Genomic and Precision Medicine

Week 6: Clinical applications of genomics — Pharmacogenomics

Jeanette McCarthy, MPH, PhD

Robert Nussbaum, MD

Jaekyu Shin, PharmD, MS, BCPS

UCSF
University of California San Francisco
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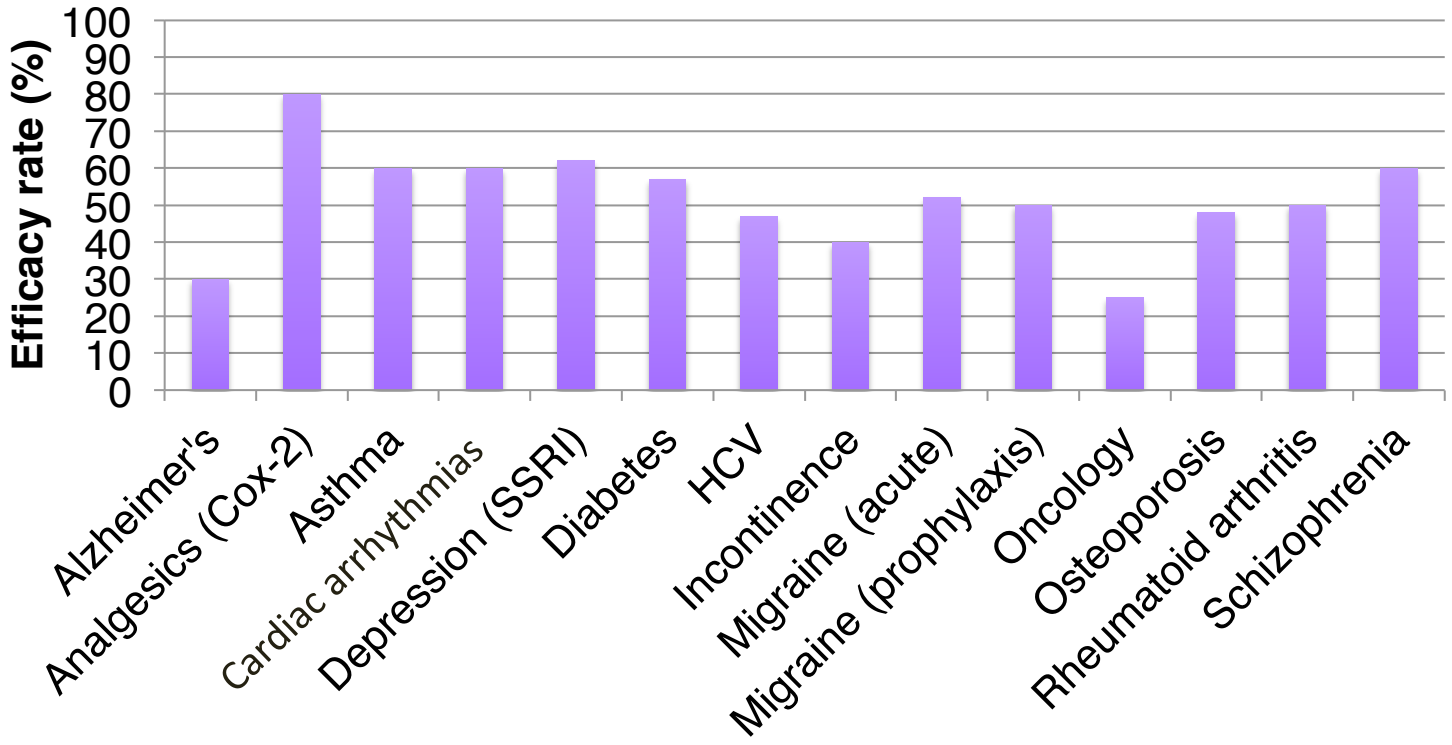
The Lecture

- **MODULE 1**: Background
  - Genetic factors influence pharmacokinetics
  - Genetic factors influencing pharmacodynamics
- **MODULE 2**: What pharmacogenomic tests are available?
- **MODULE 3**: Is my patient a candidate for pharmacogenomic testing?
- **MODULE 4**: Where to get testing done and how to interpret the results

MODULE 1: Background — Genetic factors affecting pharmacokinetics and pharmacodynamics

Drug Efficacy

- Drug response rates range from ~25-80%
- Characterized by inter-individual variability



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Adapted from: Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001; 7:201–204.

Adverse Drug Reactions

Table 1. Commonly Identified Drugs in Adverse Drug Reaction Studies

Therapeutic Category With Drug Class	Drug
Cardiovascular	
β-Blockers	Atenolol, metoprolol
Angiotensin-converting enzyme inhibitors	Lisinopril
Diuretics	Furosemide, hydrochlorothiazide
Calcium channel blocker	Diltiazem, verapamil
Inotropic agents/pressors	Digoxin
Analgesic	
Nonsteroidal anti-inflammatory drugs	Aspirin, piroxicam, ibuprofen, naproxen
Psychiatric	
Tricyclic antidepressants	Imipramine hydrochloride, nortriptyline hydrochloride
Selective serotonin reuptake inhibitor	Fluoxetine
Antibiotics	
Penicillin	Amoxicillin
Antitubercular agents	Isoniazid, rifampin
Macrolides	Erythromycin
Other	
Anticoagulants	Warfarin sodium
Corticosteroids	Prednisone
Anticonvulsants	Carbamazepine, phenytoin
Antidiabetic agents	Insulin
Bronchodilators	Theophylline
Electrolytes	Potassium
Antiemetic or antihistamine	Meclizine hydrochloride

	Incidence of ADRs
Outpatients	2% (1.2-3.2%)
Inpatients	1.6% (0.1-51%)

- ADR: unintented and noxious
- ADRs, although individually rare, are collectively common

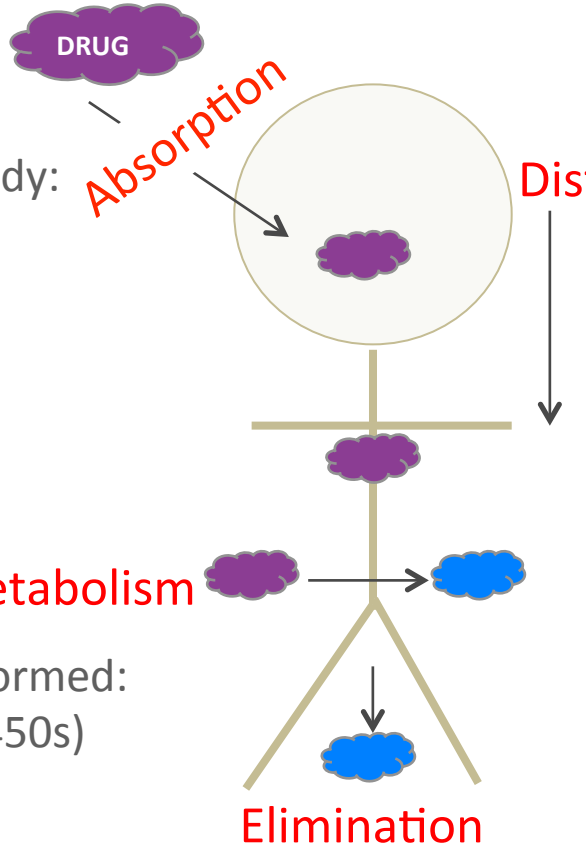
(Hakkarainen KM, et. al. PLoS ONE, 2012;7(3):e33236)

Pharmacogenomics

- Using a patient's genomic information to improve the efficacy and/or reduce the side effects of drugs

Pharmacokinetics

- How the drug concentration changes as it moves through the body



How drug gets into body:
- Orally
- Intravenously
- Inhaled

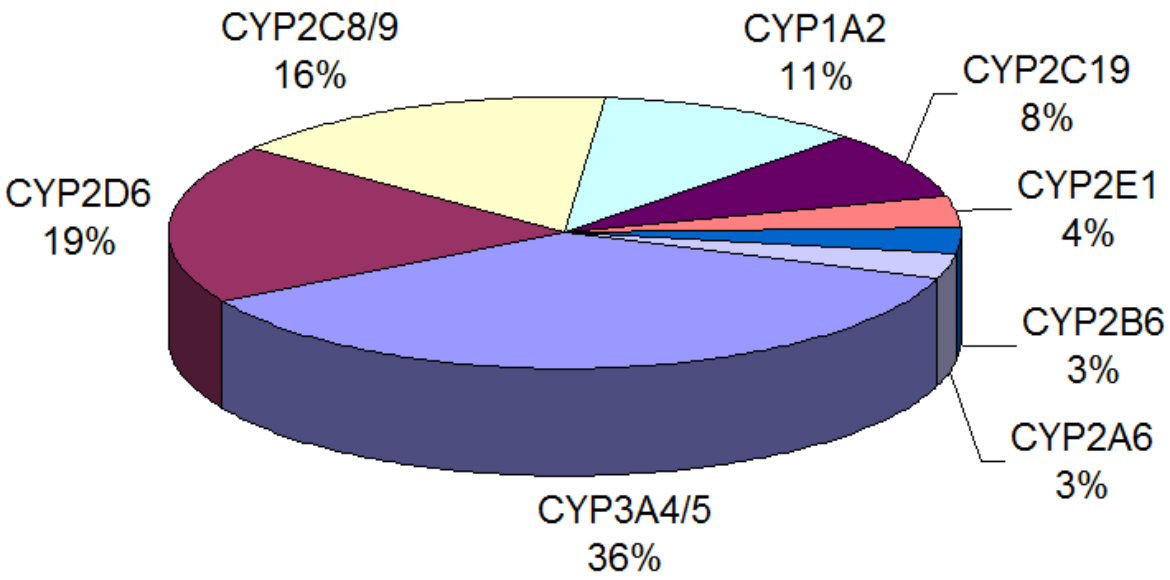
How drug gets into tissues and fluids:
- Circulatory system
- Transporters (e.g. SLCO1B1)

How drug is biotransformed:
- Enzymes (e.g. CYP450s)

How drug is excreted from body:
- Urine (renal/kidney)
- Feces
- Breath

Many drugs are metabolized by the polymorphic Cytochrome P450 enzymes

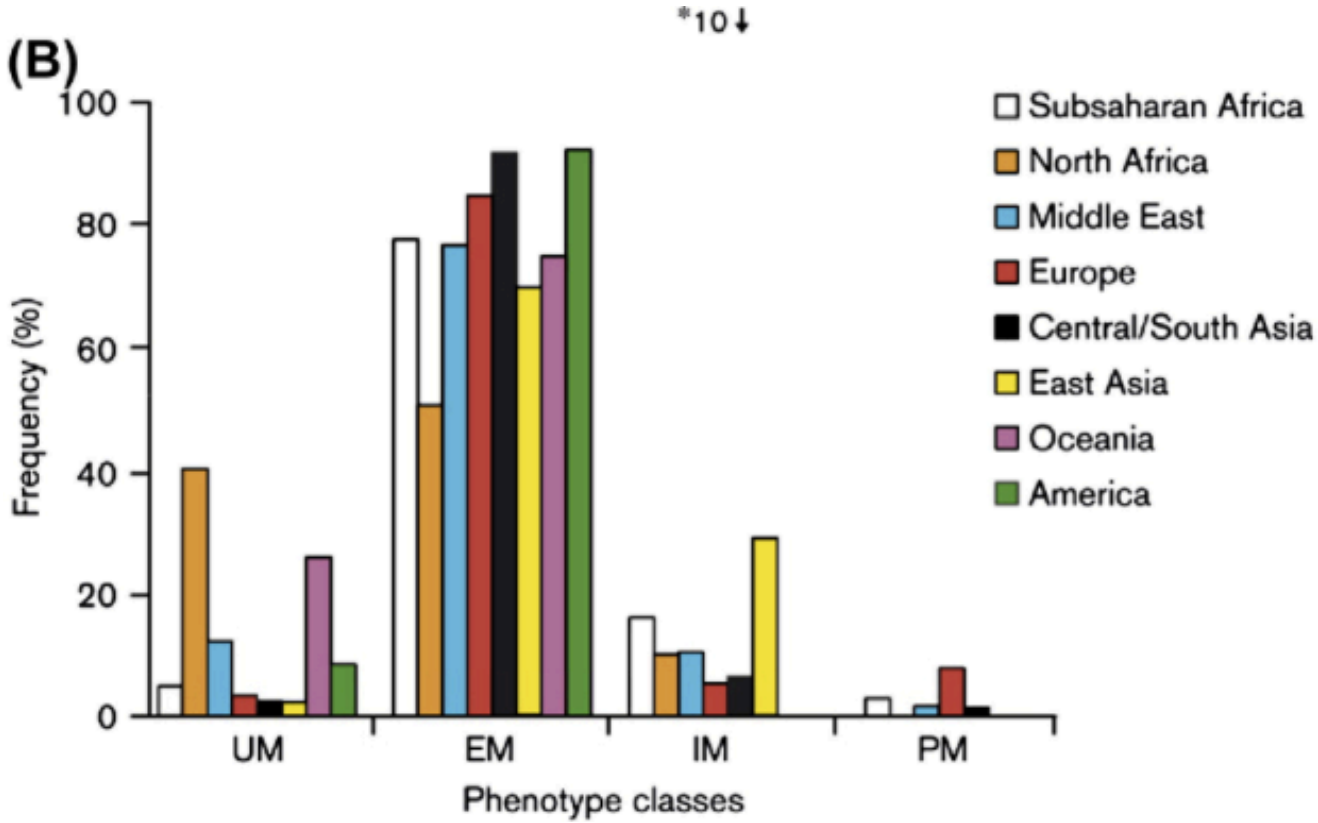
Proportion of all drugs metabolized by different CYP450s



