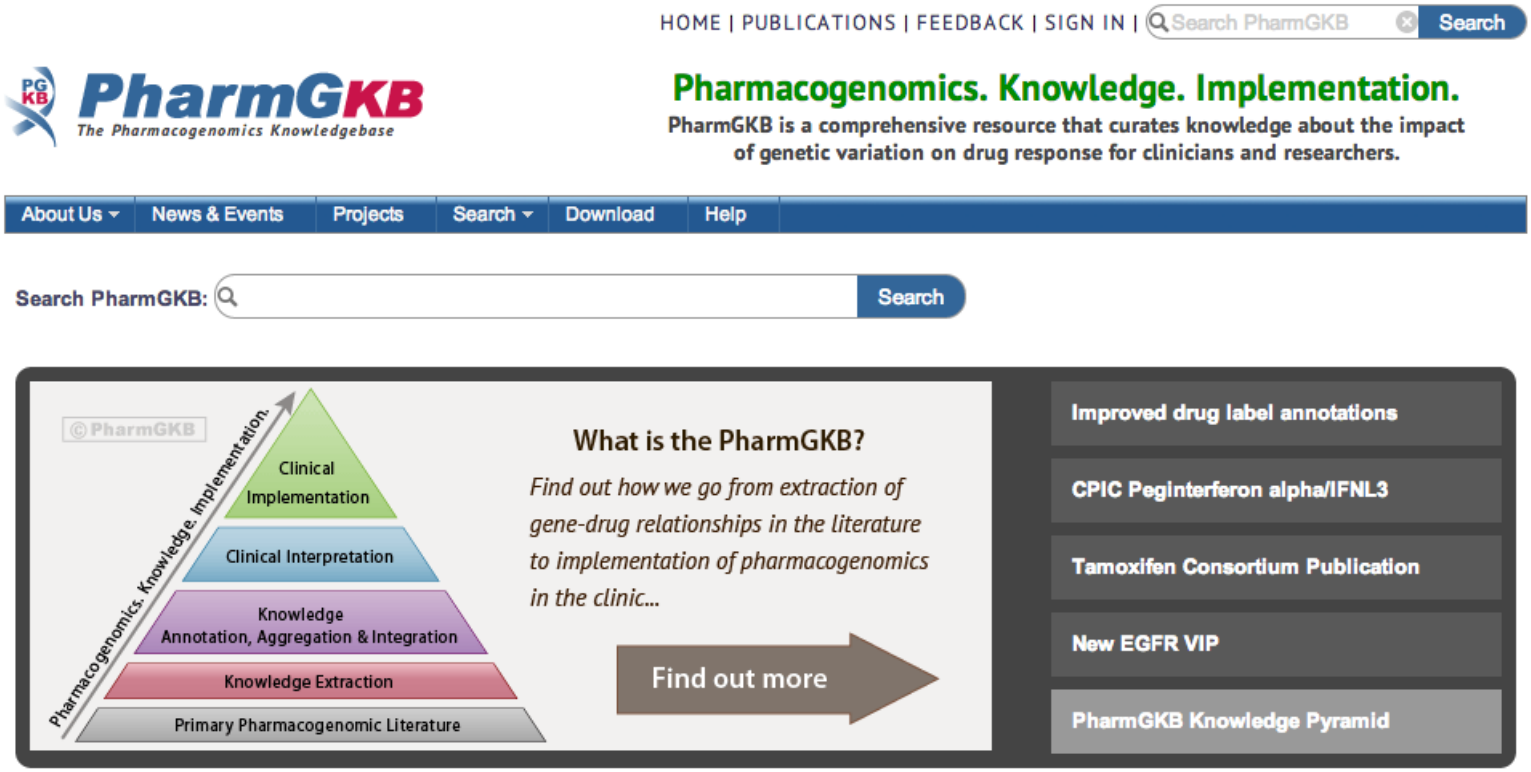
MODULE 4:Where to get testing done and how to interpret the results?

