>	102 patients undergoing lower abdominal surgery managed postop with intravenous PCA with morphine	<ul style="list-style-type: none"> • 48-h cumulative postop morphine dose 	<ul style="list-style-type: none"> • <i>OPRM1</i> A118G and <i>COMT</i>G1947A variants alone not associated with 48-h morphine consumption • Joint <i>OPRM1</i> and <i>COMT</i> variants significantly associated with 48-h morphine consumption: <ul style="list-style-type: none"> ○ For <i>OPRM1</i> G carriers and <i>COMT</i>G carriers: total morphine dose, 51.9 mg ○ For <i>OPRM1</i> WT homozygotes: total morphine dose, 66.2 (p<0.05)
Landau et al (2008)	<i>OPRM1</i> A118G SNV	147 nulliparous women receiving combined spinal-epidural anesthesia with fentanyl for labor	<ul style="list-style-type: none"> • ED50 after fentanyl analgesia (estimated by up-down sequential allocation in 50 subjects and random-dose allocation in 97 subjects) 	<ul style="list-style-type: none"> • <i>OPRM1</i> 304 A/G variant associated with fentanyl dose requirement (median ED50 ratio for 304A homozygosity vs 304A/G heterozygotes and 304 G/G homozygotes): <ul style="list-style-type: none"> ○ For sequential allocation: median ED50 ratio, 1.51 (95% CI, 1.18 to 2.01; p=0.009) ○ For random allocation: median ED50 ratio, 2.14 (95% CI, 1.30 to 5.17; p=0.002)
Zhang et al (2010)	<i>OPRM1</i> A118G SNV	177 women undergoing total abdominal hysterectomy or myomectomy managed postop with intravenous PCA with fentanyl	<ul style="list-style-type: none"> • 24-h mean VAS pain intensity • 24-h fentanyl consumption 	<ul style="list-style-type: none"> • <i>OPRM1</i> A118G variants not associated with initial VAS scores or first 24-h mean VAS scores • <i>OPRM1</i> A118G variants showed significant association with 24-h fentanyl consumption (p<0.05 for linear trend): <ul style="list-style-type: none"> ○ For A/A homozygotes: mean 24-h fentanyl consumption, 363 µg ○ For A/G heterozygotes: mean 24-h fentanyl consumption, 391 µg ○ For G/G homozygotes: mean 24-h fentanyl consumption, 485 µg
Cajanus et al (2014)	<i>OPRM1</i> A118G SNV	1000 women undergoing breast cancer surgery managed with intravenous oxycodone	<ul style="list-style-type: none"> • Oxycodone dose required for adequate postop analgesia 	<ul style="list-style-type: none"> • <i>OPRM1</i> A118G variants associated with oxycodone dose required for the first state of adequate analgesia (regression coefficient, 0.016; p=0.003)
Liu et al (2014)	Multiple <i>OPRM1</i> SNVs	178 women undergoing elective endometrial polypectomy or hysteroscopic cervical canal ring resection managed intraoperatively with remifentanyl	<ul style="list-style-type: none"> • Pain intensity at dilatation and intraoperatively on VAS • Incidence of intra- and postop medication-related complications 	<ul style="list-style-type: none"> • Presence of 2 minor (G) alleles at rs558025 significantly associated with intraoperative remifentanyl requirement • Other <i>OPRM1</i> SNVs evaluated not associated with medication dose or side effects

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

Xu et al (2015)	<i>OPRM1</i> A118G SNV	161 women undergoing elective cesarean delivery managed using PCEA with sufentanil and ropivacaine	• Total PCEA dose over 24 h postop	• No significant differences across <i>OPRM1</i> genotype found in PCEA dose
Bialecka et al (2016)	<i>IL6</i> (rs1800795: -174G>C)	196 individuals undergoing total hip replacement	• Dose, frequency, and timing of opioid requirement	• Presence of the G allele <i>IL6</i> gene (-174G>C) variant found to be an independent factor predisposing to a higher dose and more frequent administration of opioids in the first days after total hip replacement

CI: confidence interval; ED50: median effective dose; NRS: numeric rating scale; NSAIDs: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled anesthesia; PCEA: patient-controlled epidural analgesia; postop: postoperative; SNV: single-nucleotide variant; VAS: visual analog scale; WT: wild-type.

CYP450 and Metabolism of Oxycodone

Zwisler et al (2010) reported the results of a case-control study that found no difference in total oxycodone consumption between *CYP2D6* EMs (14.7 mg) and PMs (13 mg; p=0.42) following surgery (primarily thyroid or hysterectomy) in 270 patients.

CYP450 and Metabolism of Fentanyl

Liao et al (2013) evaluated the association between *CYP3A4* variants and interactions with *OPRM1* A118G variants and postoperative fentanyl requirements among 97 patients undergoing radical gastrectomy. Patients with the *CYP3A4**18B/*18B genotype used less fentanyl via patient-controlled analgesia in the 48 hours after surgery (16.3 µg/kg) compared with patients in the *1/*1 group (22.5 µg/kg; p=0.032). Although *OPRM1* A118G variants were not significantly associated with cumulative fentanyl dose at 24 or 48 hours postsurgery, the joint genotype combination between *CYP3A4* and *OPRM1* was significantly associated with 48-hour cumulative fentanyl dose (p=0.021). VAS scores and frequency of adverse events (nausea, vomiting, dizziness) did not differ significantly across *CYP3A4* groups.