	Enzyme activity
UM	Ultrarapid metabolizer
EM	Extensive (normal) metabolizer
IM	Intermediate metabolizer
PM	Poor metabolizer

Variable activity of CYP2D6 by ethnicity

Activity of CYP450 enzymes varies by race



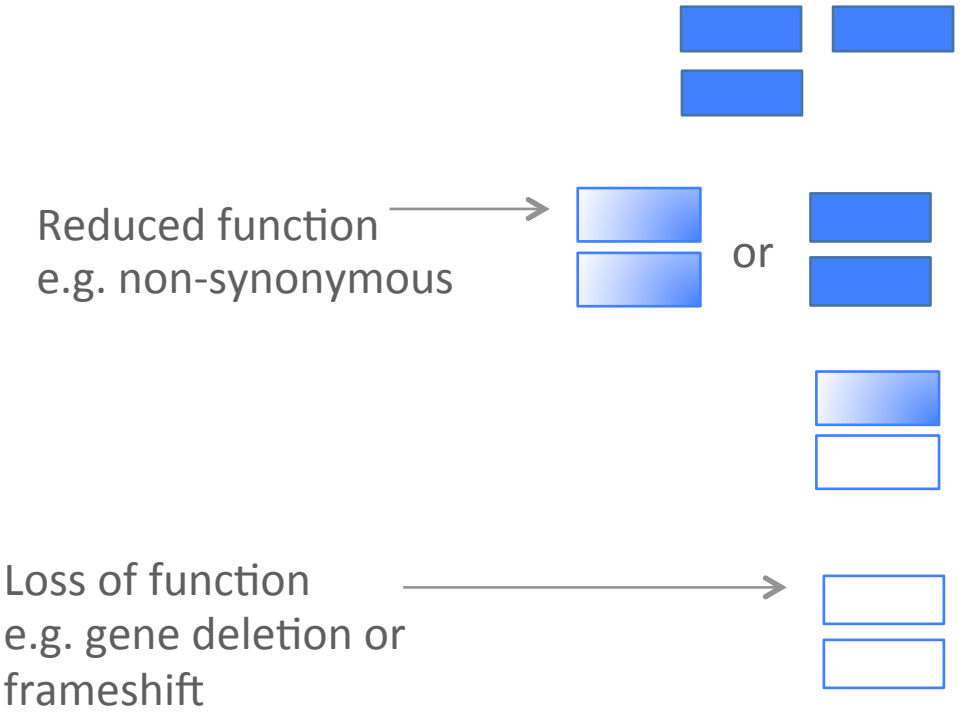
PMs are mainly found in European populations

UMs are mainly found in North Africa

Sistonen J et al. Pharmacogenet Genomics. 2007 Feb;17(2):93-101.

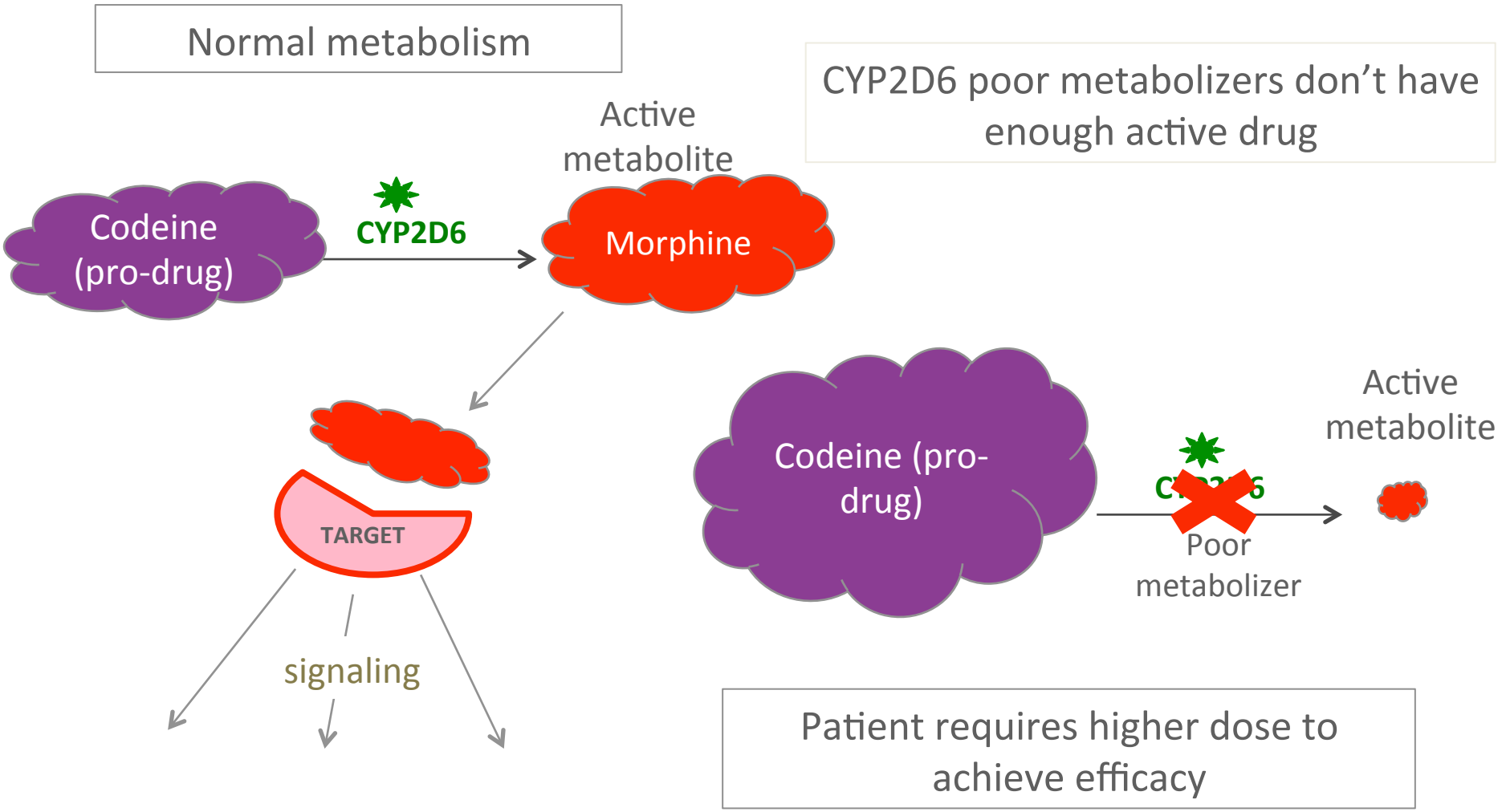
Polymorphic effect of CYP2D6 variants

Dozens of genetic variants can lead to reduced or complete loss of gene function



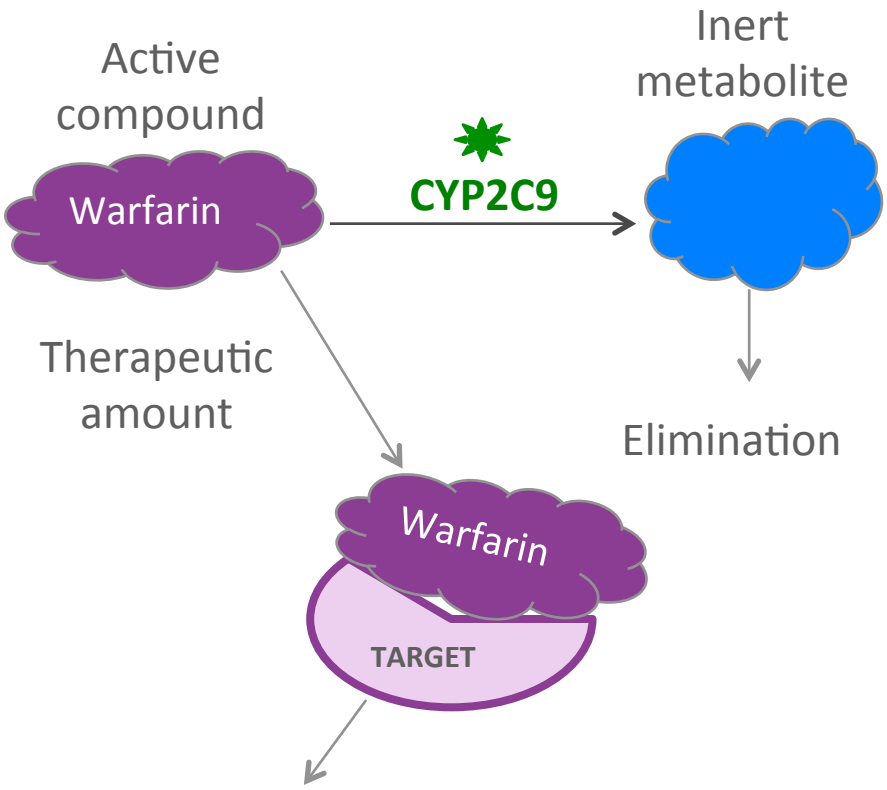
	Underlying genetics
UM	Extra copy(s) of gene
EM	Normal functioning genes (most people)
IM	One non-functioning and one reduced functioning allele
PM	Two non-functioning alleles

Pharmacogenomics — Codeine metabolism

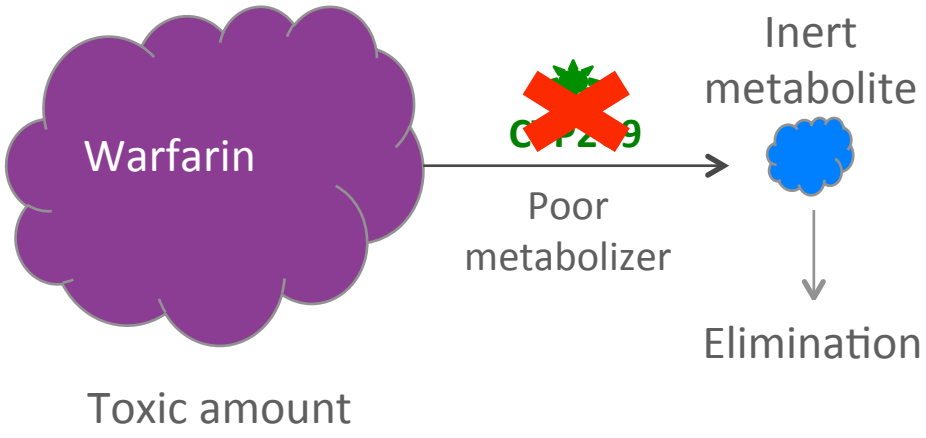


Pharmacogenomics — Warfarin metabolism

Normal metabolism



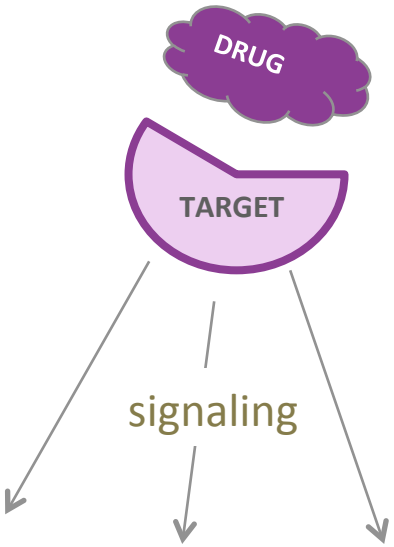
CYP2C9 poor metabolizers have too much drug (toxicity)