Selecting a lab and test

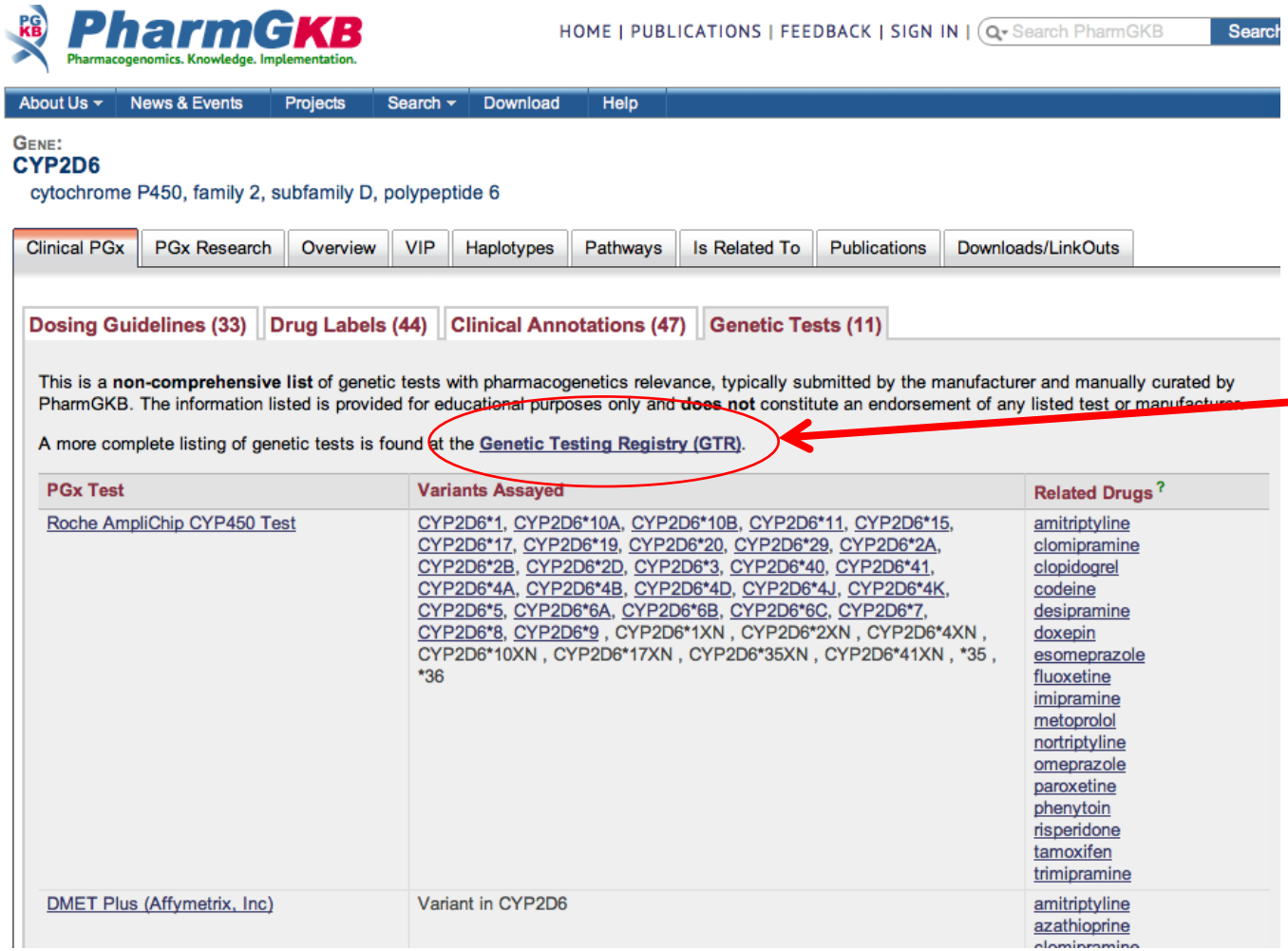
- **Where to find a CLIA-certified testing lab**
  - **PharmGKB and GTR**
- Testing method and limitations
  - Single gene vs gene panel
  - Targeted analysis vs mutation screening
  - Deletion/duplication analysis

