MODULE 2:What pharmacogenic tests are available?

Pharmacogenomic Biomarkers in Drug Labeling

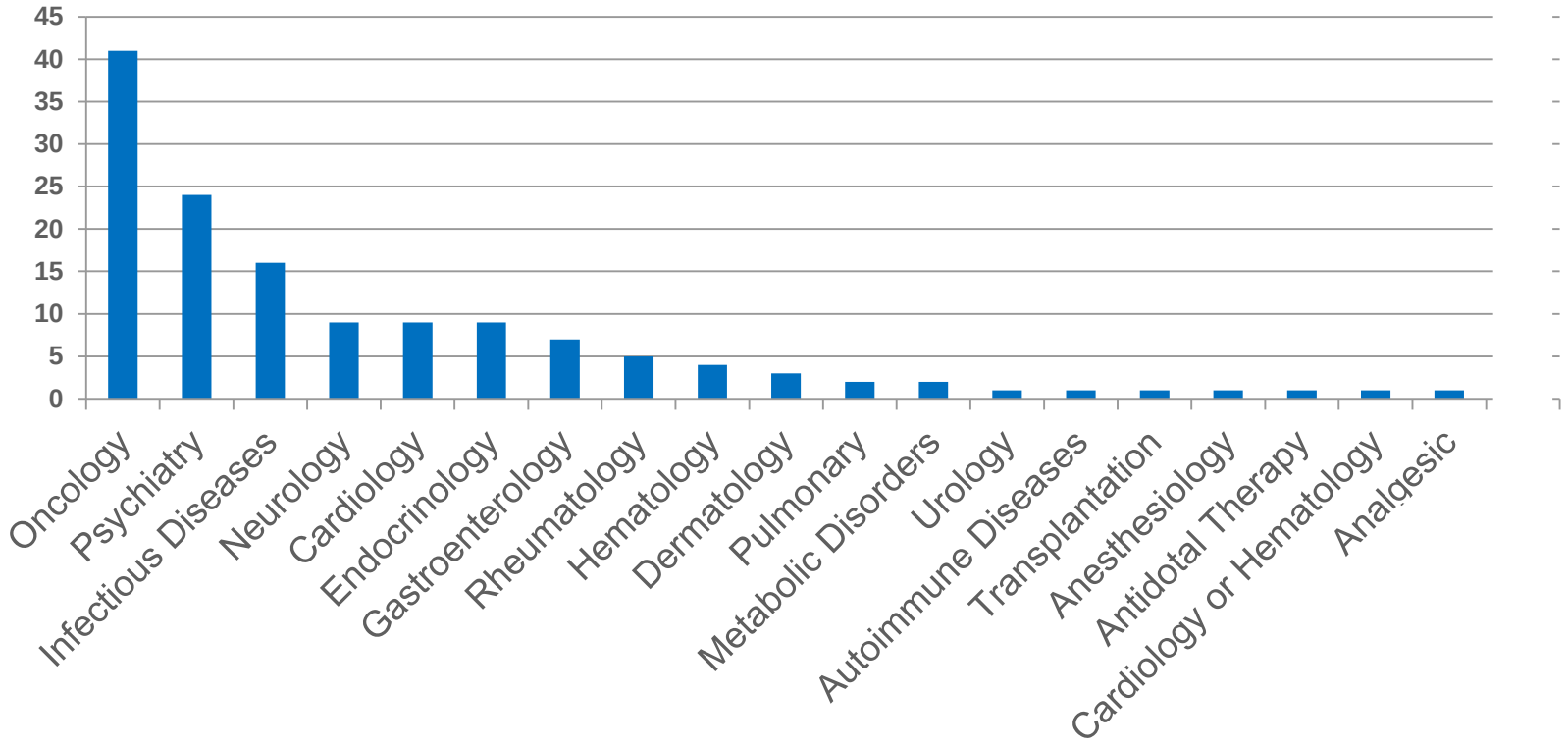
Drug	Therapeutic Area	HUGO Symbol	Referenced Subgroup	Labeling Sections
Abacavir	Infectious Diseases	HLA-B	HLA-B*5701 allele carriers	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information
Ado-Trastuzumab Emtansine	Oncology	ERBB2	HER2 protein overexpression or gene 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)



