PHARMACOGENETIC
TESTING FOR PAIN SPECIALISTS

LabCorp

LabCorp Pharmacogenetic Testing for Common Medications Prescribed by Pain Specialists

The cytochrome P450 (CYP450) enzymes metabolize many drugs. The effects of individual genetic differences in cytochrome P450 activity can range from total absence of metabolism to ultrafast metabolism of certain drugs. This can lead to adverse medication reactions or a lack of therapeutic effect under standard therapy conditions. The metabolism of drugs can also be influenced by a number of other factors such as ethnicity, chronic diseases, organ failure, diet and other drugs. These factors may reduce the predictive utility of pharmacogenetic testing.

Pharmacogenetic testing can assist with customizing drug therapy by providing additional information that may explain patient drug responses due to genetic variability. The key genetic tests used by pain specialists are for the four CYP450 genes: 2D6, 2C19, 3A4, and 3A5.

		LabCorp Test N° (CYP450 genetic test)	511380	511675
Drug Class	**Drug Name**	**Brand Name**	**2D6[1,3,7]**	**2C19[1,6-8]**
Medications associated with chronic pain				
OPIOIDS	buprenorphine	Butrans, Suboxone, Subutex, Zubsolv		
	codeine*	codeine	Metabolized by	
	dihydrocodeine	Synalgos	Metabolized by	
	fentanyl*	Actiq, Duragesic, Sublimaze		
	hydrocodone	Vicodin, Norco, Lortab, Zohydro	Metabolized by	
	methadone	Dolophine, Methadose	Metabolized by (minor)	Metabolized by (minor)
	oxycodone	Percocet, Tylox, OxyContin	Metabolized by	
	tramadol*	Ultram	Metabolized by	
BENZODIAZEPINES	alprazolam	Xanax		
	diazepam	Valium		Metabolized by
	midazolam	Versed		
	triazolam	Halcion		
MUSCLE RELAXANTS	carisoprodol	Soma		Metabolized by
ANTIDEPRESSANTS	amitriptyline*	Elavil	Metabolized by	Metabolized by
	citalopram*	Celexa		Metabolized by
	clomipramine*	Anafranil	Metabolized by & Inhibits	Metabolized by
	desipramine*	Norpramin	Metabolized by	
	doxepin*	Sinequan	Metabolized by	Metabolized by
	duloxetine	Cymbalta	Metabolized by	
	fluoxetine	Prozac	Metabolized by & Inhibits	
	fluvoxamine*	Luvox	Metabolized by	Inhibits
	imipramine*	Tofranil	Metabolized by	Metabolized by
	nortriptyline*	Pamelor, Aventyl	Metabolized by	
	nefazodone	Serzone		
	paroxetine	Paxil	Metabolized by & Inhibits	
	sertraline*	Zoloft	Metabolized by	Metabolized by
	venlafaxine	Effexor	Metabolized by	
Coprescribed medications for patients with chronic pain**				
ANTIPSYCHOTICS	aripiprazole*	Abilify	Metabolized by	
	haloperidol*	Haldol	Metabolized by	
	risperidone	Risperdal	Metabolized by	
	thioridazine	Mellaril	Metabolized by	

**These metabolic activity results may also be relevant when interpreting other coprescribed medications that are not listed.

The table below includes tests offered by LabCorp to evaluate patients for each respective CYP450 gene. Locate the drug class and name for the drug of interest, then select the appropriate LabCorp test number. Common drugs that inhibit or induce enzyme metabolism are also listed in the table. Caution should be used when combining a drug—that inhibits or induces—with drugs that are metabolized by the same CYP450 enzyme. Please note that some drugs may be metabolized by other CYP450 enzymes or additional pathways that are not listed on this table.

Pharmacogenetic outcome studies have been performed for the drugs marked with an asterisk (*).