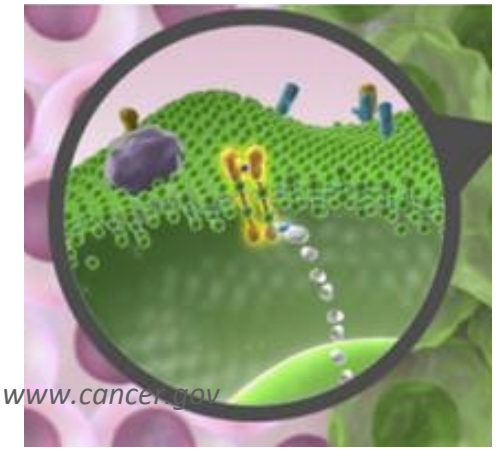


Patient requires lower dose to prevent toxic side effects

Pharmacodynamics

How the drug exerts its effect on the body (potency)



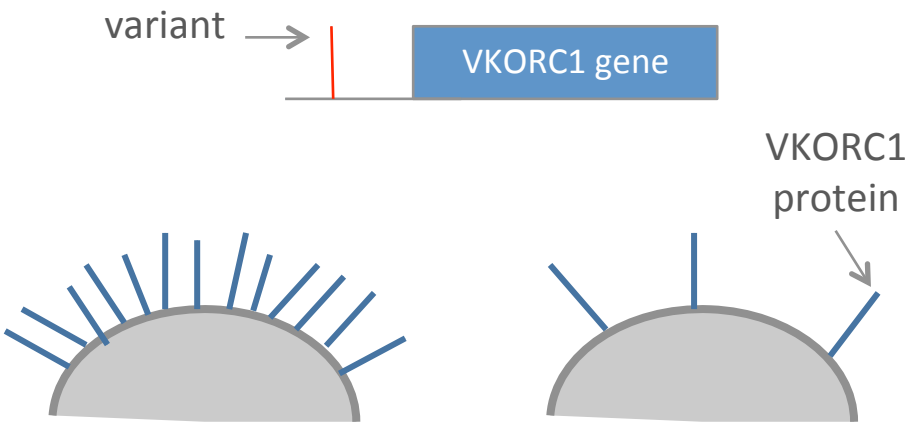


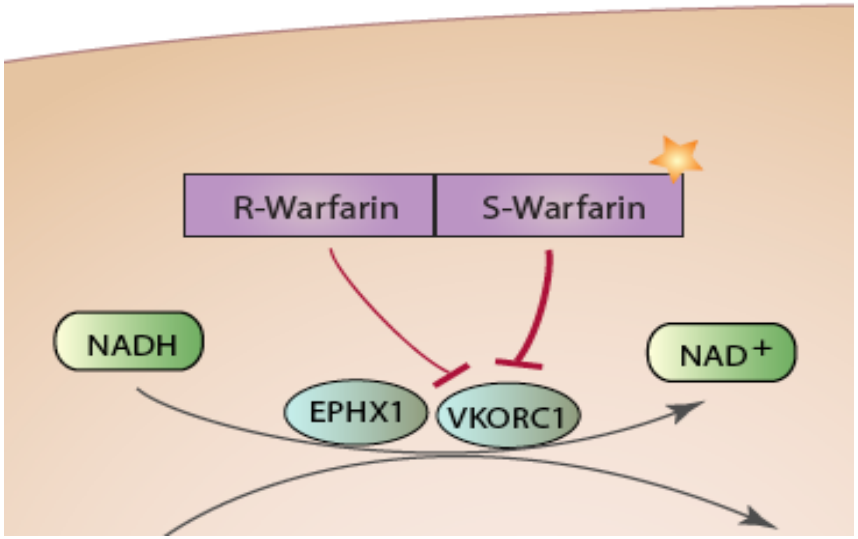
www.cancer.gov

Pharmacodynamics — Warfarin target

VKORC1, target of courmarin derivatives (e.g. Warfarin)

Variant upstream of VKORC1 leads to reduced expression





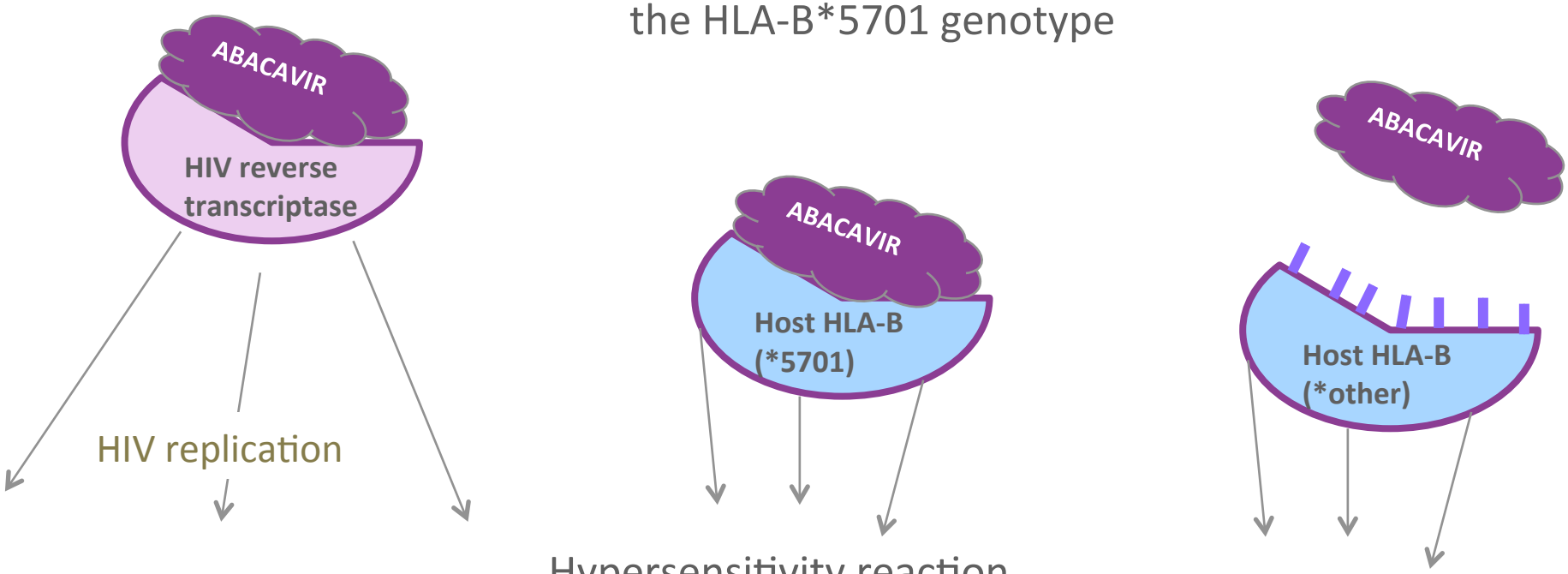
https://www.pharmgkb.org/pathway/PA145011114

More sensitive to inhibition by Warfarin; lower dose required

Off target effects — Abacavir hypersensitivity

Drug affects target, but also interacts with unintended target

Abacavir binds to host HLA-B in patients with the HLA-B*5701 genotype



Hypersensitivity reaction, potentially life-threatening

Patients should avoid drug

No reaction

Patient is fine

Question

Genetic variation in cytochrome P450 genes can impact a drug's:

A. Efficacy
B. Toxicity
C. Both

Answer

C. BOTH

We saw examples of CYP450 polymorphisms affecting efficacy (codeine) and toxicity (warfarin)

MODULE 2: What pharmacogenic tests are available?

Pharmacogenomic Biomarkers in Drug Labeling

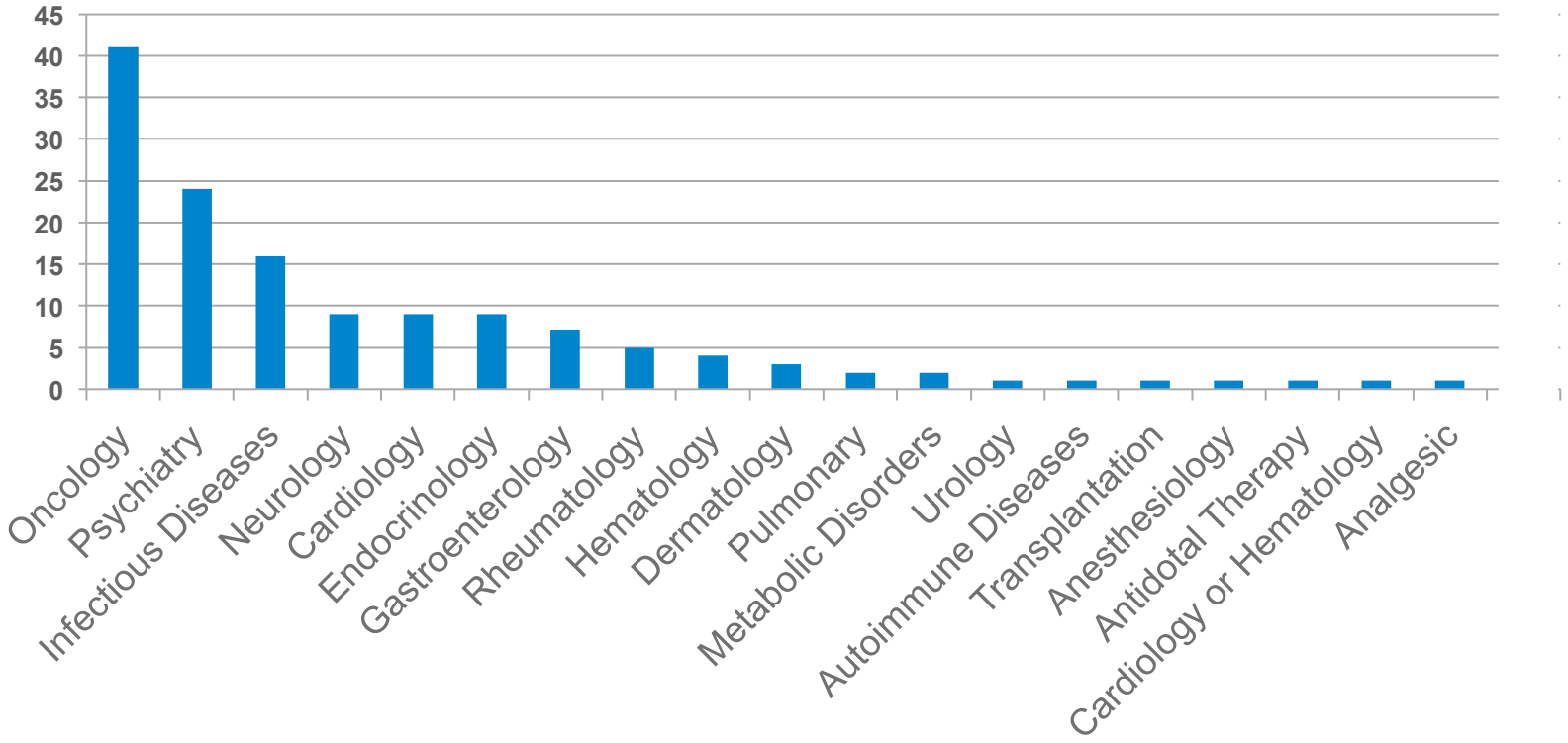
Drug	Therapeutic Area	HUGO Symbol	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene amplification positive	Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies

- 2006 – PGx in drug label
- 158 drug-biomarker pairs
- 12% of 385 drugs approved 1998-2012
- Not all PGx markers in drug label are clinically valid
- Commercial test may not even be available

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

FDA table of pharmacogenomic biomarkers in drug labeling

- Most in therapeutic area of oncology (tumor markers)



http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

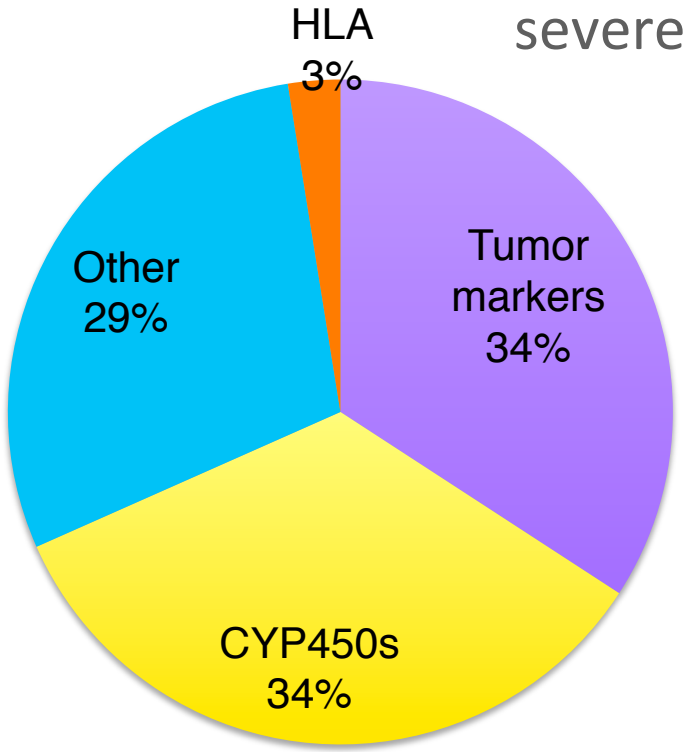
FDA table of pharmacogenomic biomarkers in drug labeling (cont'd)

Variation in HLA genes increasingly associated with severe adverse events

Over half of non-cancer biomarkers are in three CYP450 enzymes

- CYP2C9
- CYP2C19
- CYP2D6

Safety-related



http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

PharmGKB – PGx biomarker levels

Testing required

- Label states or implies that some sort of gene, protein or chromosomal testing 'should be performed' before using drug. This includes labels that state that the variant is an indication for the drug.