UCSF

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

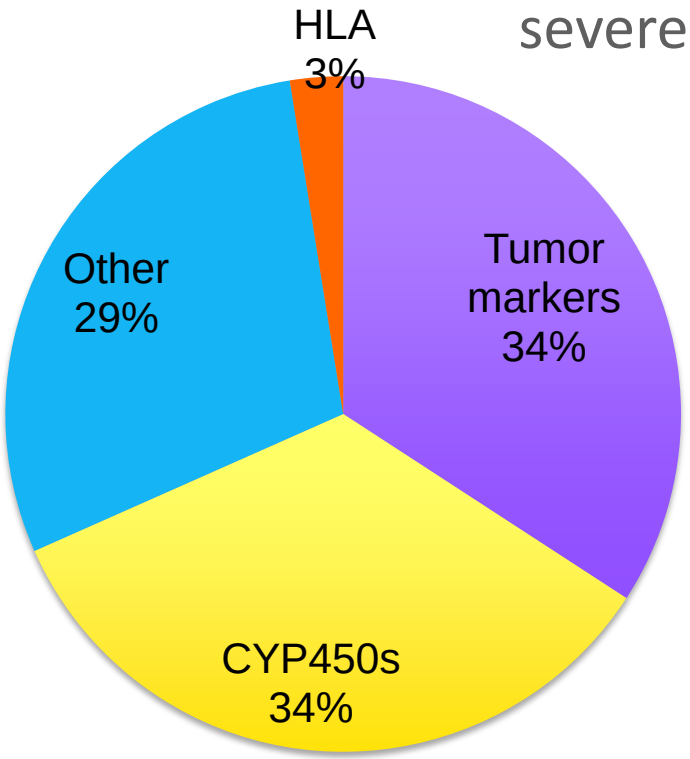
FDA table of pharmacogenomic biomarkers in drug labeling (cont'd)

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

UCSF

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

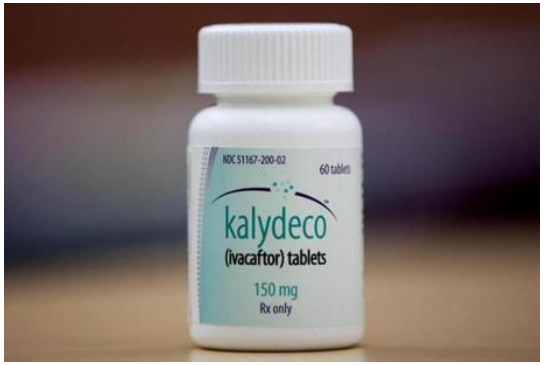
SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

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.

… 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.

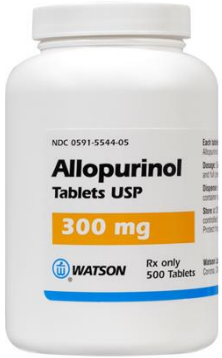
- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- 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