PharmGKB

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



PharmGKB — genetic tests



Lists testing labs and test manufacturers

GTR

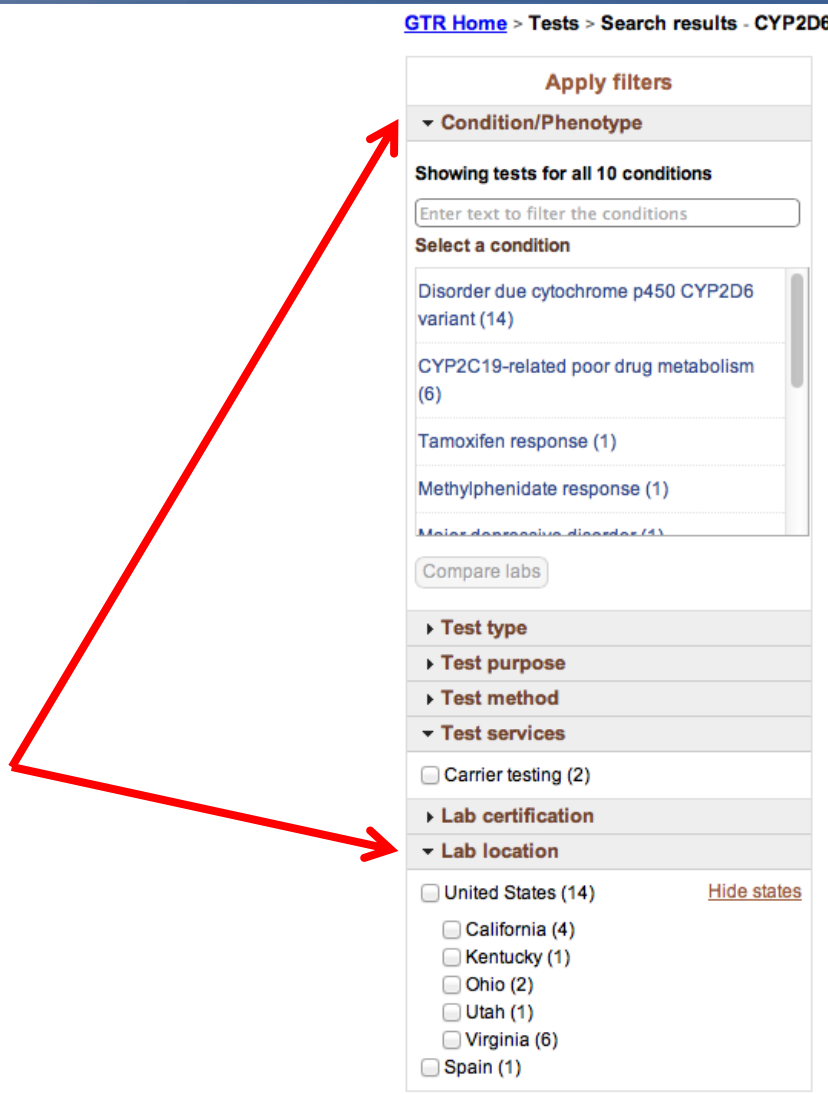
Genetic Testing Registry (GTR)

NCBI

GTR: GENETIC TESTING REGISTRY

Search for CYP2D6 gene tests

Can filter on different aspects



https://www.ncbi.nlm.nih.gov/gtr/

Many different vendors

GeneSight Psychotropic

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

Conditions	Test targets
Major depressive disorder	CYP1A2
Depression	CYP2B6
Major depressive disorder 1	CYP2C19
Total conditions (4)	Total targets (8)

Cytochrome P450, 2D6

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

Conditions	Test targets
Disorder due cytochrome p450 CYP2D6 variant	CYP2D6
Methylphenidate response	
Tamoxifen response	

