

# **MODULE 4: Where to get testing done and how to interpret the results?**

# Selecting a lab and test

- **Where to find a CLIA-certified testing lab**
  - **PharmGKB and GTR**
- Testing method and limitations
  - Single gene vs gene panel
  - Targeted analysis vs mutation screening
  - Deletion/duplication analysis

# PharmGKB

- Manually curated pharmacogenomics knowledge base including information from drug label, clinical testing labs and dosing guidelines (<http://www.pharmgkb.org>)

HOME | PUBLICATIONS | FEEDBACK | SIGN IN |  Search

**PharmGKB**  
The Pharmacogenomics Knowledgebase

**Pharmacogenomics. Knowledge. Implementation.**  
PharmGKB is a comprehensive resource that curates knowledge about the impact of genetic variation on drug response for clinicians and researchers.

About Us ▾ News & Events Projects Search ▾ Download Help

Search PharmGKB:  Search

**What is the PharmGKB?**  
*Find out how we go from extraction of gene-drug relationships in the literature to implementation of pharmacogenomics in the clinic...*

Find out more

- Improved drug label annotations
- CPIC Peginterferon alpha/IFNL3
- Tamoxifen Consortium Publication
- New EGFR VIP
- PharmGKB Knowledge Pyramid

# PharmGKB — genetic tests



HOME | PUBLICATIONS | FEEDBACK | SIGN IN |  Search

About Us ▾ News & Events Projects Search ▾ Download Help

GENE:  
**CYP2D6**  
cytochrome P450, family 2, subfamily D, polypeptide 6

Clinical PGx PGx Research Overview VIP Haplotypes Pathways Is Related To Publications Downloads/LinkOuts

Dosing Guidelines (33) Drug Labels (44) Clinical Annotations (47) Genetic Tests (11)

This is a **non-comprehensive list** of genetic tests with pharmacogenetics relevance, typically submitted by the manufacturer and manually curated by PharmGKB. The information listed is provided for educational purposes only and **does not** constitute an endorsement of any listed test or manufacturer.

A more complete listing of genetic tests is found at the [Genetic Testing Registry \(GTR\)](#).

PGx Test	Variants Assayed	Related Drugs?
<a href="#">Roche AmpliChip CYP450 Test</a>	<a href="#">CYP2D6*1</a> , <a href="#">CYP2D6*10A</a> , <a href="#">CYP2D6*10B</a> , <a href="#">CYP2D6*11</a> , <a href="#">CYP2D6*15</a> , <a href="#">CYP2D6*17</a> , <a href="#">CYP2D6*19</a> , <a href="#">CYP2D6*20</a> , <a href="#">CYP2D6*29</a> , <a href="#">CYP2D6*2A</a> , <a href="#">CYP2D6*2B</a> , <a href="#">CYP2D6*2D</a> , <a href="#">CYP2D6*3</a> , <a href="#">CYP2D6*40</a> , <a href="#">CYP2D6*41</a> , <a href="#">CYP2D6*4A</a> , <a href="#">CYP2D6*4B</a> , <a href="#">CYP2D6*4D</a> , <a href="#">CYP2D6*4J</a> , <a href="#">CYP2D6*4K</a> , <a href="#">CYP2D6*5</a> , <a href="#">CYP2D6*6A</a> , <a href="#">CYP2D6*6B</a> , <a href="#">CYP2D6*6C</a> , <a href="#">CYP2D6*7</a> , <a href="#">CYP2D6*8</a> , <a href="#">CYP2D6*9</a> , <a href="#">CYP2D6*1XN</a> , <a href="#">CYP2D6*2XN</a> , <a href="#">CYP2D6*4XN</a> , <a href="#">CYP2D6*10XN</a> , <a href="#">CYP2D6*17XN</a> , <a href="#">CYP2D6*35XN</a> , <a href="#">CYP2D6*41XN</a> , *35, *36	<a href="#">amitriptyline</a> <a href="#">clomipramine</a> <a href="#">clopidogrel</a> <a href="#">codeine</a> <a href="#">desipramine</a> <a href="#">doxepin</a> <a href="#">esomeprazole</a> <a href="#">fluoxetine</a> <a href="#">imipramine</a> <a href="#">metoprolol</a> <a href="#">nortriptyline</a> <a href="#">omeprazole</a> <a href="#">paroxetine</a> <a href="#">phenytoin</a> <a href="#">risperidone</a> <a href="#">tamoxifen</a> <a href="#">trimipramine</a>
<a href="#">DMET Plus (Affymetrix, Inc)</a>	Variant in CYP2D6	<a href="#">amitriptyline</a> <a href="#">azathioprine</a> <a href="#">clomipramine</a>