	504155	
	3A4 & 3A5[1,7,8]	Active Compound[2-9]
	Metabolized by (minor)	Both (3A4)
	Metabolized by	Metabolite (2D6)
	Metabolized by	Both (2D6)
	Metabolized by	Parent (3A4)
	Metabolized by	Both (2D6)
	Metabolized by	Parent (2D6, 2C19, 3A4)
	Metabolized by	Both (2D6, 3A4)
	Metabolized by	Metabolite (2D6)
	Metabolized by	Parent (3A4)
	Metabolized by	Both (2C19, 3A4)
	Metabolized by	Both (3A4)
	Metabolized by	Both (3A4)
	Induces	Both (2C19)
		Parent (2D6), Both (2C19)
	Metabolized by (minor)	Parent (2C19)
	Metabolized by (minor)	Parent (2D6), Both (2C19)
		Parent (2D6)
		Parent (2D6), Both (2C19)
		Both (2D6)
		Parent (2D6)
	Metabolized by (minor)	Parent (2D6), Both (2C19, 3A4)
		Parent (2D6)
	Inhibits (3A5)	
		Parent (2D6)
		Both (2D6, 2C19)
	Metabolized by (minor)	Both (2D6)
	Metabolized by	Both (2D6)
	Metabolized by	Parent (2D6)
	Metabolized by (minor)	Both (2D6)
		Both (2D6)

Active Compound - "**Metabolite**": Refers to drugs that have little or no intrinsic activity and are metabolized to the pharmacologically active compound.
"**Parent**": Refers to drugs that have intrinsic activity and are inactivated when metabolized.
"**Both**": Refers to drugs for which both the parent compound and one or more metabolites have significant pharmacologic activity. The possible effect for either ultrarapid or poor metabolic activity is noted as variable when there is variation between individuals or when publications have conflicting results.

Result Interpretation

Metabolized by: Refers to a drug that is metabolized by the listed CYP450 enzyme. Minor metabolism is noted as (minor) when there are multiple enzymes involved, and the enzyme is known as a minor pathway. Minor pathways are less likely to have significant clinical effect. Patient test results may indicate the following:

- **Ultrarapid metabolizers** (UM) have elevated enzyme activity. For drugs that are active when administered, ultrarapid metabolizers may not reach therapeutic levels due to rapid clearance. For drugs that require activation, ultrarapid metabolizers may be at increased risk for adverse reactions due to higher-than-expected concentrations of active metabolite. The UM type does not occur for CYP3A4 and CYP3A5.
- **Normal (Extensive) metabolizers** (EM) are anticipated to have normal enzyme activity.
- **Intermediate metabolizers** (IM) have reduced enzyme activity, and may experience some, or none of the consequences similar to poor metabolizers.
- **Poor metabolizers** (PM) have significantly reduced or absent enzyme activity. Drugs are metabolized slowly or not at all. For drugs that are active when administered, poor metabolizers may have increased concentrations of active drug with potential for serious side effects. For drugs that require activation, poor metabolizers may have lower than expected concentrations of active metabolite and limited effect of the therapy.

Inhibits: Refers to drugs that inhibit or slow down the metabolism of drugs that utilize a particular enzyme pathway. Drugs indicated are documented as strong inhibitors.

Induces: Refers to drugs that induce or activate the metabolism of drugs that utilize a particular enzyme pathway. Drugs indicated are documented as strong inducers.

Examples of Medication Effects and Dosing Considerations

Active Compound	Patient Metabolic Activity	Possible Effect	Dosing Consideration
Metabolite	Ultrarapid metabolizer	Toxicity	Decrease dose/ alternate drug
	Poor metabolizer	Therapy failure	Alternate drug
Parent	Ultrarapid metabolizer	Therapy failure	Increase dose/ alternate drug
	Poor metabolizer	Toxicity	Decrease dose