Zhang et al (2011) reported no association between *CYP3A5**3 variants and 24-hour postoperative fentanyl consumption in 203 women following total abdominal hysterectomy or myomectomy.

Genetic Variants and Analgesic Requirements: Other Gene Associations

While the largest body of research related to the clinical validity of genetic testing for pain management appears to be related to *OPRM1* and *CYP450* SNVs, the association between multiple other genes and responses to analgesics has been reported. A summary of studies evaluating the associations between some of these other genes and pain management outcomes are shown in Table 6.

Genetic Variants and Medication-Related Adverse Events

Some studies have evaluated the association between genetic variants and medication-related adverse events, which translate to a clinical use of dose optimization (to avoid an unwanted effect) OR to drug selection (appropriate drug) or avoidance (to identify individuals at high risk of adverse events).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Genetic Variants and Medication-Related Adverse Events: CYP2D6 and Respiratory Depression/Central Nervous System Depression

There has been particular interest in evaluating the role of *CYP2D6* in the metabolism of codeine and other narcotics in children, particularly after tonsillectomy or adenoidectomy, and in nursing mothers after several cases of fatal overdoses. Codeine is metabolized to its active metabolite, morphine, via *CYP2D6* activity. Individuals with higher than average *CYP2D6* activity may have increased morphine formation, leading to higher toxicity risk, whereas those with lower than average *CYP2D6* activity may have reduced morphine formation, leading to insufficient pain relief.

Madadi et al (2009) reported the results of a case-control study evaluating the association between maternal *CYP2D6* variants and respiratory depression among infants of breastfeeding mothers treated with codeine. The study included 72 mother-child pairs whose mothers used codeine while breastfeeding, of which 17 (24%) of breastfed infants were reported to exhibit central nervous system (CNS) depression while their mothers used codeine. CNS depression was by maternal report. Two (11.8%) mothers of symptomatic infants were *CYP2D6* UMs (in combination with a *UGT2B7*2/*2* genotype), compared with 0% of mothers among nonsymptomatic infants. Mothers of symptomatic cases were more likely to have a combined *CYP2D6* UM and *UGT2B7*2/*2* genotype than expected based on the average expected frequency (OR=8.4; 95% CI, 4.7 to 47; p<0.001).

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Table 6: Summary of Clinical Validity Studies of Other Genes and Pain Management

Study	Gene(s)	Population	Primary Outcomes	Main Results
Aoki et al (2010) ³⁷	5HT2A	135 patients after open abdominal surgery, managed with continuous epidural anesthesia with opioids	<ul style="list-style-type: none"> Index of analgesic requirement (expressed as equivalent dose of systemic pentazocine) 5-point NRS pain score 	<ul style="list-style-type: none"> Total rescue analgesic plus antipyretic frequency higher for 102T/T vs T/C genotype (1.34 vs 0.84; p=0.011) For female subjects: <ul style="list-style-type: none"> Total rescue analgesic plus antipyretic frequency higher for 102T/T vs C/C genotype (1.75 vs 0.636; p=0.009) Total rescue analgesic frequency higher for 102T/T vs T/C genotype (1.63 vs 0.533; p=0.003) Total systemic pentazocine equivalent dose higher for 102T/T vs T/C (27.7 vs 9; p=0.016) and vs C/C (27.7 vs 8.18; p=0.044) No significant association between genotype and NRS pain scores
Aoki et al (2013) ³⁸	DRD4	355 patients undergoing mandibular sagittal split ramus osteotomy	<ul style="list-style-type: none"> Intraoperative fentanyl dose and postop PCA fentanyl dose Spontaneous pain intensity on 100-mm VAS 	<ul style="list-style-type: none"> 24-h postop fentanyl use higher with shorter DRD4 VNTR: fentanyl dose 4.09 µg/kg for SHORT/SHORT vs 2.24 µg/kg for any LONG (p=0.0118) 3-h VAS scores did not significantly differ among VNTR groups
Jensen et al (2009) ³⁹	COMT (val[158]met)	43 healthy subjects subjected to thermal pain after short-acting opioid (remifentanyl) administration	<ul style="list-style-type: none"> Pain intensity on VAS after 5 blocks of 30-s heat administration 	<ul style="list-style-type: none"> At all 5 points, presence of met allele associated with higher pain scores: <ul style="list-style-type: none"> For met homozygotes vs val homozygotes: p=0.010 (difference in normalized pain score at time 5 estimated from chart: ≈0.5) For met homozygotes vs val-met heterozygotes: p=0.042 (difference in normalized pain score at time 5 estimated from chart: ≈0.25) Analgesia induced by remifentanyl in all groups without separating different genotype groups (p=0.042)
Rakvag et al (2005) ⁴⁰	COMT	207 cancer patients receiving morphine therapy	<ul style="list-style-type: none"> Daily morphine dose Measure of "average pain" in the prior 24 h using BPI 	<ul style="list-style-type: none"> COMT Val158Met variant associated with morphine requirements (p=0.025): <ul style="list-style-type: none"> For Val/Val genotype (n=44): mean 24-h morphine requirement, 155 mg/24 h For Val/Met genotype (n=96): mean 24-h morphine requirement, 117 mg/24 h For Met/Met genotype (n=67): mean 24-h morphine requirement, 95 mg/24 h Other symptoms, including pain scores and adverse effect symptoms, did not differ significantly across groups
Kim et al (2006) ⁴¹	Multiple genes	221 adults undergoing 3rd molar extraction including at least 1 impacted 3rd molar	<ul style="list-style-type: none"> Pain intensity on VAS before and after ketorolac administration 	

