Listing of drugs with their clinical utility, associated polymorphisms and phenotypic effect of the genetic variant[1]

Drug	Clinical Utility	Genes	Phenotypic Effect of the Genetic Variant
Codeine	Management of mild- to moderately-severe pain	**CYP2D6** **UGTB7**	• Poor metabolizers may fail to reach adequate analgesia • Ultrarapid metbolizers may reach high levels of morphine following low to standard dosing leading to increased risk of toxic systemic concentrations of morphine • Loss of function mutation in UGTB7 is associated with decreased metabolism of morphine, resulting in increased risk of toxicity
Tramadol	Management of pain severe enough to require an opioid analgesic and for which alternative nonopioid treatments are inadequate	**CYP2D6**	• Poor metabolizers may fail to reach adequate analgesia • Ultrarapid metbolizers may experience life-threatening serotonin or opioid receptor-mediated adverse events
Hydrocodone	Management of pain severe enough to require daily around-the-clock opioid, long-term treatment and for which alternative treatment options are inadequate	**CYP2D6** **CYP3A4**	• CYP2D6 enzyme demethylates hydrocodone into hydromorphone, which has stronger mu receptor binding activity. Ultrarapid metabolizers may reach higher levels of hydromorphone from conversion of hydrocodone and thus be at higher risk of toxicity • Poor CYP2D6 metabolizers may not reach desired analgesic effect with standard dosing
Oxycodone	Pain management in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain	**CYP3A4** **CYP2D6**	• Patients designated as poor metabolizers have been reported to need more oxycodone to achieve adequate analgesia • Complex phenotypic effects impacted by parent drug's inherent analgesic effect • Weak evidence suggests a higher risk of side effects such as respiratory depression, tiredness, or nausea
Morphine	Management of pain severe enough for which alternative treatments are inadequate that require an opioid analgesic	**ABCB1** **OPRM1**	• Associations between ABCB1 polymorphisms and prolonged recovery room stays and postoperative morphine requirement • GG genotype for OPRM1 associated with increased requirement for postoperative opioids
Diamorphine	Not recommended clinical utility to date	**hCE-1** **hCE-2** **OPRK1** **OPRD1**	• Variation in OPRK1 and OPRD1 may be connected to potential for addiction
Fentanyl	Surgery: adjunct to general or regional anesthesia; preoperative medication; analgesic during anesthesia and in the immediate postoperative period Transdermal device: acute postoperative pain Transdermal patch: management of pain in opioid-tolerant patients Transmucosal: management of breakthrough cancer pain in opioid-tolerant patients	**OPRM1** **ABCB1**	• Variations in median effective dose required to exhibit analgesia among polymorphisms such as ABCB1
Buprenorphine	Use for moderate to severe pain Opioid dependence	**CYP3A4** **OPRD1**	• OPRD1 SNPs such as rs58111 and rs529520 may help predict outcomes of buprenorphine use in treating opioid dependence
NSAIDS	Pain for which an opioid analgesic is not required	**CYP2C9** **PTGS1** **PTGS2**	• Two variants of CYP2C9, CYP2C9*2 and CYP2C9*3, result in decreased inactivation of NSAID, increasing risk for side effects such as GI bleed • Mutations resulting in varying concentrations of PTGS1/2 associated with variable response based on selectivity of NSAID for COX1 or COX2
Ketamine	Induction and maintenance of general anesthesia and procedural sedation/analgesia	**CYP2B6** **CYP3A4** **CYP2C**	• Decreased enzyme binding and reduced drug clearance in polymorphisms have been noted, but clinical significance has yet to be identified
Lidocaine	Local and regional anesthesia by infiltration, nerve block, epideral, or spinal techniques	**SCN9A** **MCR1**	• Reduced efficacy in polymorphisms

[1] Kaye AD, Garcia AJ, Hall OM, et al. Update on the pharmacogenomics of pain management. Pharmgenomics Pers Med. 2019;12:125-143. Published 2019 Jul 3. doi:10.2147.PGPM.S179152

CMS Medical Necessity Guidelines[1,2]

The clinical record must clearly show the use of or intent to prescribe a drug that has known drug-gene interactions that require a PGx test to be ordered to define the safe use of that drug in that patient.

In order for any of the above services to be covered, the patient's medical record must clearly reflect the following:

1. The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary, and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.

2. The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgement, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects), the patient's past medical history and when pertinent family history and the patient's preferences and values.

3. The provider performing the service must have a record of what drug(s) is/are being considered and for what indication(s) to ensure the test performed is reasonable and necessary.

Rxight PGx Gene Table	
ADRA2A(C-1291G)	GRIK4
ANKK1	HTR2C(2565G>C)
COMT(Val158Met)	HTR2C(-759C>T)
CYP2B6	MTHFR (A1298C)
CYP2C19	MTHFR (C677T)
CYP2C8	OPRM1(A118G)
CYP2C9	SLCO1B1
CYP2D6	TPMT
CYP3A5	UGT2B15
DPYD	VKORC1

[1] Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing (L38335)
[2] Other insurance carriers' coverage may vary