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

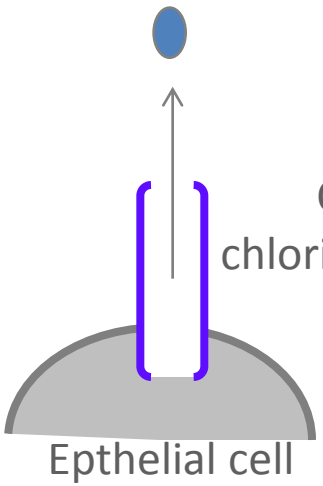
Consider pharmacogenomic testing if…

It is required for efficacy

CFTR genotype-dependent efficacy of Ivacaftor

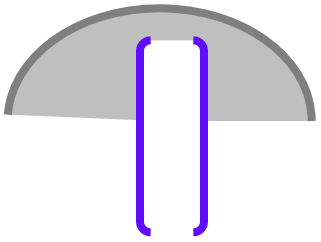
Health individual

Normal ion transport

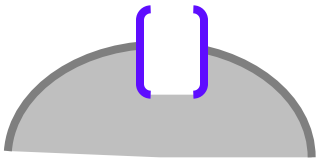


CFTR – chloride channel

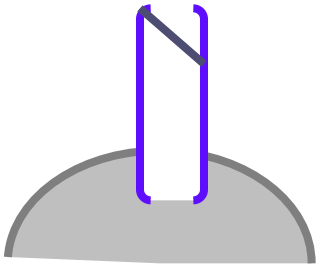
Epthelial cell



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

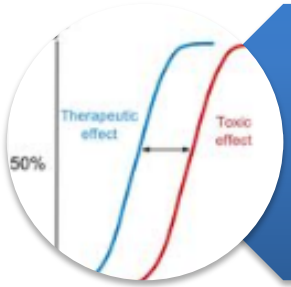
(Simvastatin)

Liver failure/death

(Valproic Acid)

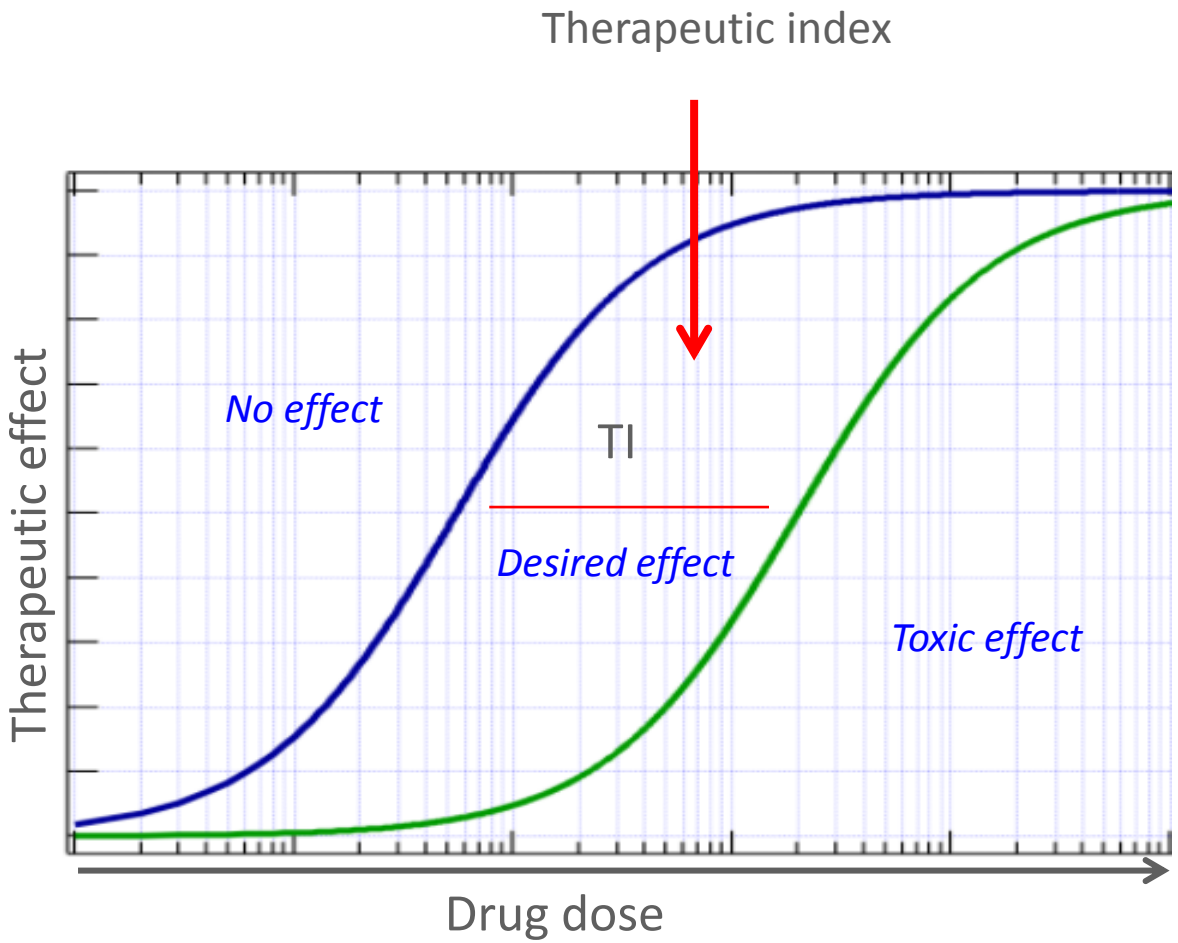
Stevens-Johnson's syndrome
Myelosuppression
Toxic epidermic necrolysis
long QT syndrome