Other medications that are known inhibitors or inducers for each CYP450 enzyme

Drug Class	Drug Name	Brand Name	2D6[1]	2C19[1,10]	3A4 & 3A5[1]
ANTIARRHYTHMICS	amiodarone	Cordarone	Inhibits		Inhibits
	quinidine		Inhibits		
ANTICONVULSANTS	carbamazepine	Carbatrol, Tegretol			Induces
	felbamate	Felbatol		Inhibits	Induces
	oxcarbazepine	Trileptal			Induces
	phenytoin	Dilantin		Induces	Induces
	primidone	Mysoline			Induces
	topiramate	Topamax			Induces
ANTIFUNGALS	itraconazole	Sporanox			Inhibits
	fluconazole	Diflucan			Inhibits
	ketoconazole	Nizoral			Inhibits
	miconazole	Monistat			Inhibits
	terbinafine	Lamisil	Inhibits		
	voriconazole	Vfend		Inhibits	
ANTIHISTAMINES	diphenhydramine	Benadryl	Inhibits		
ANTIHYPERTENSIVES	hydralazine	Apresoline			Inhibits
ANTITUBERCULOSIS AGENTS	rifampicin	Rifadin		Induces	Induces
BARBITURATES	phenobarbital	phenobarbital			Induces
CALCIUM CHANNEL BLOCKERS	verapamil	Calan, Isoptin			Inhibits
CORTICOSTEROIDS	dexamethasone	Baycadron			Induces
DIETARY SUPPLEMENTS	grapefruit, sevilla orange				Inhibits
	licorice				Inhibits
	milk thistle				Inhibits
	St. John's Wort				Induces
GLUCOCORTICOIDS	methylprednisolone	Medrol			Inhibits
HIV TREATMENT – COMBINATION DRUGS	efavirenz	Atripla, Sustiva			Induces
HIV TREATMENT – PROTEASE INHIBITORS	atazanavir	Reyataz			Inhibits
	darunavir	Prezista			Inhibits
	fosamprenavir	Lexiva			Inhibits
	indinavir	Crixivan			Inhibits
	nelfinavir	Viracept			Inhibits
	ritonavir	Norvir		Induces	
H_2 BLOCKERS	cimetidine	Tagamet	Inhibits		Inhibits
IMMUNOSUPPRESSANTS	cyclosporine	Sandimmune			Inhibits
MACROLIDE ANTIBIOTICS	clarithromycin	Biaxin			Inhibits
	erythromycin				Inhibits
	roxithromycin				Inhibits
ORAL CONTRACEPTIVES	formulations including ethinyl estradiol			Inhibits	
PROTEIN-TYROSINE KINASE INHIBITOR	imatinib	Gleevec			Inhibits
PROTON-PUMP INHIBITORS	esomeprazole	Nexium		Inhibits	
	lansoprazole	Prevacid		Inhibits	
	omeprazole	Prilosec		Inhibits	
SYMPATHOMIMETICS	diltiazem	Cardizem			Inhibits
TETRACYCLINE ANTIBIOTICS	doxycycline	Vibramycin, Oracea, Doxy 100, Doryx			Inhibits

Which patients to consider for testing

This testing is not suggested for all patients. However, there are several clinical situations among patients in the pain specialist setting when this testing may be appropriate. Examples of these situations include:

- Unexpected or past therapy failure
- Adverse drug events
- Patients requiring higher than recommended doses
- Patients prescribed multiple medications

Testing is needed only once in a patient's lifetime because these genetic test results do not change.

Unexpected or Past Therapy Failure

In situations where patients do not have sufficient pain relief, variations in metabolic activity may explain why the patient's current therapy is failing. For example, if a patient claims insufficient pain relief and is prescribed standard dosing for tramadol, a 2D6 metabolic activity of poor may indicate he/she is not metabolizing sufficient drug and therefore has lower than expected concentrations of active metabolite and limited therapeutic effect. In this case, selecting an alternative drug may be a possible consideration. When considering alternative therapies, the physician may consider alternative drugs that utilize different metabolic pathways (ie, do not select oxycodone for this patient with poor 2D6 metabolic activity).[11]