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

Gene	Variant	Study	Findings
<i>COMT</i>			<ul style="list-style-type: none"> • <i>COMT</i>rs740603 showed significant association with maximum postop pain (p=0.039): <ul style="list-style-type: none"> ○ For A/A homozygotes: mean, 52.6 (95% CI, 44.5 to 60.6) ○ For A/G heterozygotes: mean, 62.8 (95% CI, 58.4 to 67.2) ○ For G/G homozygotes: mean, 63.9 (95% CI, 57.5 to 64.5)
<i>SLC6A2</i>			<ul style="list-style-type: none"> • <i>SLC6A2</i>rs40434 showed significant association with analgesia onset time (p=0.011): <ul style="list-style-type: none"> ○ For G/G homozygotes: mean, 20.2 min (95% CI, 9.7 to 30.6 min) ○ For A/G heterozygotes: mean, 9.5 min (95% CI, 7.8 to 11.2 min) ○ For GG homozygotes: mean, 11.3 min (95% CI, 7.3 to 15.3 min)
<i>SLC6A4</i>			<ul style="list-style-type: none"> • <i>SLC6A4</i>rs2066713 showed significant association with onset of postop pain (p=0.025): <ul style="list-style-type: none"> ○ For T/T homozygotes: mean, 145.7 min (95% CI, 124.3 to 167.0 min) ○ For T/C heterozygotes: mean, 124.4 min (95% CI, 115.4 to 133.5 min) ○ For C/C homozygotes: mean, 117.6 min (95% CI, 105.2 to 130.0 min)
Kim et al (2013) ²⁵	Multiple	196 patients undergoing laparoscopic or total abdominal hysterectomy managed postop with intravenous PCA with fentanyl	<ul style="list-style-type: none"> • 48-h cumulative postop fentanyl dose
	<i>OPRM1</i> (A118G)		<ul style="list-style-type: none"> • <i>OPRM1</i> A118G variant not associated with 48-h fentanyl consumption: <ul style="list-style-type: none"> ○ For A/A homozygotes: mean cumulative fentanyl dose, 1044.9 µg ○ For A/G heterozygotes: mean cumulative fentanyl dose, 1019.8 µg ○ For G/G homozygotes: mean cumulative fentanyl dose, 1013.5 µg
	<i>CYP3A4</i>		<ul style="list-style-type: none"> • <i>CYP3A4</i>*18 and *3 variants not significantly associated with 48-h fentanyl consumption
	<i>ABCB1</i>		<ul style="list-style-type: none"> • <i>ABCB1</i> 2667G>A/T and 3435C>T variants not significantly associated with 48-h fentanyl consumption
Kosek et al (2009) ³²	5-HTT	43 healthy subjects subjected to thermal pain after short-acting opioid (remifentanyl) administration	<ul style="list-style-type: none"> • Pain intensity on VAS after 5 blocks of 30-s heat administration • For triallelic 5-HTTLPR: <ul style="list-style-type: none"> ○ At baseline, no differences between mean VAS after painful stimulus between high-, intermediate-, and low-expressing groups ○ After remifentanyl administration, subjects with low 5-HTT expression had better analgesia vs subjects homozygous for 5-HTTLPR LA allele (p<0.02; VAS absolute difference estimated from chart: ~20 mm).

BIS: bispectral index; BPI: Brief Pain Inventory; CI: confidence interval; ED50: median effective dose; 5-HTT: 5-HTT: hereditary hemorrhagic telangiectasia type 5; 5-HTTLPR: serotonin-transporter-linked polymorphic region; NRS: numeric rating scale; PCA: patient-controlled anesthesia; postop: postoperative; SNV: single-nucleotide variant; VAS: visual analog scale; VNTR: varying number of tandem repeats.

Genetic Variants and Medication-Related Adverse Events: *CYP2D6* and Other Adverse Events

The effect of *CYP450* genotype on outcomes other than respiratory depression has also been evaluated. Prows et al (2014) conducted a prospective study to evaluate factors, including *CYP2D6* genotype, associated with codeine-related adverse drug events in children following tonsillectomy. The study enrolled 249 children ages 5 to 19 years scheduled to undergo tonsillectomy. Symptoms were recorded in a symptom diary. Of 134 children given codeine, 106 (79%) reported at least 1 adverse event, most commonly lightheadedness and dizziness in white children and nausea and vomiting in African American children. The presence of a high risk *CYP2D6* gene (EM or IM), compared with a low risk *CYP2D6* gene (IM or PM), was associated with a higher adverse drug reaction risk (p=0.044).