Testing recommended

- Label states or implies that some sort of gene, protein or chromosomal testing is recommended or 'should be considered' before using drug.

Actionable

- Label contains information about changes in efficacy, dosage or toxicity due to such variants, but does not discuss genetic testing

Informational

- Label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response

Adapted from PharmGKB website: http://www.pharmgkb.org/page/drugLabelLegend

Small number of non-cancer biomarkers are 'required' or 'recommended'

REQUIRED

- HLA- Carbamazapine
- CFTR – Ivacaftor
- CYP2D6 – Tetrabenazine
- OTC, POLG – Valproic acid
- *CYP2D6 – Pimozide*

RECOMMENDED

- HLA – Abacavir
- TPMT – Azathioprine
- CYP2C19 – Clopidogrel
- *CYP2D6 – Dextromethorphan/quinidine*

Highlights from the drug label

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

See full prescribing information for complete boxed warning.

Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:

- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

RECENT MAJOR CHANGES

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

INDICATIONS AND USAGE

Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:

- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:

- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

DOSAGE AND ADMINISTRATION

- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg (3)

CONTRAINDICATIONS

- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

WARNINGS AND PRECAUTIONS

- Neutropenia (2.4% incidence; may occur suddenly; typically resolves within 1–2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

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Placement of pharmacogenomic information in the drug label is inconsistent

Label Section	Number of Drugs
Clinical Pharmacology	79
Indications & Usage	39
Clinical Studies	38
Drug Interactions	34
Warnings and Precautions	34
Dosage & Administration	23
Adverse Reactions	19
Precautions	15
Warnings	14
Boxed Warning	8

Required tests — usually in Boxed Warning or Indications section……

Boxed Warning

Biomakers predictive of serious adverse events

e.g. Carbamazapine

WARNING

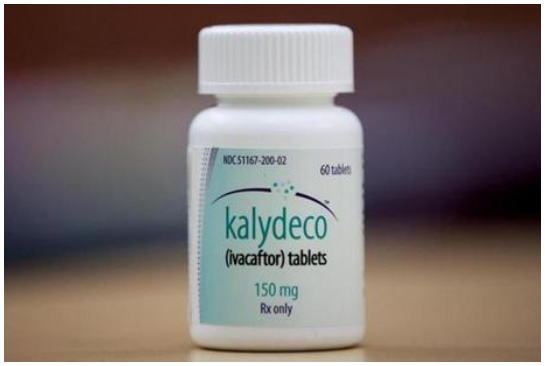
SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS/LABORATORY TESTS**).

Indications

Targeted therapies, efficacious for specific biomarker-defined patient population

e.g. Ivacaftor



1 INDICATIONS AND USAGE

KALYDECO is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *G551D* mutation.

Limitations of Use

KALYDECO is not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene and has not been studied in other populations of patients with CF.

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… but not always

- Required tests not always found in boxed warning or indications section of label

Tetrabenazine

- Sometimes found in Warnings, Dosing and Administration, Precautions, etc.

Excerpts from the tetrabenazine drug label:

> DOSAGE AND ADMINISTRATION.
> Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM).
> The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg.
> The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg.

Recommended tests- can also be found in Boxed Warnings section

Clopidigrel Boxed Warning – efficacy

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

Abacavir Boxed Warning – SAE

WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)

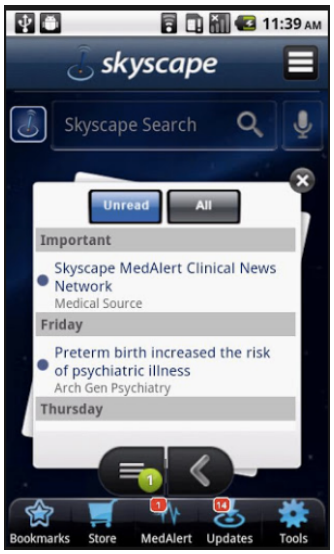
Clinician discretion whether to test or not

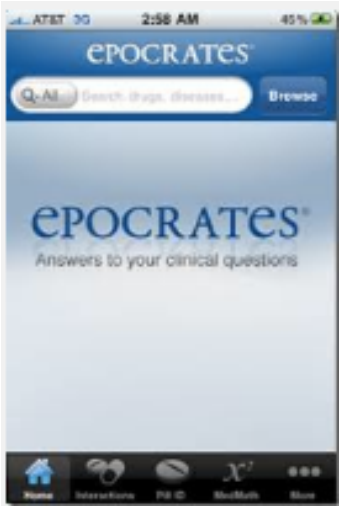
Not all PGx markers are in drug label

Simvastatin – SLCO1B1 typing for myopathy

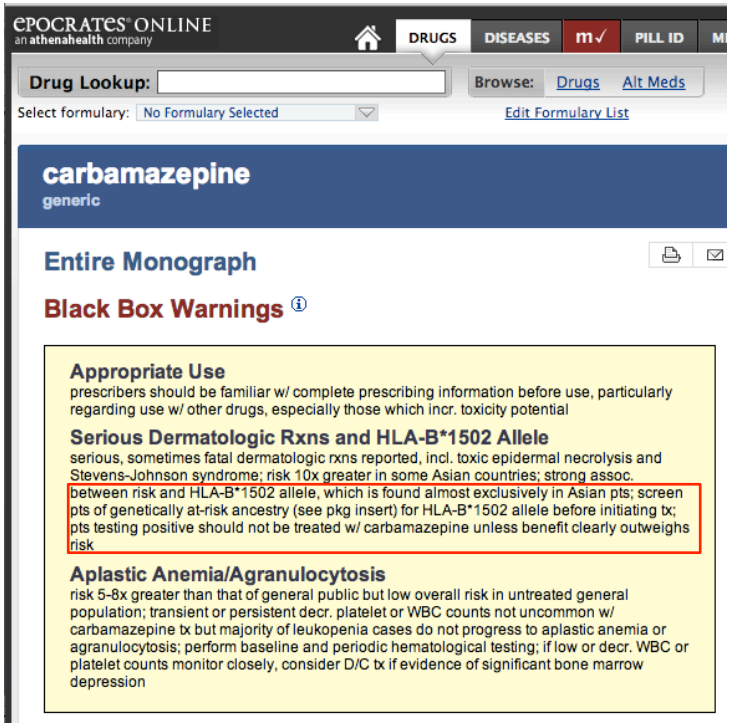
Allopurinol – HLA-B typing for severe cutaneous adverse reactions (drug hypersensitivity syndrome, Stevens-Johnson sydrome and toxic epidermal necrolysis)

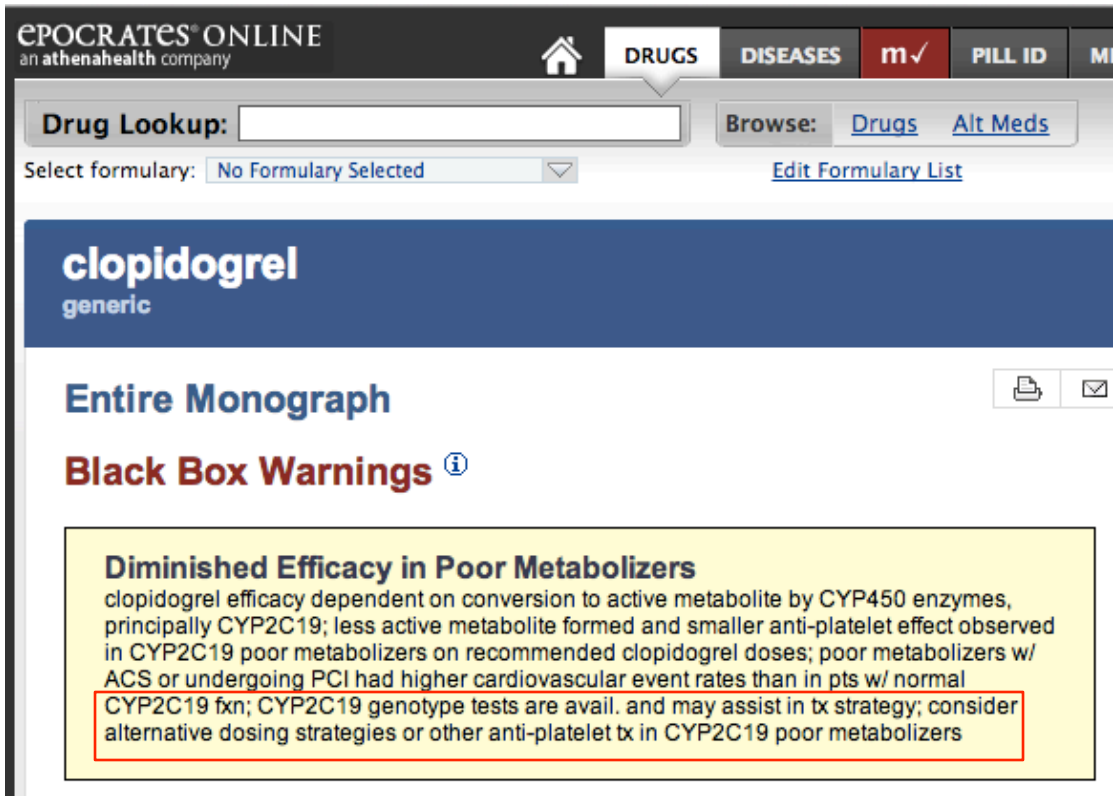
POC medical apps





POC Medical Apps mirror FDA label





Question

Presence of pharmacogenomic marker information in an FDA drug label implies that the marker is clinically validated

A. True

B. False

Answer

B. False

Pharmacogenomic markers in the drug label can appear for informational purposes only, without clinical validation.

What the FDA label does NOT tell you

- How clinically valid or useful the PGx biomarker is
- Whether your patient is a candidate for testing
- Whether a test for the biomarker is even available
- How to interpret results of testing

MODULE 3: Is my patient a candidate for pharmacogenomic testing?

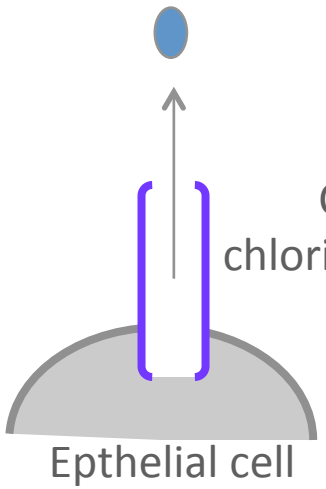
Consider pharmacogenomic testing if…

It is required for efficacy

CFTR genotype-dependent efficacy of Ivacaftor

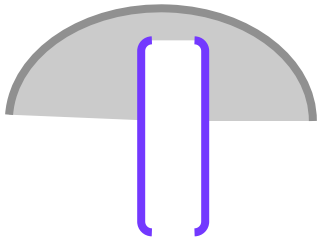
Health individual

Normal ion transport

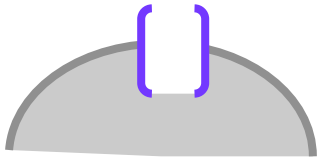


CFTR – chloride channel

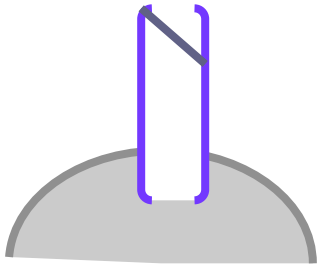
Epthelial cell



ΔF508 affects folding; channel doesn't reach surface (85% of patients)



W1282X results in truncated protein



G551D affects function (gating) of channel (4% of patients)

Drug effective only in patients with G551D mutation

>1000 mutations lead to Cystic Fibrosis, each affecting CFTR protein in different ways

Just approved for 8 more mutations!