Adverse Drug Events

In situations where patients are experiencing adverse drug events, variations in metabolic activity may explain why the individual patient may be experiencing these side effects. For example, if a patient is prescribed standard dosing for tramadol and claims to be experiencing symptoms (eg, nausea, vomiting, constipation, respiratory depression), a 2D6 metabolic activity of ultrarapid may indicate that the symptoms may be caused by faster than normal metabolic activity that is leading to higher than expected concentrations of active metabolite. In this case, the physician may consider decreasing the dose, or selecting an alternative drug may be a possible consideration.[11]

Patients Requiring Higher Than Recommended Doses

When patients do not experience sufficient relief using standard recommended dosing, the possibility of non-compliance or diversion may be considered. There may be some situations (such as drug allergies or use of concomitant medications with drug interactions) where selecting an alternative drug may not be an option. In these cases, one of the few available options may be to increase the dose above the standard recommended dosing. Understanding the patient's metabolic activity may provide support for prescribing higher doses to achieve sufficient relief and to assess that patient is indeed compliant with his/her dosing regimen. For example, if a patient is prescribed standard dosing for tramadol and claims to have insufficient pain relief, a 2D6 metabolic activity of intermediate may confirm that insufficient pain relief is likely caused by slower than expected drug metabolism,[11] and, as appropriate to the specific patient, decrease suspicion that the patient may be diverting a portion of the prescribed medication.

Patients Prescribed Multiple Medications

Chronic-pain conditions are commonly treated with prescription pain medications such as opioids. In addition, there are often other medications coprescribed as part of the treatment regimen. Many of these coprescribed medications are an integral part of the treatment regimen, but may introduce complexities with respect to potential drug interactions and drug metabolism. In addition, many of these medications are metabolized through different pathways. In some individual situations, a complete report that lists the relevant metabolic pathways may assist in providing a more complete picture of the medication metabolism and potential alternatives, especially when patients experience the situations listed above. Some common prescribed medications for chronic-pain patients may include:

- **Opioids** – metabolized mainly through 2D6, 3A4, and 3A5
- **Benzodiazepines** – metabolized mainly through 2C19, 3A4, and 3A5
- **Muscle relaxants** – carisoprodol/meprobamate, metabolized mainly through 2C19
- **Antidepressants** – metabolized mainly through 2D6, 2C19, 3A4, and 3A5, with some antidepressants inhibiting these pathways
- **Antipsychotics** – metabolized mainly through 2D6, 3A4, and 3A5

* All decisions of next steps and testing considerations should be based on the clinical information and specifics of the individual patient.

Test Ordering Information

LabCorp Test N°	Test Name	Specimen Requirements
511380	Opioid CYP2D6 Genotyping	7 mL whole blood or LabCorp buccal swab kit; **Minimum:** 3 mL whole blood or 2 buccal swabs
511675	Cytochrome P450 2C19 Genotyping	7 mL whole blood or LabCorp buccal swab kit; **Minimum:** 3 mL whole blood or 2 buccal swabs
504155	Cytochrome P450 3A4/3A5 Genotyping	7 mL whole blood or LabCorp buccal swab kit; **Minimum:** 3 mL whole blood or 2 buccal swabs
511905	Cytochrome P450 2D6/2C19 Genotyping	7 mL whole blood or LabCorp buccal swab kit; **Minimum:** 3 mL whole blood or 2 buccal swabs

Example of Acceptable Collection Tubes for Whole Blood Specimens

1 lavender top (EDTA) whole blood tube, OR

1 yellow top (ACD) whole blood tube

Example of Acceptable Collection Device for Buccal Cell Specimens

LabCorp's Buccal Swab Kit (peoplesoft # 3177)