Lists testing labs and test manufacturers

GTR

# Genetic Testing Registry (GTR)



GTR: GENETIC TESTING REGISTRY

Search for CYP2D6 gene tests

Can filter on different aspects

[GTR Home](#) > Tests > Search results - CYP2D6

**Apply filters**

▼ **Condition/Phenotype**

Showing tests for all 10 conditions

Enter text to filter the conditions

Select a condition

- Disorder due cytochrome p450 CYP2D6 variant (14)
- CYP2C19-related poor drug metabolism (6)
- Tamoxifen response (1)
- Methylphenidate response (1)
- Major depressive disorder (1)

Compare labs

▶ **Test type**

▶ **Test purpose**

▶ **Test method**

▼ **Test services**

Carrier testing (2)

▶ **Lab certification**

▼ **Lab location**

United States (14) [Hide states](#)

- California (4)
- Kentucky (1)
- Ohio (2)
- Utah (1)
- Virginia (6)
- Spain (1)

# Many different vendors

## **C** GeneSight Psychotropic

**Lab:** AssureRx Health, Inc. Mason, Ohio, United States

Conditions

Major depressive disorder

Depression

Major depressive disorder 1

Total conditions (4)

Test targets

CYP1A2

CYP2B6

CYP2C19

Total targets (8)

Private companies

## **C** Cytochrome P450, 2D6

**Lab:** Molecular Genetics Laboratory ARUP Laboratories Salt Lake City, Utah, Unit

Conditions

Disorder due cytochrome p450 CYP2D6 variant

Methylphenidate response

Tamoxifen response

Test targets

CYP2D6

Commercial labs  
(ARUP, Quest,  
LabCorp)

## **C** Genetic Pharmacology Testing

**Lab:** Molecular Genetics Laboratory Cincinnati Children's Hospital Medical Center

Conditions

Disorder due cytochrome p450 CYP2D6 variant

Disorder due cytochrome p450 CYP2C19 variant

Disorder due cytochrome p450 CYP2C9 variant

Test targets

CYP2C19

CYP2C9

CYP2D6

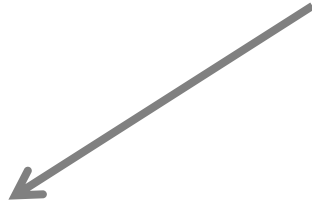
Hospital/academic  
labs



# Clinical versus Research test

GTR: GENETIC TESTING REGISTRY

Run in a CLIA-certified lab



**C** Clinical test, **R** Research test

---

Showing 1 to 14 of 14 tests for 1 condition in 6 labs

**C** Cytochrome P450, 2D6

# Selecting a lab and test

- Where to find a CLIA-certified testing lab
  - PharmGKB and GTR
- **Testing method and limitations**
  - **Single gene vs gene panel**
  - **Targeted analysis vs mutation screening**
  - **Deletion/duplication analysis**



# GTR results for CYP2D6

**C** Clinical test, **R** Research test

Showing 1 to 3 of 3 tests for 7 conditions in 3 labs

**C** [Toxicity to drugs: CYP2D6 gene \(alleles \\*3, \\*4 and \\*6\) screening](#)

**Lab:** [GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases](#) Malaga, Andalucia, Spain

Conditions  
[Disorder due cytochrome p450 CYP2D6 variant](#)