Consider pharmacogenomic testing…

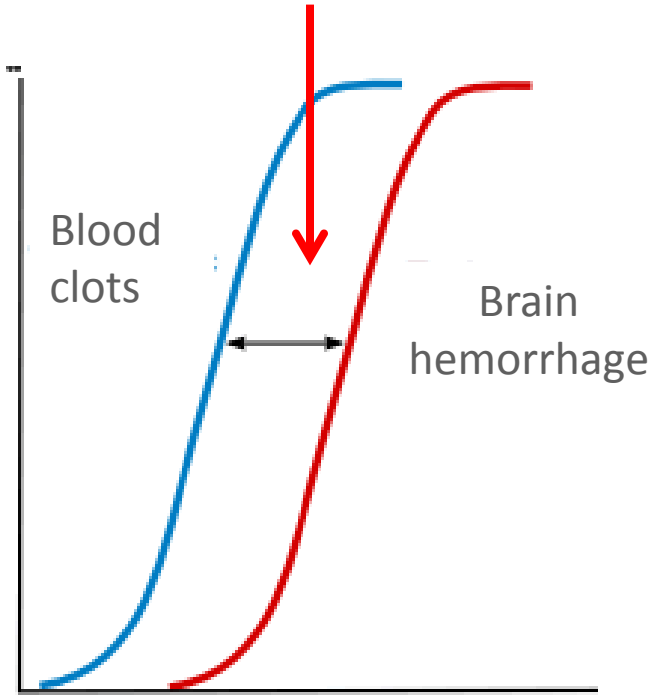


It can help dose a drug with a narrow therapeutic index

Correction for multiple testing



Anti-thrombotic



Pharmacogenomics may help with dosing

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Are alternative therapies available?