Buccal Swab Collection Instructions for Molecular Genetic Testing

1. Before collection of the sample, print the patient's name, sample collection date, and the name and telephone number of the physician in the patient information section on the front of this card.
2. Print the patient's name and sample collection date on each of the enclosed adhesive labels.
3. Remove the swabs from the sterile package. Do not touch the swabs to any surface prior to collection.
4. Swabs must be collected one at a time. You will use one swab per cheek quadrant (A-D), as shown in the diagram on the kit.
5. Before you collect each swab, have the patient swallow. This is not a saliva test. Do not have the patient suck on the swab.
6. Swab the inside of the cheek up and down several times in the first quadrant as shown in the diagram. Use an amount of pressure similar to brushing your teeth.
7. Gently wave the swab in the air for one minute to help the drying process.
8. Place a label around the swab at the end opposite the cotton tip.
9. Place swab in foam holder as indicated below.
10. Continue steps 5-9 for the remaining 3 swabs, collecting one from each quadrant of the mouth.
11. Upon completion, close the swab kit, place it inside the mailing envelope, and seal. Provide to LabCorp with a completed LabCorp test request form.

Resources
1. Samer CF, Lorenzini KI, Rollason V, et al. Applications of CYP450 testing in the clinical setting. *Mole Diagn Ther.* 2013;17(3):165-184. PubMed 23588782
2. Baselt, RC. *Disposition of Toxic Drugs and Chemicals in Man.* 10th ed. Seal Beach, CA: Biomedical Publications; 2014: 212-215, 812-815, 1253-1254, 1413-1415, 1705-1707.
3. 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.* 2014;95(4):376-382. PubMed 24458010
4. Vuilleumier PH, Stamer UM, Landau R. Pharmacogenomic considerations in opioid analgesia. *Pharmgenomics Per Med.* 2012;5:73-87. *Erratum in Pharmgenomics Pers Med.* 2013;6:1. PubMed 23226064
5. Barratt DT, Bandak B, Klepstad P, et al. Genetic, pathological and physiological determinants of transdermal fentanyl pharmacokinetics in 620 cancer patients of the EPOS study. *Pharmacogenetics Genomics.* 2014;24(4):185-194. PubMed 24469018
6. Bramness JG, Skurtveit S, Fauske L, et al. Association between blood carisoprodol:Meprobamate concentration ratios and CYP2C19 genotype in carisoprodol-drugged drivers: decreased metabolic capacity in heterozygous CYP2C19*1/CYP2C19*2 subjects? *Pharmacogenetics.* 2003;13(7):383-388. PubMed 12835613
7. Hicks JK, Swen JJ, Thorn CF, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013 May;93(5):402-408. PubMed 23486447
8. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015 Aug;98(2):127-134. PubMed 2594703
9. Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part II. *Clin Pharmacokinet.* 2009;48(12):761-804. PubMed 25801146
10. Mwinyi J, Cavaco I, Pederson RS, et al. Regulation of CYP2C19 expression by estrogen receptor a: implications for estrogen-dependent inhibition of drug metabolism. *Mol Pharmacol.* 2010;78(5):886-894. PubMed 20675569
11. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: From Bench to Byte – An Update of Guidelines. *Clin Pharmacol Ther.* 2011;89(5):662-673. PubMed 21412232

Additional Resources
Birdwell KA, Decker B, Barbarina JM, et al. Clinical pharmacogenetics implementation consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing. *Clin Pharmacol Ther.* 2015 Jul;98(1):19-24. PubMed 25801146

Elens L, Becker ML, Haufroid V. Novel CYP3A4 intron 6 single nucleotide polymorphism is associated with simvastatin-mediated cholesterol reduction in the Rotterdam Study. *Pharmacogenetics Genomics*. 2011;21:861-866. PubMed 21946898

Deupree JD, Montgomery MD, Bylund DB. Pharmacological properties of the active metabolites of the antidepressants desipramine and citalopram. *Eur J Pharmacol.* 2007;576(1)-3):55-60. PubMed 17850785

Kalgutkar AS, Vaz AD, Lame ME, et al. Bioactivation of the nontricyclic antidepressant nefazodone to a reactive quinone-imine species in human liver microsomes and recombinant cytochrome P450 3A4. *Drug Metab Dispos*. 2005;33(5):243-253. PubMed 15523046

Trescot AM, Faynboym MD. A review of the role of genetic testing in pain medicine. *Pain Physician.* 2014;17:425-445. PubMed 25247900

www.LabCorp.com