Consider pharmacogenomic testing if…

It can help avoid a severe adverse reaction

Consequence of ADR?

Depression

(Tetrabenazine)

Myopathy

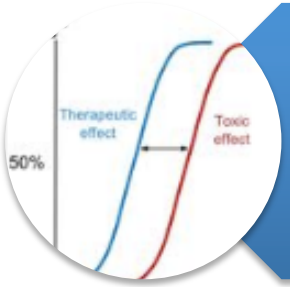
(Simvastatin)

Liver failure/death

(Valproic Acid)

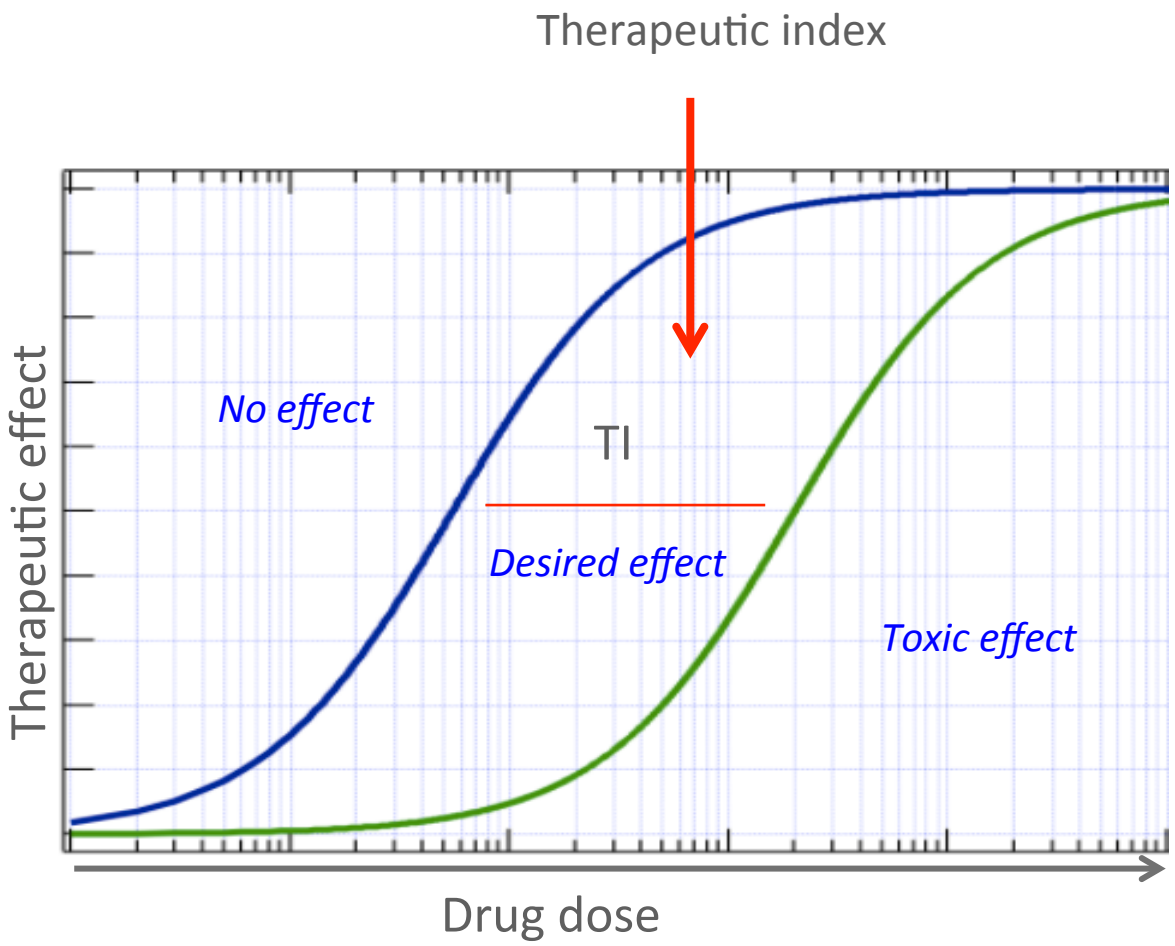
Stevens-Johnson's syndrome
Myelosuppression
Toxic epidermic necrolysis
long QT syndrome

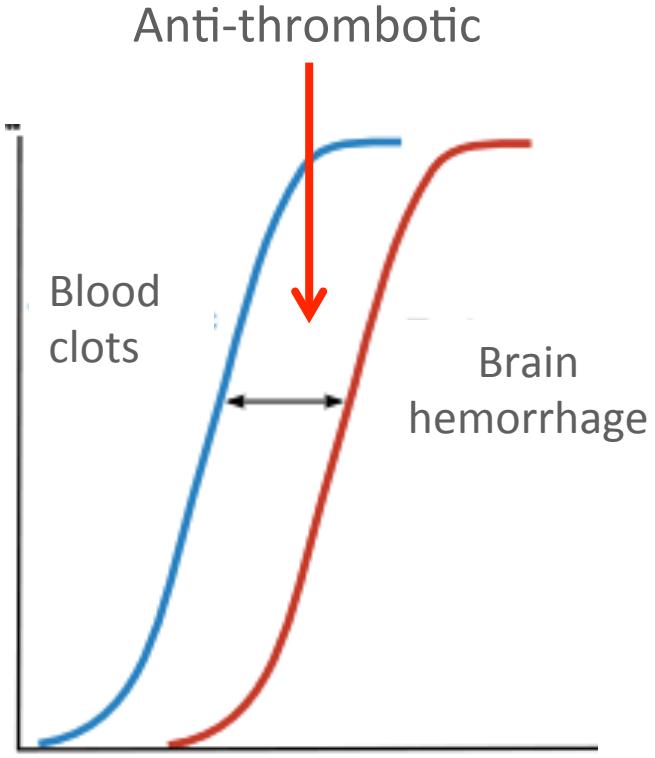
Consider pharmacogenomic testing…



It can help dose a drug with a narrow therapeutic index

Correction for multiple testing





Pharmacogenomics may help with dosing

Are alternative therapies available?

- Clopidogrel vs ticagrelor

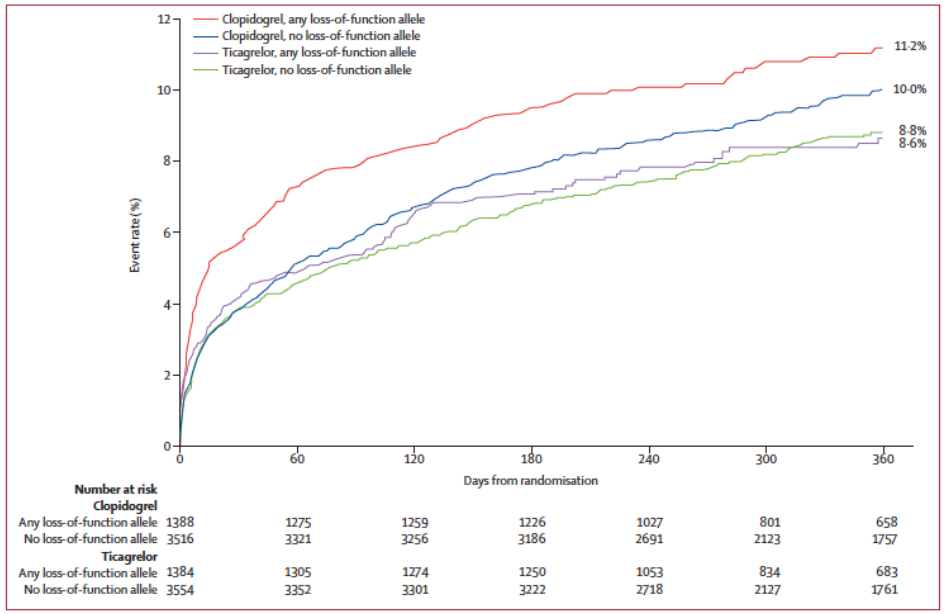
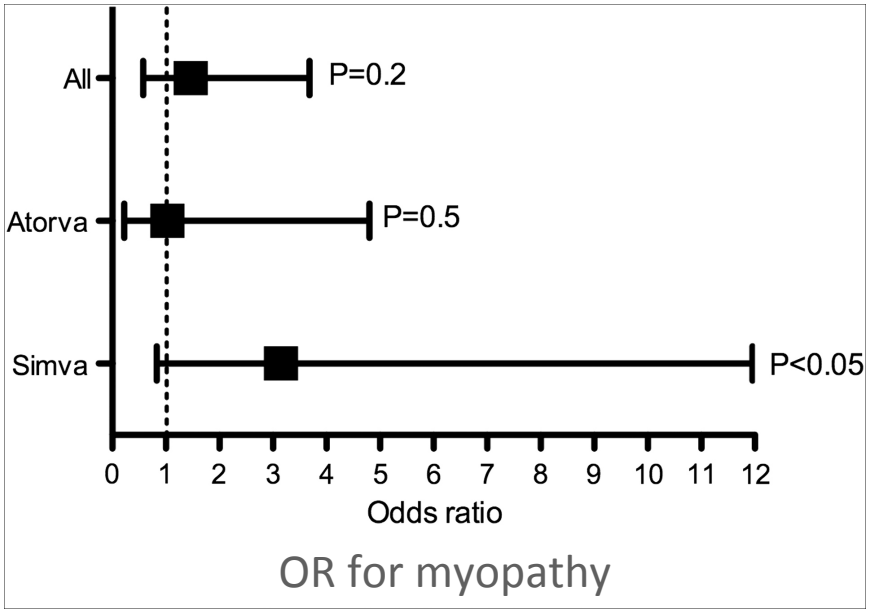


Figure 1: Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype

Wallentin L et al. Lancet 2010: 376 (9749): 1320-1328.

- Simvastatin vs atorvastatin



Brunham L, et al Pharmacogenomics J 2012; 12:233-237.

Consider using alternative therapy

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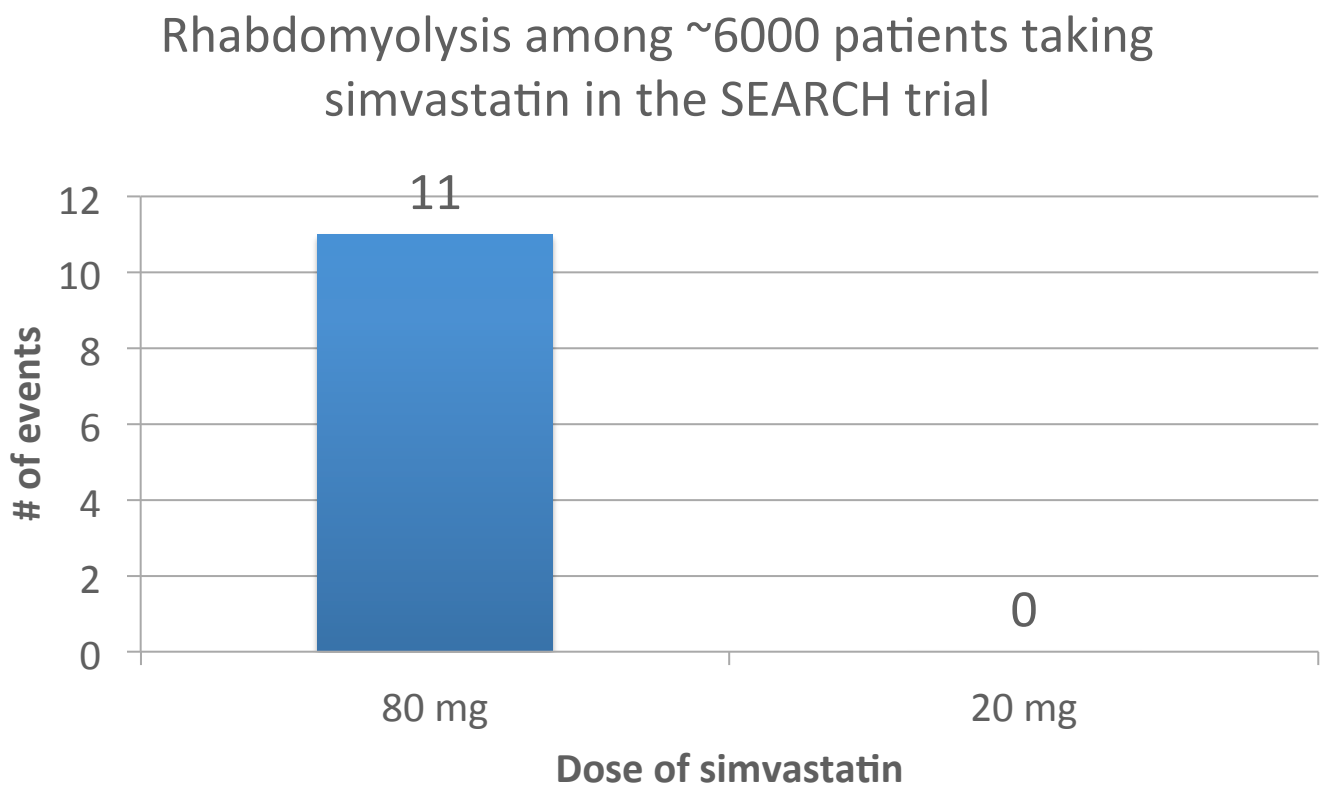
Is the ADR dose-dependent?