- Clopidogrel vs ticagrelor

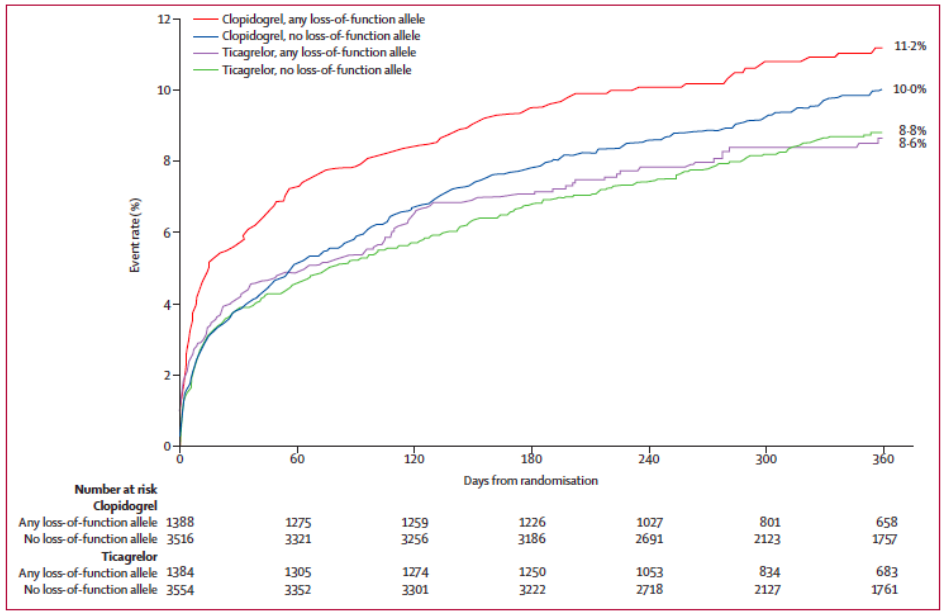
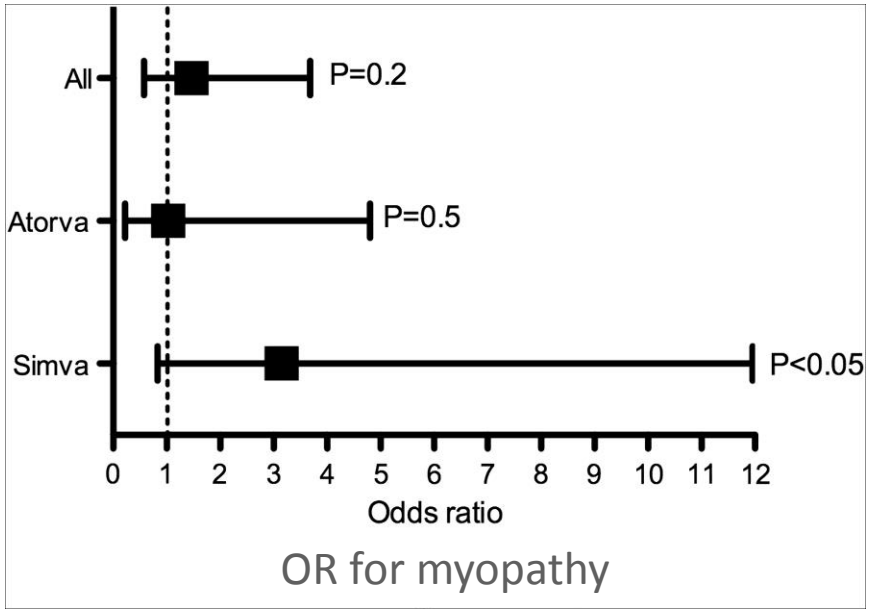


Figure 1: Kaplan-Meier estimates of events of the primary efficacy outcome in relation to the *CYP2C19* genotype