Test targets  
[CYP2D6](#)

Methods  
**E** Sequence analysis of select exons

**C** [Genetic Pharmacology Testing](#)

**Lab:** [Molecular Genetics Laboratory Cincinnati Children's Hospital Medical Center](#) Cincinnati, Ohio, United States

Conditions  
[Disorder due cytochrome p450 CYP2D6 variant](#)  
[Disorder due cytochrome p450 CYP2C19 variant](#)  
[Disorder due cytochrome p450 CYP2C9 variant](#)

Test targets  
[CYP2C19](#)  
[CYP2C9](#)  
[CYP2D6](#)

Methods  
**T** Targeted variant analysis

**C** [GeneSight Psychotropic](#)

**Lab:** [AssureRx Health, Inc.](#) Mason, Ohio, United States

Conditions  
[Major depressive disorder](#)  
[Depression](#)  
[Major depressive disorder 1](#)

Test targets  
[CYP1A2](#)  
[CYP2B6](#)  
[CYP2C19](#)

Methods  
**D** Deletion/duplication analysis  
**T** Targeted variant analysis

Total conditions (4)

Total targets (8)

Single gene  
vs gene  
panel

Targeted vs  
mutation  
screening

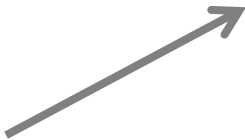
Other  
methods?

# Recognize limitations of tests


- Known, common alleles (functional or not)
- Known rare alleles

CYP2D6	African	Caucasian	East Asian
*1	39%	54%	34%
*2	20%	27%	13%
*4	3%	19%	<1%
*5	6%	3%	6%
*10	7%	3%	42%
*17	20%	18%	<1%
*41	11%	9%	2%
*3	<1%	<1%	<1%
*6	3%	<1%	<1%
*7	<1%	<1%	<1%
*8	<1%	<1%	<1%
*9	<1%	2%	<1%
*14	<1%	<1%	<1%
*36	<1%	<1%	2%
Duplications	5%	4%	<1%

Some only test for most common alleles



Some assay may not be able to detect duplications



# Table 1: Summary of *CYP2D6* variants and alleles detected by three commercial platforms

From

## Laboratory testing of *CYP2D6* alleles in relation to tamoxifen therapy

Elaine Lyon PhD, FACMG, Julie Gastier Foster PhD, FACMG, Glenn E. Palomaki PhD, Victoria M. Pratt PhD, FACMG, Kristen Reynolds PhD, M. Fernanda Sábato MS, Stuart A. Scott PhD, FACMG & Patrik Vitazka MD, PhD ; A working group of the Molecular Genetics Subcommittee on behalf of the American College of Medical Genetics and Genomics (ACMG) Laboratory Quality Assurance Committee  
*Genetics in Medicine* (2012) 14, 990–1000 | doi:10.1038/gim.2012.108