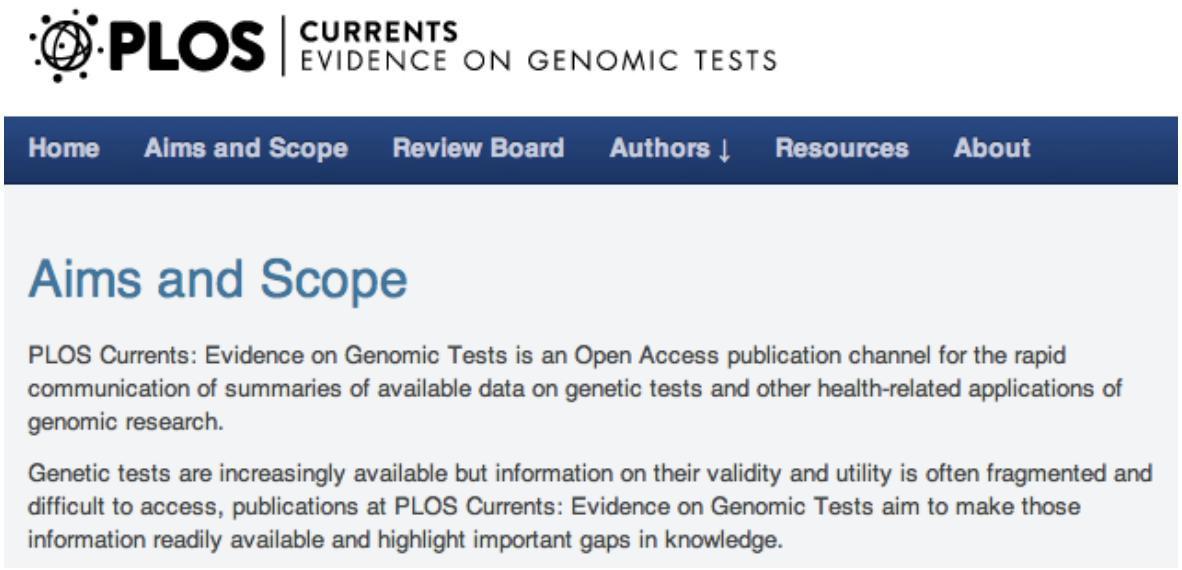


Conservative dosing may mitigate risk of ADR

Before ordering a test, have a sense of the clinical validity and utility

- **Where to find information on clinical validity and utility**
  - **PLoS Currents: Evidence on Genomic Tests**
  - **Professional guidelines, literature**
- Evaluating PPV and NPV of test
- Considering other factors
- Is the test appropriate in all ethnicities?

PLoS Currents



Eight non-cancer* PGx reviews available

clopidogrel
warfarin
thiopurines
abacavir
interferon-alpha
simvastatin
tamoxifen
statins

*Non-tumor-based

- CLINICAL SCENARIO
- TEST DESCRIPTION
- PUBLIC HEALTH IMPORTANCE
- PUBLISHED RECOMMENDATIONS AND GUIDELINES
- EVIDENCE OVERVIEW
  - Analytic validity
  - Clinical validity
  - Clinical utility

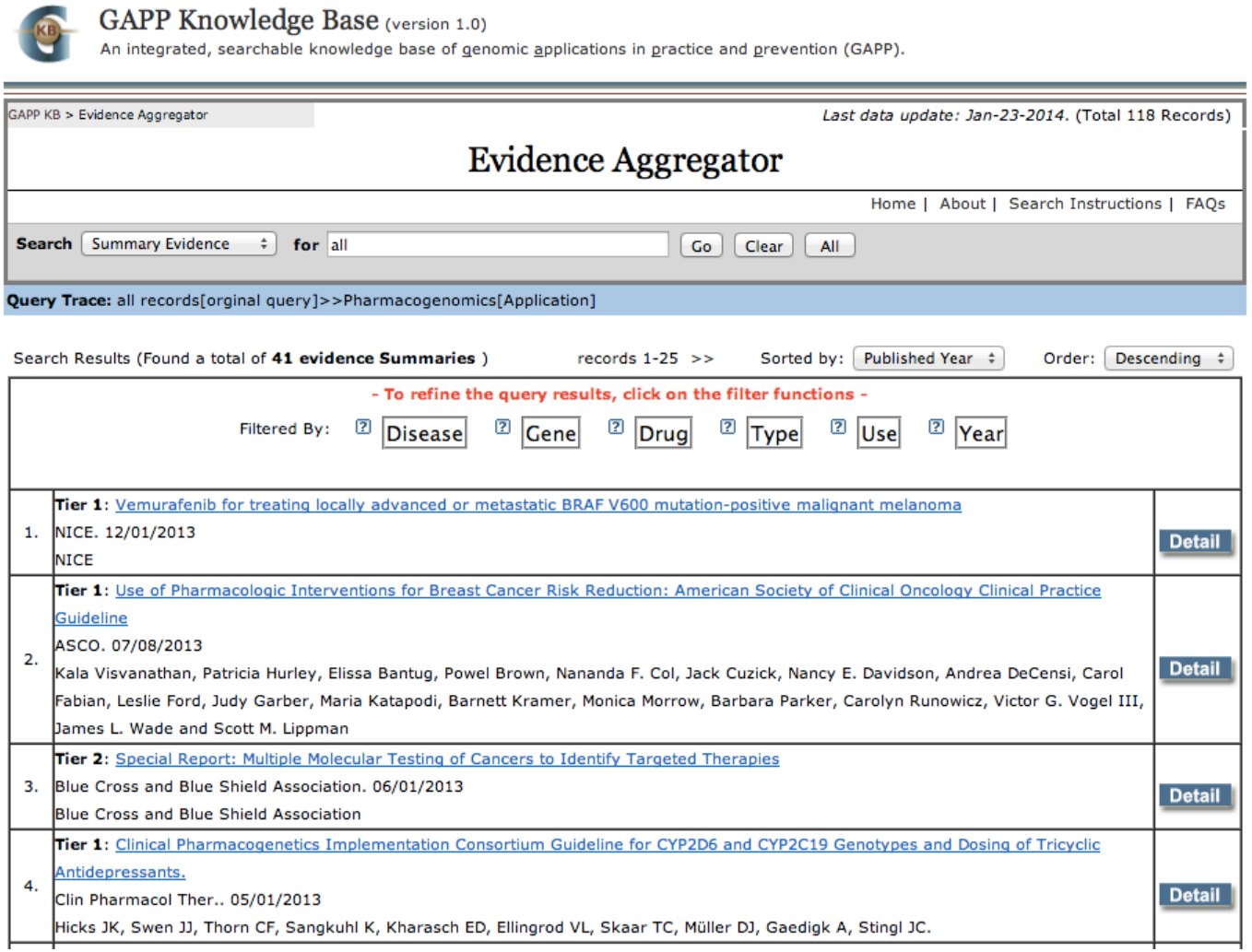
PLoS Currents example: HLA-B*5701 testing for abacavir hypersensitivity

Clinical Validity **:** Test accuracy and reliability in predicting abacavir hypersensitivity (predictive value).

- The prevalence of the *HLA-B*5701* allele is highest in Caucasian populations (5-8%) [3][18][19][20]. In African-American, Asian, and Hispanic populations, the prevalence is 0.26-3.6% [19][20][21][22]. In a review of the adult and adolescent antiretroviral guidelines and the abacavir prescribing information [12][16], the prevalence of the *HLA-B*5701* allele between ethnic populations has no impact on clinical recommendations.
- In studies conducted in North America, Europe, and Australia where patients were diagnosed with an abacavir hypersensitivity reaction based on symptom presentation, HLA-B*5701 test sensitivity was 46-78% [22][23][24]. In contrast, HLA-B*5701 test sensitivity was 94-100% in patients with an immunologically confirmed (via skin patch testing) abacavir hypersensitivity reaction [25][26][27]. There is suggestion that the discrepancy of lower estimates of test sensitivity was the inclusion of non-abacavir related hypersensitivity reactions [28].
- HLA-B*5701 test specificity, regardless of whether the abacavir hypersensitivity reaction is based on symptom presentation or immunologic confirmation, is 90-100% [22][23][24][25][26][27].
- Pooled data from 3 study populations reported a positive predictive value and negative predictive value of 82% (95% Confidence Interval [CI] 71-90%) and 85% (95% CI 81-88%), respectively [22][23][24].
- A report by Hughes et al. suggested a "high genetic penetrance of HLA-B*5701 in predisposing [patients] to abacavir hypersensitivity" [24].

Ma JD, et al. ***PLoS Currents Evidence on Genomic Tests****. 2010 Dec 7.*

Professional guidelines, literature



GAPP Knowledge Base (version 1.0)

An integrated, searchable knowledge base of genomic applications in practice and prevention (GAPP).

GAPP KB > Evidence Aggregator

Last data update: Jan-23-2014. (Total 118 Records)

Evidence Aggregator

Home | About | Search Instructions | FAQs

Search Summary Evidence **for** all Go Clear All

Query Trace: all records[orginal query]>>Pharmacogenomics[Application]

Search Results (Found a total of **41 evidence Summaries**) records 1-25 >> Sorted by: Published Year Order: Descending

- To refine the query results, click on the filter functions -

Filtered By: Disease Gene Drug Type Use Year

1.	**Tier 1**: Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma NICE. 12/01/2013 NICE	Detail
2.	**Tier 1**: Use of Pharmacologic Interventions for Breast Cancer Risk Reduction: American Society of Clinical Oncology Clinical Practice Guideline ASCO. 07/08/2013 Kala Visvanathan, Patricia Hurley, Elissa Bantug, Powel Brown, Nananda F. Col, Jack Cuzick, Nancy E. Davidson, Andrea DeCensi, Carol Fabian, Leslie Ford, Judy Garber, Maria Katapodi, Barnett Kramer, Monica Morrow, Barbara Parker, Carolyn Runowicz, Victor G. Vogel III, James L. Wade and Scott M. Lippman	Detail
3.	**Tier 2**: Special Report: Multiple Molecular Testing of Cancers to Identify Targeted Therapies Blue Cross and Blue Shield Association. 06/01/2013 Blue Cross and Blue Shield Association	Detail
4.	**Tier 1**: Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants. Clin Pharmacol Ther.. 05/01/2013 Hicks JK, Swen JJ, Thorn CF, Sangkuhl K, Kharasch ED, Ellingrod VL, Skaar TC, Müller DJ, Gaedigk A, Stingl JC.	Detail

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http://64.29.163.162:8080/GAPPKB/evidencerStartPage.do

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  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature
- **Evaluating PPV and NPV of test**
- Considering other factors
- Is the test appropriate in all ethnicities?

Evaluating PPV and NPV

	HLA-B*5801 – Allopurinol – related SCAR	IFNL3 – PegIFNα efficacy
Incidence	0.4% (ADR)	50% (efficacy)
PPV	2.6%	90.7%
NPV	100%	58.8%

Rare outcomes can never lead to high PPV, no matter how good the sensitivity/ specificity of the test

Rule out ADR

- 100% of SCAR patients have *5801
- 20% of pop. carries *5801, most will not have SCAR

Identify likely responders

- Variant – high likelihood of responding
- improved adherence to drug?