Candiotti et al (2005) evaluated the association between *CYP2D6* gene copy number and the presence of postoperative nausea and vomiting after prophylaxis with the antiemetic ondansetron among 243 women undergoing general anesthesia. Eighty-eight women experienced postoperative nausea and/or vomiting requiring breakthrough medication. Metabolizer status, based on number of functioning *CYP2D6* copy numbers (PM, IM, EM, UM), was significantly associated with vomiting incidence, with vomiting occurring in 5 (45.5%) of 11 UMs, compared with 1 (8.3%) of 12 PMs, 5 (16.7%) of 30 IMs, and 26 (14.7%) of 176 EMs (p=0.007 for UMs vs all other groups). However, nausea was not associated with genotype.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Genetic Variants and Medication-Related Adverse Events: OPRM1 and Fentanyl-Associated Nausea and Vomiting

The association between other genes and analgesic-related adverse events has also been reported. Zhang et al (2011) evaluated the association between the *OPRM1* A118G variant and fentanyl-associated postoperative nausea and vomiting among 165 women undergoing elective total abdominal hysterectomy or myomectomy who received intravenous patient-controlled fentanyl - postoperatively. The study found no statistically significant differences between genotype groups in terms of frequencies or scores of nausea and vomiting. Tsai et al (2010) evaluated the association between the *OPRM1* A118G variant and pruritus related to epidural morphine used as postoperative analgesia among 212 women who received epidural morphine for post-Caesarian section analgesia. Pruritus was evaluated using the Itching Severity Scale (ISS; score range, 0-4), with significant pruritus considered to be an ISS score of 2 to 4. Among the 25 patients with the *OPRM1* GG genotype, 3 (12%) had pruritus with ISS grade 2 to 4, while among the 187 patients with the *OPRM1* AA or AG genotype, 59 (31.6%) had significant pruritus ($p=0.031$). While this suggests that *OPRM1* genotype is associated with morphine-related pruritus, the study did not report morphine dose requirements for the different genotypes, making it difficult to exclude confounding by drug dose.

Genetic Variants and Addiction Risk

A number of studies have reported on the association between various genes and risk of addiction to or abuse of opioid pain medications and nonprescription opioids and other nonprescription substances, with some overlap between the 2 categories. Studies with a focus on genes associated with risk of addiction to or abuse of prescription medications, rather than cocaine, nicotine, or other substances, are outlined next. These studies would translate to a clinical use of *drug selection or avoidance* (to identify individuals in whom opioids should be used with caution). Other studies have evaluated the role of genotype in the efficacy of methadone therapy for a variety of addictions; while there is likely overlap between the genes involved in methadone metabolism and response and those involved in the metabolism and response of other opioids, studies evaluating methadone as a treatment for addiction are not included here.

Genetic Variants and Addiction Risk: OPRM1 and Opioid Dependence

In 2013, Haerian et al published a meta-analysis of studies evaluating the association between the *OPRM1* A118G (rs1799971) variant and opioid dependence. Reviewers included 18 studies overall. There were 13 studies including 9385 subjects ($n=4601$ with opioid dependence, $n=4784$ controls), which reported *OPRM1* genotypes for cases and controls. In pooled analysis of all included studies, the presence of the A allele (vs the G allele) was not significantly associated with heroin dependence risk (pooled odds ratio [OR], 0.95; 95% CI, 0.77 to 1.17). In pooled analysis evaluating the risk of addiction to all opioids (excluding African-American subjects), the presence of the AA or AG genotype (vs the GG genotype) was significantly associated with opioid dependence (pooled OR=0.78; 95% CI, 0.63 to 0.97). Reviewers concluded that *OPRM1* variants may be associated with opioid dependence among Asians.

In 2009, Collier et al published a meta-analysis of case-control studies evaluating the association between the *OPRM1* A118G SNV allelic and genotypic frequencies and opioid dependence. Reviewers included 16

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

case-control studies (including 5169 subjects), which reported *A118G* genotype frequencies, included a group with opioid dependence and a control group, and had genotype samples that were in Hardy-Weinberg equilibrium. Similar to the Haerian meta-analysis, most studies (n=11) included evaluated the association between *A118G* genotype and heroin dependence, with 5 studies reporting on associations with opioids in general. In pooled analysis, no difference in *A118G* SNV genotype frequencies between opioid-dependent and control groups was observed, with a pooled odds ratio of 1.28 (95% CI, 0.77 to 2.11; p=0.34). No difference in *A118G* SNV allelic frequencies between opioid-dependence and control groups was observed, with a pooled odds ratio of 1.16 (95% CI, 0.91 to 1.47; p=0.23).

Other earlier meta-analyses (2006, 2007) of the *OPRM1* *A118G* SNV and substance dependence similarly reported no significant association between *A118G* SNVs and dependence.