Allele	Protein effect	Luminex xTag V3	Roche Amplichip	Autogenomics INFINITI
*1	F	Presumed	Presumed	Presumed
*2	F	<b>-1584G</b> , 1661G>C, <b>2850C&gt;T</b> , 4180G>C	<b>-1584G</b> , 1039C>T, 1661G>C, <b>2850C&gt;T</b> , <b>4180G&gt;C</b>	<b>2850C&gt;T</b>
*3	NF	<b>2549delA</b>	<b>2549delA</b>	<b>2549delA</b>
*4	NF	100C>T, 1661G>C, <b>1846G&gt;A</b> , 4180G>C	100C>T, 1039C>T, 1661G>C, <b>1846G&gt;A</b> , 2850C>T, 4180G>C	<b>1846G&gt;A</b>
*5	NF	Deletion	Deletion	Deletion
*6	NF	<b>1707delT</b>	<b>1707delT</b> , 1976G>A, 4180G>C	<b>1707delT</b>
*7	NF	<b>2935A&gt;C</b>	<b>2935A&gt;C</b>	<b>2935A&gt;C</b>
*8	NF	1661G>C, <b>1758G&gt;T</b> , 2850C>T, 4180G>C	1661G>C, <b>1758G&gt;T</b> , 2850C>T, 4180G>C	<b>1758G&gt;T</b>
*9	DF	<b>2613-2615delAGA</b>	<b>2613-2615delAGA</b>	<b>2615_7delAAG</b>
*10	DF	<b>100C&gt;T</b> , 1661G>C, 4180G>C	<b>100C&gt;T</b> , 1039C>T, 1661G>C, 4180G>C	<b>100C&gt;T</b>
*11	NF	<b>883G&gt;C</b> , 1661G>C, 2850C>T, 4180G>C	<b>883G&gt;C</b> , 1661G>C, 2850C>T, 4180G>C	Not tested
*12	NF	<b>124G&gt;A</b> , 1661G>C, 2850C>T, 4180G>C	Not tested	<b>124G&gt;A</b>
*14	NF	<b>1758G&gt;A</b> , 2850C>T, 4180G>C	Not tested	<b>1758G&gt;A</b>
*15	NF	<b>138insT</b>	<b>138insT</b>	Not tested
*17	DF	<b>1023C&gt;T</b> , 1661G>C, 2850C>T, 4180G>C	<b>1023C&gt;T</b> , 1661G>C, 2850C>T, 4180G>C	1023C>T
*19	NF	Not tested	1661G>C, 2539- <b>2542delAACT</b> , 2850C>T, 4180G>C	Not tested
*20	NF	Not tested	1661G>C, <b>1973insG</b> , 1978C>T, 1979T>C, 2850C>T, 4180G>C	Not tested
*29	DF	<b>1659G&gt;A</b> , 1661G>C, 2850C>T, <b>3183G&gt;A</b> , 4180G>C	<b>1659G&gt;A</b> , 1661G>C, 2850C>T, <b>3183G&gt;A</b> , 4180G>C	1659G>A
*35	F	-1584C, <b>31G&gt;A</b> , 1661G>C, 2850C>T, 4180G>C	-1584C, <b>31G&gt;A</b> , 1661G>C, 2850C>T, 4180G>C	Not tested
*36	NF	Not tested	100C>T, 1039C>T, 1661G>C, 4180G>C, gene conversion to <i>CYP2D7</i> in exon 9	Not tested
*40	NF	Not tested	<b>1023C&gt;T</b> , 1661G>C, <b>1863ins(TTT CGC CCC)2</b> , 2850C>T, 4180G>C	Not tested
*41	DF	1661G>C, 2850C>T, <b>2988G&gt;A</b> , 4180G>C	<b>-1584C</b> , 1661G>C, <b>2850C&gt;T</b> , <b>4180G&gt;C</b>	2988G>A
Duplication	IF			

Nucleotide changes in bold define the allele.

DF, decreased function; F, functional; IF, increased function; NF, nonfunctional.

- Missing rare alleles
- Missing gene duplications
- Potential for misclassification

# Interpreting test results

- CPIC
- PharmGKB dosing guidelines

- Clinical Pharmacogenomics Implementation Consortium
- Purpose: to provide actionable prescribing decisions when genotype is already available in the clinical environment.
- Focus on HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered.