Genetic Pharmacology Testing

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

Conditions	Test targets
Disorder due cytochrome p450 CYP2D6 variant	CYP2C19
Disorder due cytochrome p450 CYP2C19 variant	CYP2C9
Disorder due cytochrome p450 CYP2C9 variant	CYP2D6

Private companies

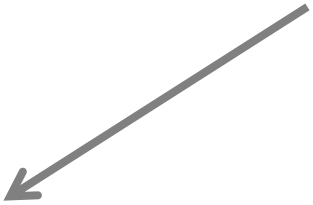
Commercial labs (ARUP, Quest, LabCorp)

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 (allleles *3, *4 and *6) screening

Lab: GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases Malaga, Andalucia, Spain

Conditions	Test targets	Methods
Disorder due cytochrome p450 **CYP2D6** variant	**CYP2D6**	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	Test targets	Methods
Disorder due cytochrome p450 **CYP2D6** variant	CYP2C19	T Targeted variant analysis
Disorder due cytochrome p450 CYP2C19 variant	CYP2C9	
Disorder due cytochrome p450 CYP2C9 variant	**CYP2D6**	

C GeneSight Psychotropic

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

Conditions	Test targets	Methods
Major depressive disorder	CYP1A2	D Deletion/duplication analysis
Depression	CYP2B6	T Targeted variant analysis
Major depressive disorder 1	CYP2C19	
Total conditions (4)	Total targets (8)	

Single gene vs gene panel

Targeted vs mutation screening

Other methods?

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Recognize limitations of tests

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

Some only test for most common alleles

Some assay may not be able to detect duplications

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%

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	**–1584G**, 1661G>C, **2850C>T**, 4180G>C	**–1584G**, 1039C>T, 1661G>C, **2850C>T**, **4180G>C**	**2850C>T**
*3	NF	**2549delA**	**2549delA**	**2549delA**
*4	NF	100C>T, 1661G>C, **1846G>A**, 4180G>C	100C>T, 1039C>T, 1661G>C, **1846G>A**, 2850C>T, 4180G>C	**1846G>A**
*5	NF	Deletion	Deletion	Deletion
*6	NF	**1707delT**	**1707delT**, 1976G>A, 4180G>C	**1707delT**
*7	NF	**2935A>C**	**2935A>C**	**2935A>C**
*8	NF	1661G>C, **1758G>T**, 2850C>T, 4180G>C	1661G>C, **1758G>T**, 2850C>T, 4180G>C	**1758G>T**
*9	DF	**2613–2615delAGA**	**2613–2615delAGA**	**2615_7delAAG**
*10	DF	**100C>T**, 1661G>C, 4180G>C	**100C>T**, 1039C>T, 1661G>C, 4180G>C	**100C>T**
*11	NF	**883G>C**, 1661G>C, 2850C>T, 4180G>C	**883G>C**, 1661G>C, 2850C>T, 4180G>C	Not tested
*12	NF	**124G>A**, 1661G>C, 2850C>T, 4180G>C	Not tested	**124G>A**
*14	NF	**1758G>A**, 2850C>T, 4180G>C	Not tested	**1758G>A**
*15	NF	**138insT**	**138insT**	Not tested
*17	DF	**1023C>T**, 1661G>C, 2850C>T, 4180G>C	**1023C>T**, 1661G>C, 2850C>T, 4180G>C	1023C>T
*19	NF	Not tested	1661G>C, 2539-**2542delAACT**, 2850C>T, 4180G>C	Not tested
*20	NF	Not tested	1661G>C, **1973insG**, 1978C>T, 1979T>C, 2850C>T, 4180G>C	Not tested
*29	DF	**1659G>A**, 1661G>C, 2850C>T, **3183G>A**, 4180G>C	**1659G>A**, 1661G>C, 2850C>T, **3183G>A**, 4180G>C	1659G>A
*35	F	–1584C, **31G>A**, 1661G>C, 2850C>T, 4180G>C	–1584C, **31G>A**, 1661G>C, 2850C>T, 4180G>C	Not tested
*36	NF	Not tested	100C>T, 1039C>T, 1661G>C, 4180G>C, gene conversion to CYP2D7 in exon 9	Not tested
*40	NF	Not tested	**1023C>T**, 1661G>C, **1863ins(TTT CGC CCC)2**, 2850C>T, 4180G>C	Not tested
*41	DF	1661G>C, 2850C>T, **2988G>A**, 4180G>C	**–1584C**, 1661G>C, **2850C>T**, **4180G>C**	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