Genetic Variants and Addiction Risk: Dopamine Pharmacogenetics and Addiction

In 2015, Patriquin et al reported on results of a systematic review of studies evaluating the role of dopaminergic gene variation in the pharmacotherapy of alcohol, opioid, and cocaine use disorders. The systematic review included a qualitative analysis of 9 studies that evaluated various genes, including *DRD2*, *ANKK1*, *DAT1*, *DBH*, and *DRD4*. Four studies included addressed the treatment of opioid addiction (and/or cocaine addiction in 3 studies), and are most relevant to the scope of this evidence review. One study, evaluating 68 patients in a randomized controlled trial of disulfiram therapy for cocaine or opioid use, reported that the *DRD2* GT/TT genotype was associated with decreases in positive urine samples for cocaine among disulfiram-treated patients (67%-48%), and carriers of at least 1 minor *DRD2* or *ANKK1* allele responded better to disulfiram. In a study of 321 patients treated with methadone for opioid dependence, *DRD2*, *ANKK1*, *ABCB1*, *CYP2B6*, and *OPRM1* genotypes were together associated with methadone dose requirements. The 2 other studies reported associations between dopamine β -hydroxylase level and treatment effects.

Section Summary: Clinical Validity

The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that have evaluated associations among many different genetic variants and drug responses, risk of adverse events, and addiction risk. For genes in currently available panel tests, the largest body of evidence is related to the association between the *OPRM1* *A118G* SNV and analgesic response and addiction risk. Studies evaluating *OPRM1*'s role in analgesic response are generally relatively small cross-sectional studies conducted in the postoperative setting and have reported mixed findings, with some studies showing associations between *OPRM1* genotype and analgesic dose and/or measures of pain intensity, and others showing no significant associations. Results of several meta-analyses have not consistently demonstrated an association between *OPRM1* variants and addiction risk.

For other genes, the body of evidence evaluating associations between variant and analgesic response, adverse events, or addiction risk is small and inconclusive.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

Clinical Utility

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs.

Pharmacogenetic testing for pain management has a potential role for clinical utility in several settings, including drug selection or avoidance or in dose optimization. For drug selection, pharmacogenetic testing could be used to identify individuals not likely to respond to a particular drug, or to identify individuals at high risk of an adverse drug reaction. For dose optimization, pharmacogenetic testing could be used to identify individuals who are likely to be sensitive or resistant to a particular drug, or to estimate dose and dosing frequency.

Gammal et al (2016) reported on the feasibility of implementing a pre-emptive genetic test for *CYP2D6* metabolizer status into their electronic clinical decision support system to guide prescribing of codeine with the goal of preventing its use after tonsillectomy or adenoidectomy and in *CYP2D6* UM and PM (high-risk) genotypes. The authors did not report on any clinical outcomes, and did they report any outcomes pre or post implementation of the clinical decision support system for genetic testing for *CYP2D6*. Results were reported for a subset of 621 patients with sickle cell disease who had a *CYP2D6* genotype result. Of these, 7.1% were UMs or possible UMs, and 1.4% were PMs. None of the patients with an UM or PM genotype were prescribed codeine. The authors acknowledged the need for future studies to demonstrate the impact of their genetic testing algorithm on clinical end points such as adverse effects and pain control.

Senagore et al (2017) reported on results of a prospective cohort study of 50 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery. Prior to surgery, all patients underwent genetic testing using the NeuroIDgenetix pain panel that analyzes 9 genes, including *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A4*, *CYP3A5*, *ABCB1*, *COMT*, and *OPRM1*. Results of the panel were reported along with a list of medications classified as “Use as Directed” or “Use with Caution and/or Increased Monitoring.” Investigators used these results to guide selection of analgesics using a standard 1-to-10 VAS pain score in accordance with the results of genetic panel results. The primary outcome measure was Overall Benefit of Analgesia Score (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. 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 OBASs were significantly lower in patients managed via genotype testing than those given no testing on postoperative day 1 (3.8 vs 5.4; 1.8 vs 2.3) and day 5 (3.0 vs 4.5; 1.2 vs 2.0), all respectively (all $p < 0.05$). Need for narcotic-equivalent analgesics in the genotype tested group was lower in the group of genotype-tested patients (104.5 mg, $SD=122.1$) than in the historical controls (222.1 mg, $SD=221.1$; $p < 0.05$). Although the authors 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. Furthermore, no attempt was made to assess

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

the magnitude of any specific genetic variant combinations on drug efficacy or potency in our study population. This study was funded by the test manufacturer. Thus, multiple methodologic limitations do not permit conclusions from this study.

Chain of Evidence

It is not possible to construct an indirect chain of evidence for clinical utility due to the lack of clinical validity.