## Eleven non-cancer (tumor-based)\* PGx reviews available

clopidogrel

interferon-alpha

Allopurinol

warfarin

simvastatin

5-fu, capecetabine

thiopurines

codeine

TCA's

abacavir

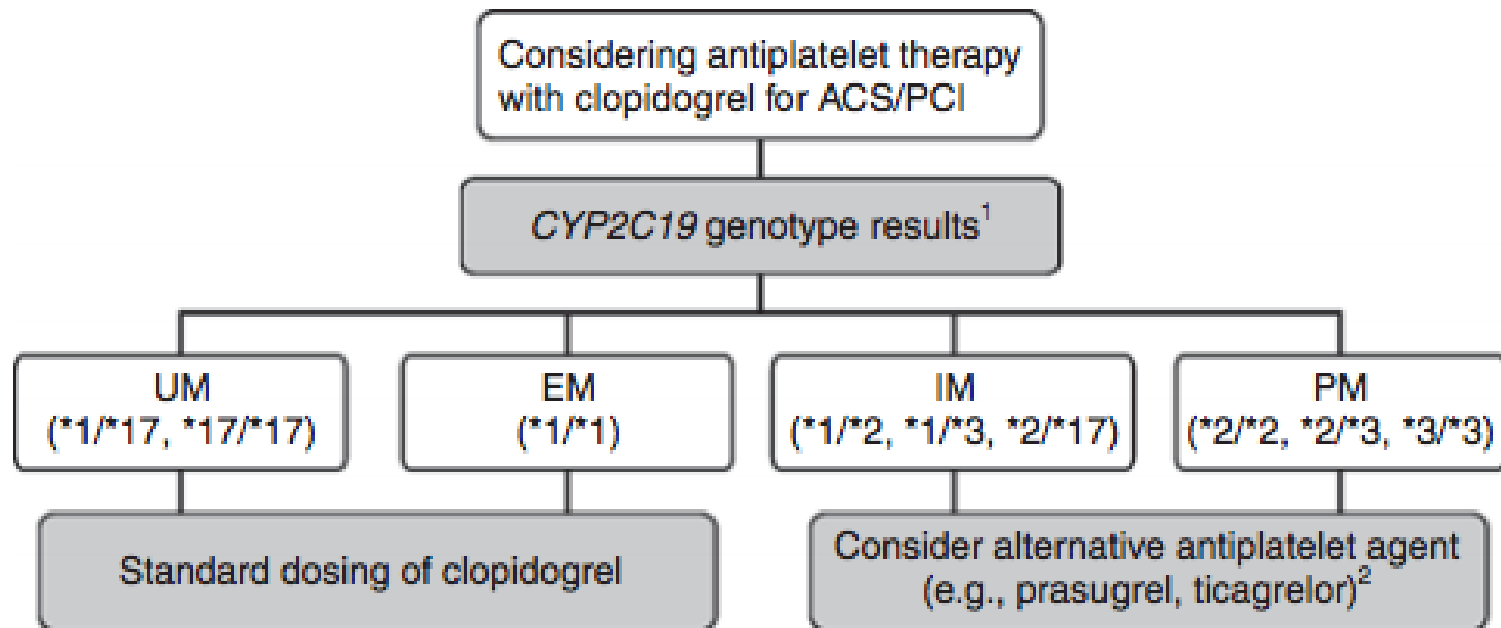
carbamazepine

**CPIC: Implementing PGx**

a **PharmGKB** & PGRN collaboration

# Example CPIC guideline

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 94 NUMBER 3 | SEPTEMBER 2013



**Figure 1** Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients

# PharmGKB – dosing/action guideline

Dosing Guidelines (6)

Drug Labels (4)

Clinical Annotations (8)

Genetic Tests (3)

## CPIC Dosing Guideline for azathioprine and TPMT

last updated 01/17/2013

### Summary

Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30-70% of target dose for patients with intermediate enzyme activity.

#### Look up your guideline

Pick TPMT alleles:

#### *Phenotype (Genotype)*

Heterozygote or intermediate activity (one functional allele - \*1, plus one nonfunctional allele - \*2, \*3A, \*3B, \*3C, or \*4)

#### *Implications*

Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP

#### *Recommendations (Strength: Strong)*

If disease treatment normally starts at the "full dose", consider starting at 30-70% of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment.

Individual testing laboratories should also provide test interpretation and treatment guidance



**The End**