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Interpreting test results

- CPIC
- PharmGKB dosing guidelines

CPIC

- 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	TCAs
abacavir	carbamazapine	

CPIC: Implementing PGx
a PharmGKB & PGRN collaboration

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Example CPIC guideline

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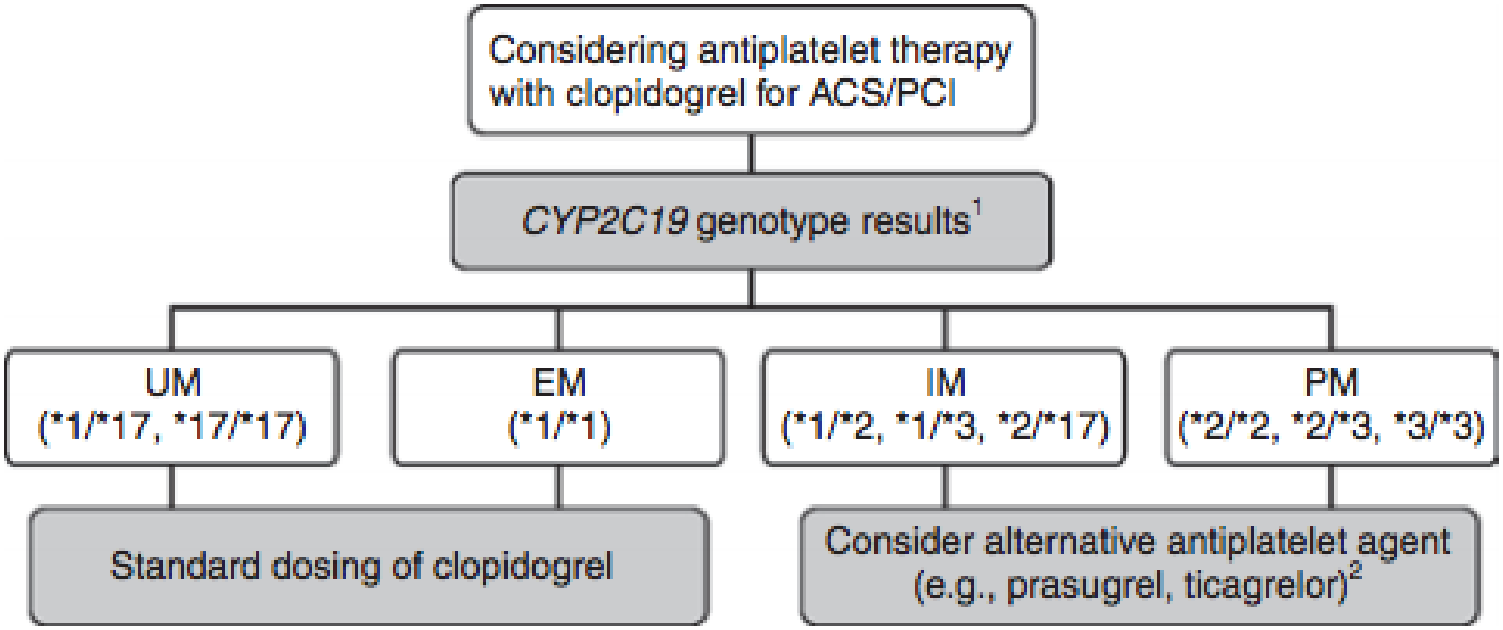

Figure 1 Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients

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: *1 | *3A

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