Section Summary: Clinical Utility

Because of the lack of established clinical validity, it is not possible to establish the clinical utility of genetic testing for pain management through a chain of evidence. Several studies have reported on a number of genes and responses to antiepileptic drugs or antiepileptic drug adverse events. How this information should be used to tailor medication management is not yet well-defined. Two studies were identified. The first reported on the use of preemptive genetic testing for *CYP2D6* metabolizer status to guide prescribing codeine to pediatric patients but the study did not report on the impact of the genetic testing algorithm on clinical end points such as adverse effects and pain control. The second study reported on the impact of genetic panel testing to guide the selection of analgesics and reported significant improvement in total scores of a composite end point that measures analgesia, patient satisfaction, and the impact of drug-associated side effects compared to a historical control. However, methodologic limitations of that study preclude assessment of the effects on outcomes.

SUMMARY OF EVIDENCE

For individuals who have need for pharmacologic pain management who receive pharmacogenetic testing to target therapy, the evidence includes genome-wide association studies, which correlate specific genetic variants with pain medication requirements or measures of pain control, case-control and cohort studies that report differences in pain medication requirements or measures of pain control for different genotypes, as well as systematic reviews and meta-analysis. Relevant outcomes are test accuracy and validity, other test performance measures, morbid events, health status measures, and medication use. The evidence on the clinical validity of pharmacogenetic testing for pain management is characterized by a large number of studies that have evaluated associations between many different genetic variants and response to analgesic medication, risk of adverse events, and addiction risk. The largest body of evidence assesses the association between the *OPRM1* A118G single-nucleotide variant and analgesic response and addiction risk, which has not consistently demonstrated significant associations. For other genes included in commercially available pain management panel tests, the evidence evaluating associations between variant and analgesic response, adverse events, or addiction risk is small. At present, the clinical utility of pharmacogenetic testing in pain management is poorly defined. Two studies were identified that reported on ways clinical management of pain can be modified based on genetic testing. The first study reported the use of preemptive genetic test for *CYP2D6* metabolizer status to guide prescribing of codeine in pediatric patients but did not report the impact of the genetic testing algorithm on clinical end points such as adverse effects and pain control. The second study reported on the impact of a genetic panel test to guide selection of analgesics and reported significant improvement in total scores of a composite end point that measured analgesia, patient satisfaction, and the impact of drug-associated side effects compared to a historical

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

control. However, methodologic limitations precluded assessment of the effects on outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Pharmacogenetic Testing for Pain Management", 2.04.131, 05:2017.
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. GeneSight. "GeneSight Analgesic". <http://genesight.com/clinicians/genesight-tests/analgesic/>. Accessed October 13, 2015.
4. Biosciences P. Patient FAQ. 2014; https://proove.com/?page_id=1125. Accessed December 15, 2014.
5. Biosciences P. Proove Opioid Response. 2015; <https://proove.com/proove-opioid-response/>. Accessed October 13, 2015.
6. Biosciences P. Proove Non Opioid Response. 2015; <https://proove.com/proove-non-opioid-response/>. Accessed October 13, 2015.
7. Carma Nabavi PG. Personal Communication. 2014.
8. Labs MT. Pain Management Panel. <http://moleculartestinglabs.com/pain-drug-interaction-panel-clinician>. Accessed October 13, 2015.
9. Genelex. Clinically Actionable Pharmacogenetic Tests. n.d.; <http://genelex.com/pharmacogenetic-tests/>. Accessed October 14, 2015.
10. Klepstad P, Fladvad T, Skorpen F, et al. Influence from genetic variability on opioid use for cancer pain: a European genetic association study of 2294 cancer pain patients. *Pain*. May 2011;152(5):1139-1145. PMID 21398039
11. Scarpi E, Calistri D, Klepstad P, et al. Clinical and genetic factors related to cancer-induced bone pain and bone pain relief. *Oncologist*. Dec 2014;19(12):1276-1283. PMID 25342315
12. Lotsch J, von Hentig N, Freynhagen R, et al. Cross-sectional analysis of the influence of currently known pharmacogenetic modulators on opioid therapy in outpatient pain centers. *Pharmacogenet Genomics*. Jun 2009;19(6):429-436. PMID 19514130
13. Blanco F, Muriel C, Labrador J, et al. Influence of UGT2B7, CYP3A4, and OPRM1 Gene Polymorphisms on Transdermal Buprenorphine Pain Control in Patients with Critical Lower Limb Ischemia Awaiting Revascularization. *Pain Pract*. Sep 2016;16(7):842-849. PMID 26407542
14. Jannetto PJ, Bratanow NC. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics*. Jul 2009;10(7):1157-1167. PMID 19604091
15. Lassen D, Damkier P, Brosen K. The pharmacogenetics of tramadol. *Clin Pharmacokinet*. Aug 2015;54(8):825-836. PMID 25910878
16. Kirchheiner J, Keulen JT, Bauer S, et al. Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of tramadol. *J Clin Psychopharmacol*. Feb 2008;28(1):78-83. PMID 18204346
17. Wang G, Zhang H, He F, et al. Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. *Eur J Clin Pharmacol*. Nov 2006;62(11):927-931. PMID 16960721
18. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *Pharmacogenomics J*. Aug 2007;7(4):257-265. PMID 16819548
19. Baber M, Chaudhry S, Kelly L, et al. The pharmacogenetics of codeine pain relief in the postpartum period. *Pharmacogenomics J*. Oct 2015;15(5):430-435. PMID 25752520
20. Camorcia M, Capogna G, Stirparo S, et al. Effect of mu-opioid receptor A118G polymorphism on the ED50 of epidural sufentanil for labor analgesia. *Int J Obstet Anesth*. Jan 2012;21(1):40-44. PMID 22153130
21. Chou WY, Yang LC, Lu HF, et al. Association of mu-opioid receptor gene polymorphism (A118G) with variations in morphine consumption for analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand*. Aug 2006;50(7):787-792. PMID 16879459
22. Fukuda K, Hayashida M, Ide S, et al. Association between OPRM1 gene polymorphisms and fentanyl sensitivity in patients undergoing painful cosmetic surgery. *Pain*. Dec 15 2009;147(1-3):194-201. PMID 19783098
23. Ginosar Y, Birnbach DJ, Shirov TT, et al. Duration of analgesia and pruritus following intrathecal fentanyl for labour analgesia: no significant effect of A118G mu-opioid receptor polymorphism, but a marked effect of ethnically distinct hospital populations. *Br J Anaesth*. Sep 2013;111(3):433-444. PMID 23592691