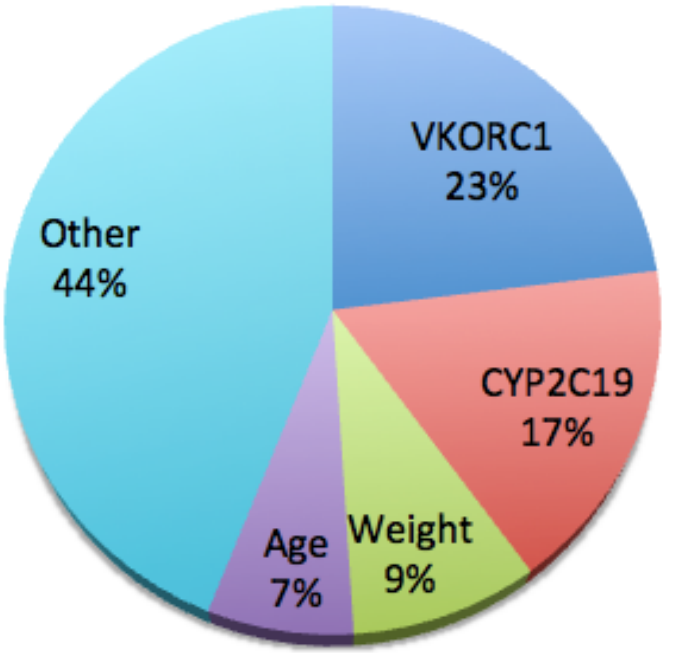
Before ordering a test, have a sense of the clinical validity and utility

- Where to find information on clinical validity and utility
  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature
- Evaluating PPV and NPV of test
- **Considering other factors**
- Is the test appropriate in all ethnicities?

Factors affecting inter-individual variability in drug response

- Genetics
- Sex
- Age
- Race
- Concomitant drugs
- Underlying disease

Factors affecting Warfarin dosing



iWarfarin App

Consider other ways to measure a patient's response

Consider other factors simultaneously

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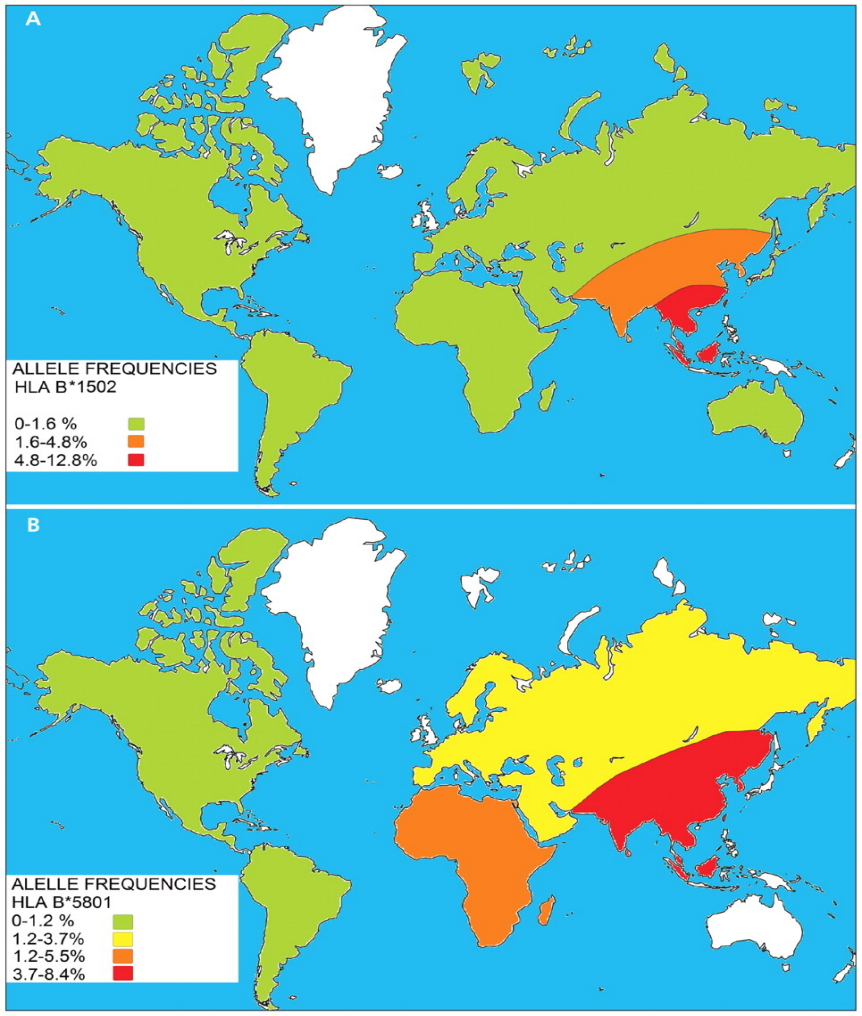
Before ordering a test, have a sense of the clinical validity and utility

- Where to find information on clinical validity and utility
  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature
- Evaluating PPV and NPV of test
- Considering other factors
- **Is the test appropriate in all ethnicities?**

Is test appropriate in patient's ethnic group?

Approximate prevalence of the human leukocyte antigen (HLA) alleles HLA-B*1502 (Carbamazepine) and HLA-B*5801 (Allopurinol) in various geographic regions of the world.



CMAJ·JAMC

UCSF

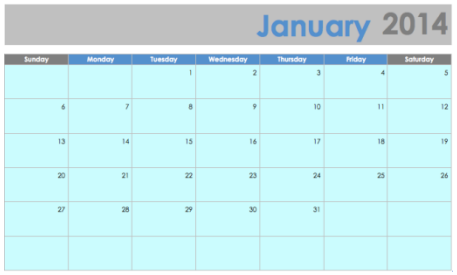
Fernando S L , and Broadfoot A J CMAJ 2010;182:476-480

Other practical considerations

- **Turn around time**
- Economics – is it covered by insurance

Turn-around time

Standard



Point of care

Pre-emptive

Other practical considerations

- Turn around time
- **Economics – is it covered by insurance**

Medicare coverage decisions

In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract

- TPMT for treatment of IBD with thiopurines — yes
- VKORC1 and CYP2C9 for Warfarin treatment — NO

Insurance coverage (U.S.)

- Many private insurance companies follow Medicare decisions

Drug	Gene	Aetna	Indep BCBS	Cigna	Humana
Clopidogrel	CYP2C19	Yes	Yes	No	No
Warfarin	CYP2C9/VKORC1	No	No	No	No
Thiopurines	TPMT	Yes	Yes	Yes	Yes
Abacavir	HLA-B	Yes	-	Yes	Yes
Carbamazepine	HLA-B	Yes	-	-	Yes

Coverage policies for pharmacogenomic tests by insurer (Aug 2012)

Adapted from Hresko and Haga. J. Pers. Med. 2012; 2: 201-216.

Question

Pharmacogenomic tests are most appropriate for drugs with:

A. a wide therapeutic index
B. dose-dependent ADRs
C. genotype-dependent efficacy

Answer

C. genotype-dependent efficacy

narrow

A. a wide therapeutic index

independent

B. dose dependent ADRs

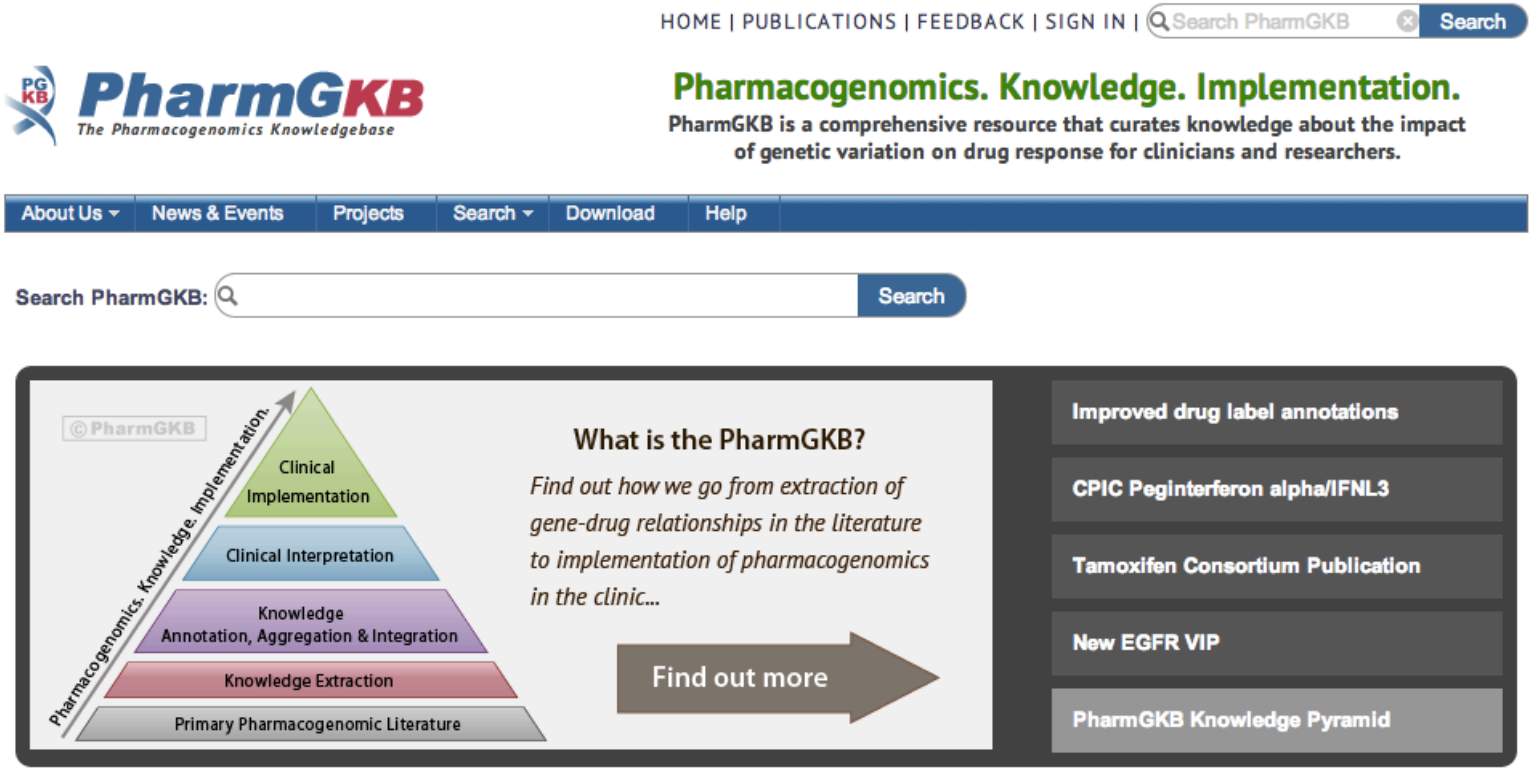
MODULE 4:Where to get testing done and how to interpret the results?