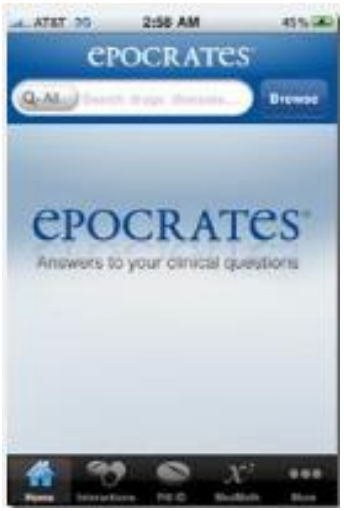
Not all PGx markers are in drug label

Simvastatin – SLCO1B1 typing for myopathy

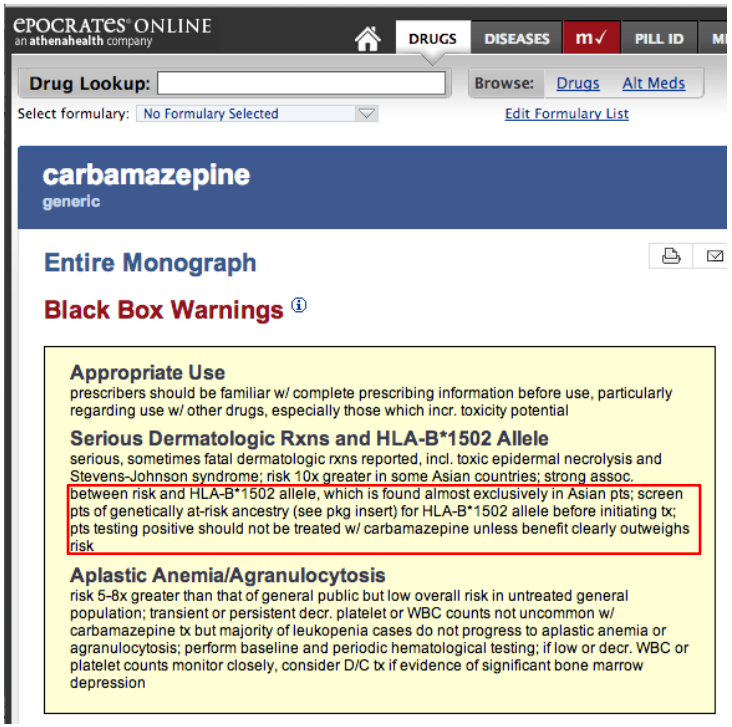
Allopurinol – HLA-B typing for severe cutaneous adverse reactions (drug hypersensitivity syndrome, Stevens-Johnson sydrome and toxic epidermal necrolysis)

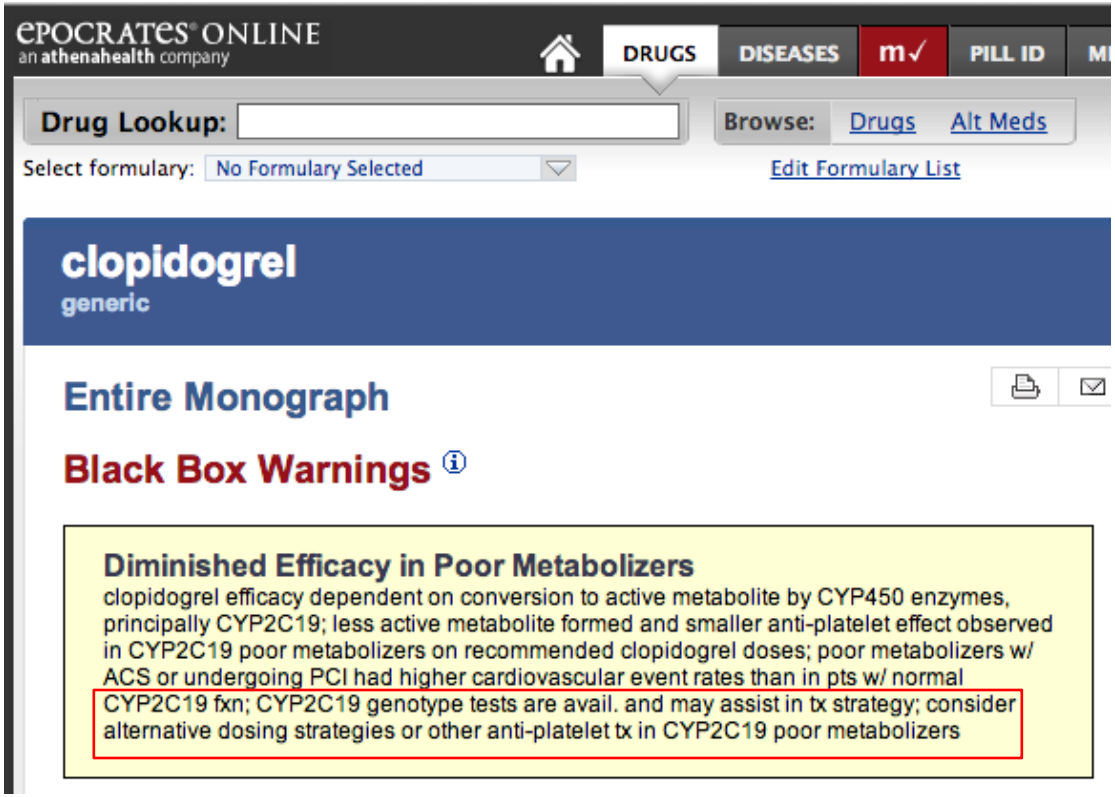


POC medical apps



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