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

24. Ginosar Y, Davidson EM, Meroz Y, et al. Mu-opioid receptor (A118G) single-nucleotide polymorphism affects alfentanil requirements for extracorporeal shock wave lithotripsy: a pharmacokinetic-pharmacodynamic study. *Br J Anaesth*. Sep 2009;103(3):420-427. PMID 19605407
25. Hayashida M, Nagashima M, Satoh Y, et al. Analgesic requirements after major abdominal surgery are associated with OPRM1 gene polymorphism genotype and haplotype. *Pharmacogenomics*. Nov 2008;9(11):1605-1616. PMID 19018716
26. Kim KM, Kim HS, Lim SH, et al. Effects of genetic polymorphisms of OPRM1, ABCB1, CYP3A4/5 on postoperative fentanyl consumption in Korean gynecologic patients. *Int J Clin Pharmacol Ther*. May 2013;51(5):383-392. PMID 23557865
27. Kolesnikov Y, Gabovits B, Levin A, et al. Combined catechol-O-methyltransferase and mu-opioid receptor gene polymorphisms affect morphine postoperative analgesia and central side effects. *Anesth Analg*. Feb 2011;112(2):448-453. PMID 21127283
28. Landau R, Kern C, Columb MO, et al. Genetic variability of the mu-opioid receptor influences intrathecal fentanyl analgesia requirements in laboring women. *Pain*. Sep 30 2008;139(1):5-14. PMID 18403122
29. Zhang W, Chang YZ, Kan QC, et al. Association of human micro-opioid receptor gene polymorphism A118G with fentanyl analgesia consumption in Chinese gynaecological patients. *Anaesthesia*. Feb 2010;65(2):130-135. PMID 20003118
30. Cajanus K, Kaunisto MA, Tallgren M, et al. How much oxycodone is needed for adequate analgesia after breast cancer surgery: effect of the OPRM1 118A>G polymorphism. *J Pain*. Dec 2014;15(12):1248-1256. PMID 25239082
31. Liu J, Hu D, Jiang Y, et al. Association between single nucleotide polymorphisms in the OPRM1 gene and intraoperative remifentanyl consumption in northern Chinese women. *Pharmacology*. 2014;94(5-6):273-279. PMID 25500932
32. Xu GH, Gao M, Sheng QY, et al. Opioid receptor A118G polymorphism does not affect the consumption of sufentanil and ropivacaine by patient-controlled epidural analgesia after cesarean section. *Ther Drug Monit*. Feb 2015;37(1):53-57. PMID 24977380
33. Bialecka M, Jurewicz A, Machoy-Mokrzynska A, et al. Effect of interleukin 6 -174G>C gene polymorphism on opioid requirements after total hip replacement. *J Anesth*. Aug 2016;30(4):562-567. PMID 27048515
34. Zwisler ST, Enggaard TP, Mikkelsen S, et al. Impact of the CYP2D6 genotype on post-operative intravenous oxycodone analgesia. *Acta Anaesthesiol Scand*. Feb 2010;54(2):232-240. PMID 19719813
35. Liao Q, Chen DJ, Zhang F, et al. Effect of CYP3A4*18B polymorphisms and interactions with OPRM1 A118G on postoperative fentanyl requirements in patients undergoing radical gastrectomy. *Mol Med Rep*. Mar 2013;7(3):901-908. PMID 23313934
36. Zhang W, Yuan JJ, Kan QC, et al. Influence of CYP3A5*3 polymorphism and interaction between CYP3A5*3 and CYP3A4*1G polymorphisms on post-operative fentanyl analgesia in Chinese patients undergoing gynaecological surgery. *Eur J Anaesthesiol*. Apr 2011;28(4):245-250. PMID 21513075
37. Madadi P, Ross CJ, Hayden MR, et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther*. Jan 2009;85(1):31-35. PMID 18719619
38. Aoki J, Hayashida M, Tagami M, et al. Association between 5-hydroxytryptamine 2A receptor gene polymorphism and postoperative analgesic requirements after major abdominal surgery. *Neurosci Lett*. Jul 19 2010;479(1):40-43. PMID 20478362
39. Aoki Y, Nishizawa D, Kasai S, et al. Association between the variable number of tandem repeat polymorphism in the third exon of the dopamine D4 receptor gene and sensitivity to analgesics and pain in patients undergoing painful cosmetic surgery. *Neurosci Lett*. May 10 2013;542:1-4. PMID 23458670
40. Jensen KB, Lonsdorf TB, Schalling M, et al. Increased sensitivity to thermal pain following a single opiate dose is influenced by the COMT val(158)/met polymorphism. *PLoS One*. 2009;4(6):e6016. PMID 19547755
41. Ravvag TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain*. Jul 2005;116(1-2):73-78. PMID 15927391
42. Kim H, Lee H, Rowan J, et al. Genetic polymorphisms in monoamine neurotransmitter systems show only weak association with acute post-surgical pain in humans. *Mol Pain*. 2006;2:24. PMID 16848906
43. Kosek E, Jensen KB, Lonsdorf TB, et al. Genetic variation in the serotonin transporter gene (5-HTTLPR, rs25531) influences the analgesic response to the short acting opioid Remifentanyl in humans. *Mol Pain*. 2009;5:37. PMID 19570226
44. Prows CA, Zhang X, Huth MM, et al. Codeine-related adverse drug reactions in children following tonsillectomy: a prospective study. *Laryngoscope*. May 2014;124(5):1242-1250. PMID 24122716
45. Candiotti KA, Birnbach DJ, Lubarsky DA, et al. The impact of pharmacogenomics on postoperative nausea and vomiting: do CYP2D6 allele copy number and polymorphisms affect the success or failure of ondansetron prophylaxis? *Anesthesiology*. Mar 2005;102(3):543-549. PMID 15731591
46. Zhang W, Yuan JJ, Kan QC, et al. Study of the OPRM1 A118G genetic polymorphism associated with postoperative nausea and vomiting induced by fentanyl intravenous analgesia. *Minerva Anesthesiol*. Jan 2011;77(1):33-39. PMID 21150856