Selecting a lab and test

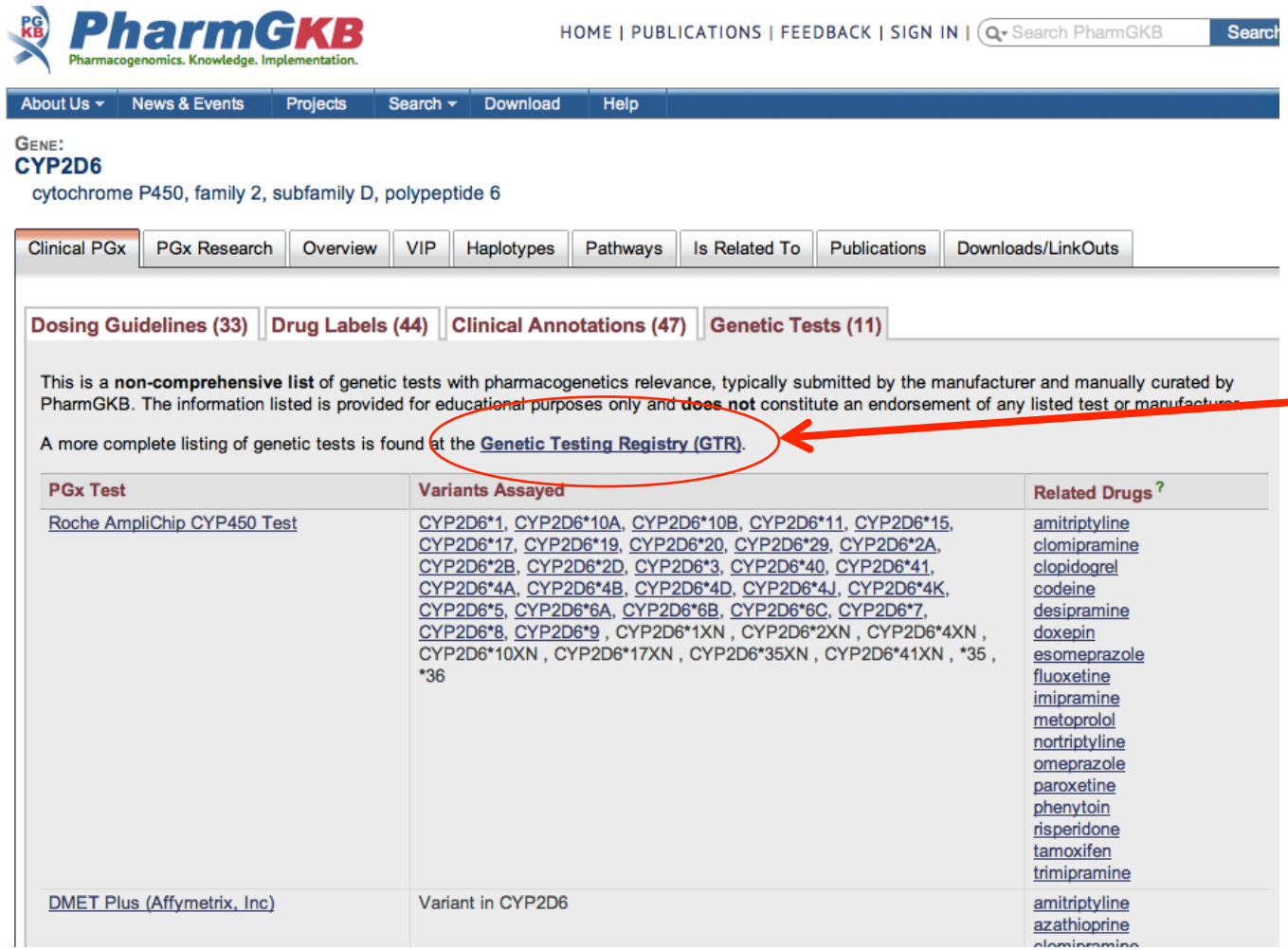
- **Where to find a CLIA-certified testing lab**
  - **PharmGKB and GTR**
- Testing method and limitations
  - Single gene vs gene panel
  - Targeted analysis vs mutation screening
  - Deletion/duplication analysis

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

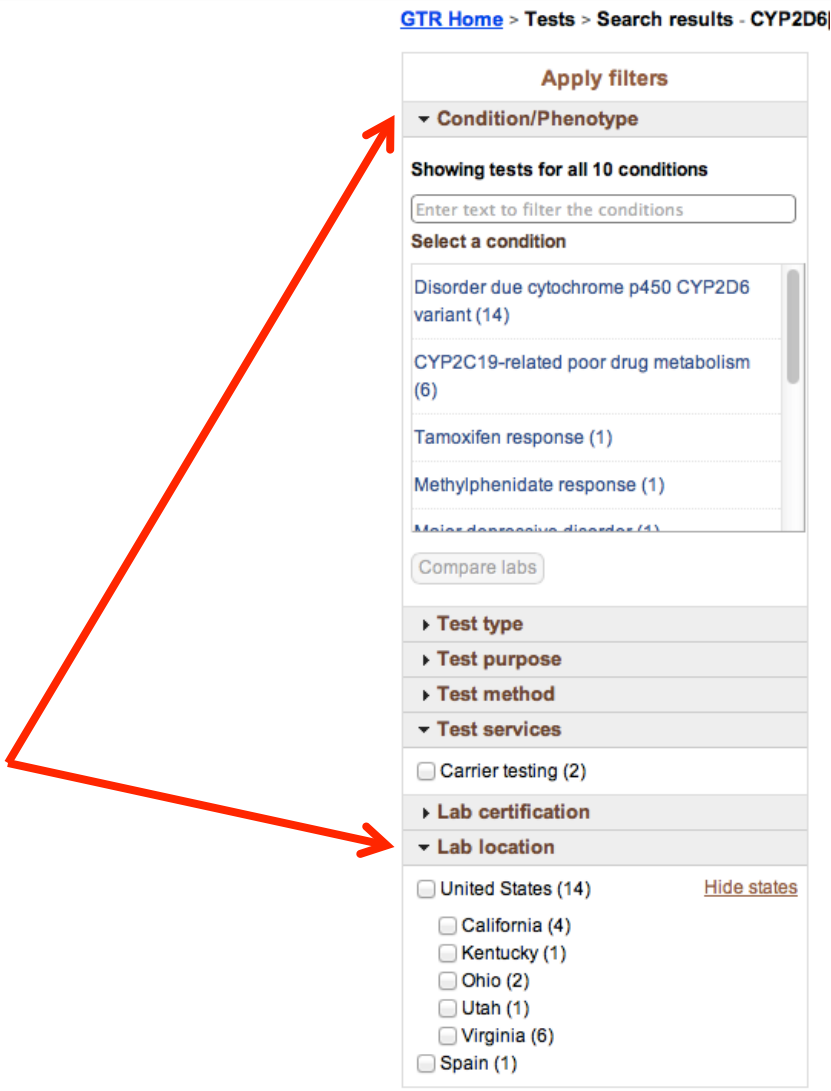
Genetic Testing Registry (GTR)

NCBI

GTR: GENETIC TESTING REGISTRY

Search for CYP2D6 gene tests

Can filter on different aspects



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

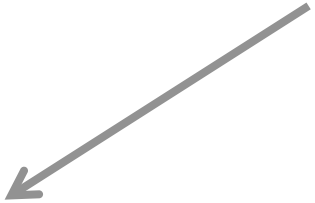
Commercial labs (ARUP, Quest, LabCorp)

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 (alleles *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?

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

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

UCSF

Example CPIC guideline

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

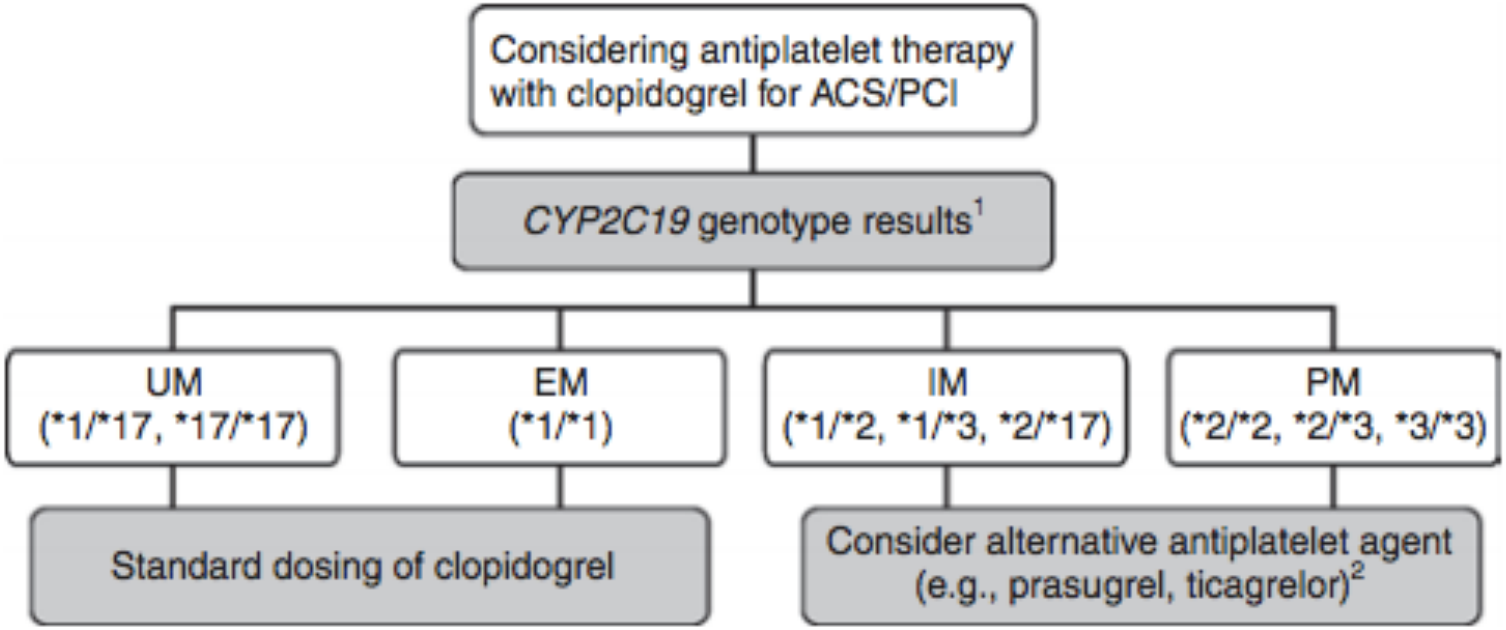
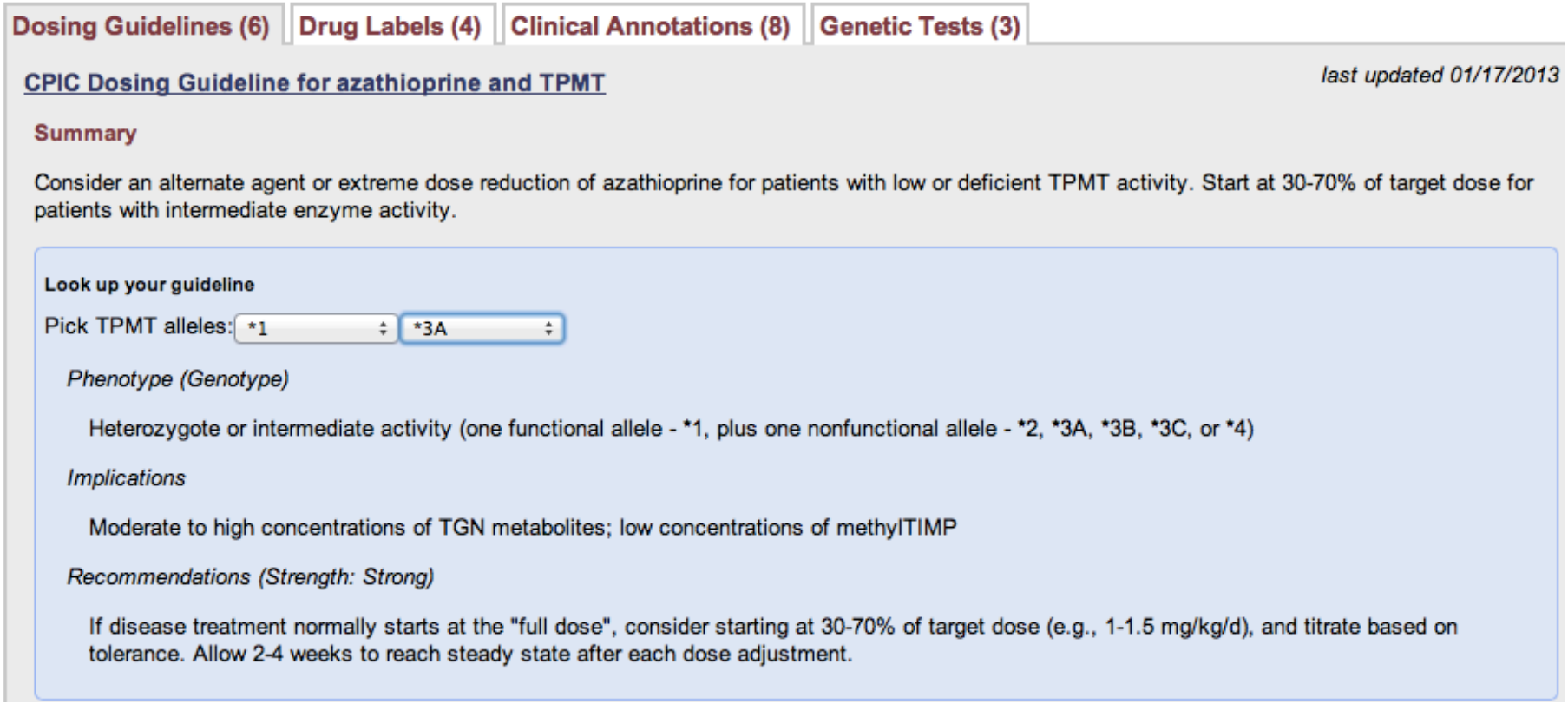


Figure 1 Algorithm for suggested clinical actions based on *CYP2C19* genotype when considering treatment with clopidogrel for ACS patients

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: *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