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

47. Tsai FF, Fan SZ, Yang YM, et al. Human opioid mu-receptor A118G polymorphism may protect against central pruritus by epidural morphine for post-cesarean analgesia. *Acta Anaesthesiol Scand*. Nov 2010;54(10):1265-1269. PMID 21039348
48. Haerian BS, Haerian MS. OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis. *Pharmacogenomics*. May 2013;14(7):813-824. PMID 23651028
49. Coller JK, Beardsley J, Bignold J, et al. Lack of association between the A118G polymorphism of the mu opioid receptor gene (OPRM1) and opioid dependence: A meta-analysis. *Pharmacogenomics Pers Med*. 2009;2:9-19. PMID 23226031
50. Glatt SJ, Bousman C, Wang RS, et al. Evaluation of OPRM1 variants in heroin dependence by family-based association testing and meta-analysis. *Drug Alcohol Depend*. Oct 8 2007;90(2-3):159-165. PMID 17416470
51. Arias A, Feinn R, Kranzler HR. Association of an Asn40Asp (A118G) polymorphism in the mu-opioid receptor gene with substance dependence: a meta-analysis. *Drug Alcohol Depend*. Jul 27 2006;83(3):262-268. PMID 16387451
52. Patriquin MA, Bauer IE, Soares JC, et al. Addiction pharmacogenetics: a systematic review of the genetic variation of the dopaminergic system. *Psychiatr Genet*. Oct 2015;25(5):181-193. PMID 26146874
53. Gammal RS, Crews KR, Haidar CE, et al. Pharmacogenetics for safe codeine use in sickle cell disease. *Pediatrics*. Jul 2016;138(1). PMID 27335380
54. 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
55. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype. *Clin Pharmacol Ther*. Feb 2012;91(2):321-326. PMID 22205192
56. 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):376-382. PMID 24458010
57. Franklin GM. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology*. Sep 30 2014;83(14):1277-1284. PMID 25267983
58. Biosciences P. Patient FAQ. 2014; https://proove.com/?page_id=1125. Accessed December 15, 2014.
59. Gammal RS, Crews KR, Haidar CE, et al. Pharmacogenetics for safe codeine use in sickle cell disease. *Pediatrics*. Jul 2016;138(1). PMID 27335380
60. 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

Policy History

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. New policy.
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. No change to coverage.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. No change to coverage. Added policy guidelines.
10/01/2018	Coding update
Next Scheduled Review Date:	07/2019

Coding

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468
 Original Effective Date: 04/20/2015
 Current Effective Date: 07/11/2018

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81225, 81226, 81227, 81291, 81401, 81479 Code deleted 1/1/18: 0015U Code added eff 1/1/18: 0029U, 0031U, 0032U Code added eff 10/1/18: 0078U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

† Indicated trademarks are the registered trademarks of their respective owners.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Pharmacogenetic Testing for Pain Management

Policy # 00468

Original Effective Date: 04/20/2015

Current Effective Date: 07/11/2018

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.