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

- Simvastatin vs atorvastatin

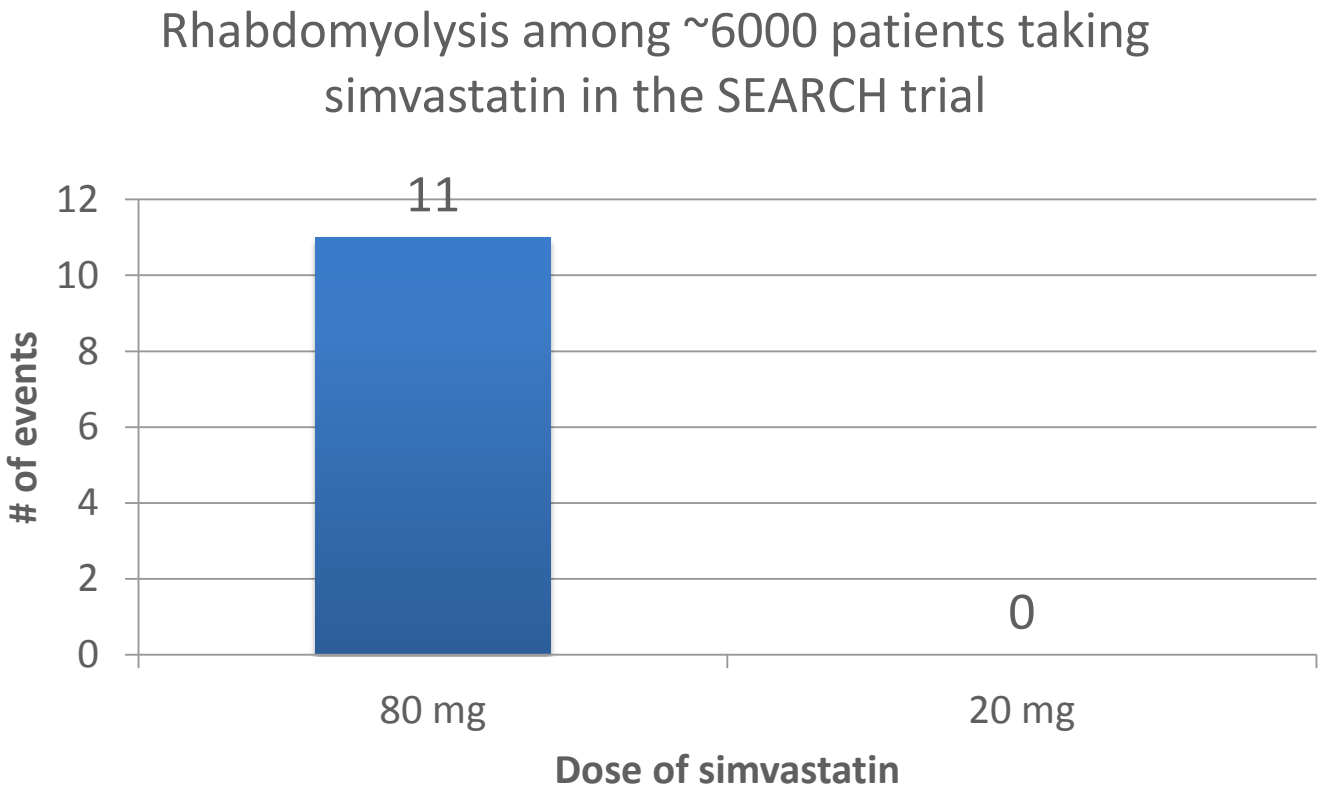


Brunham L, et al Pharmacogenomics J 2012; 12:233-237.

Consider using alternative therapy

UCSF

Is the ADR dose-dependent?

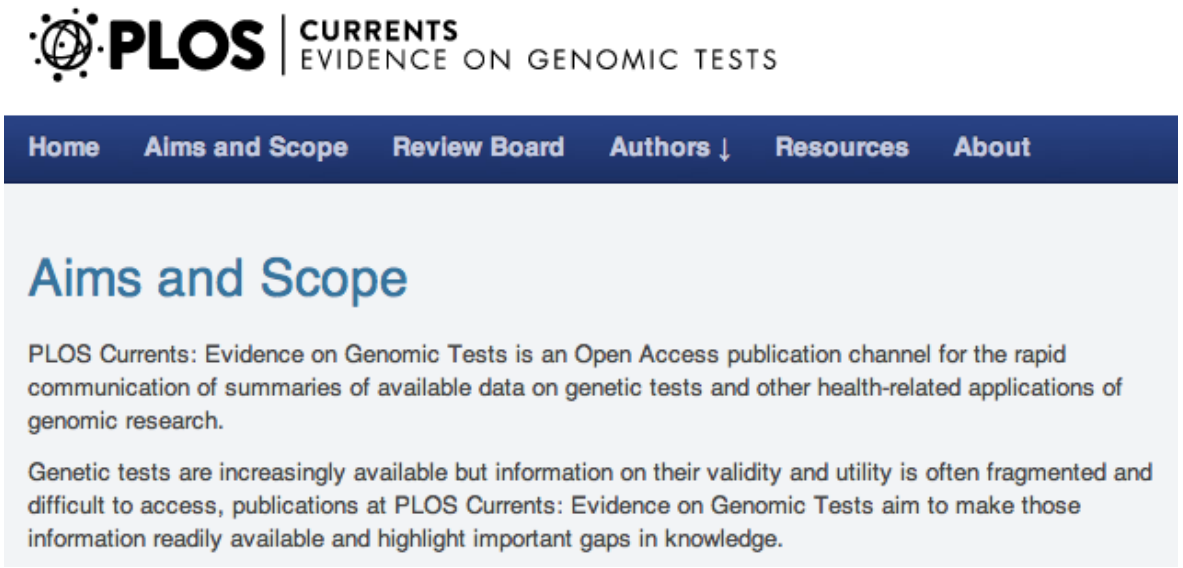


Conservative dosing may mitigate risk of ADR

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

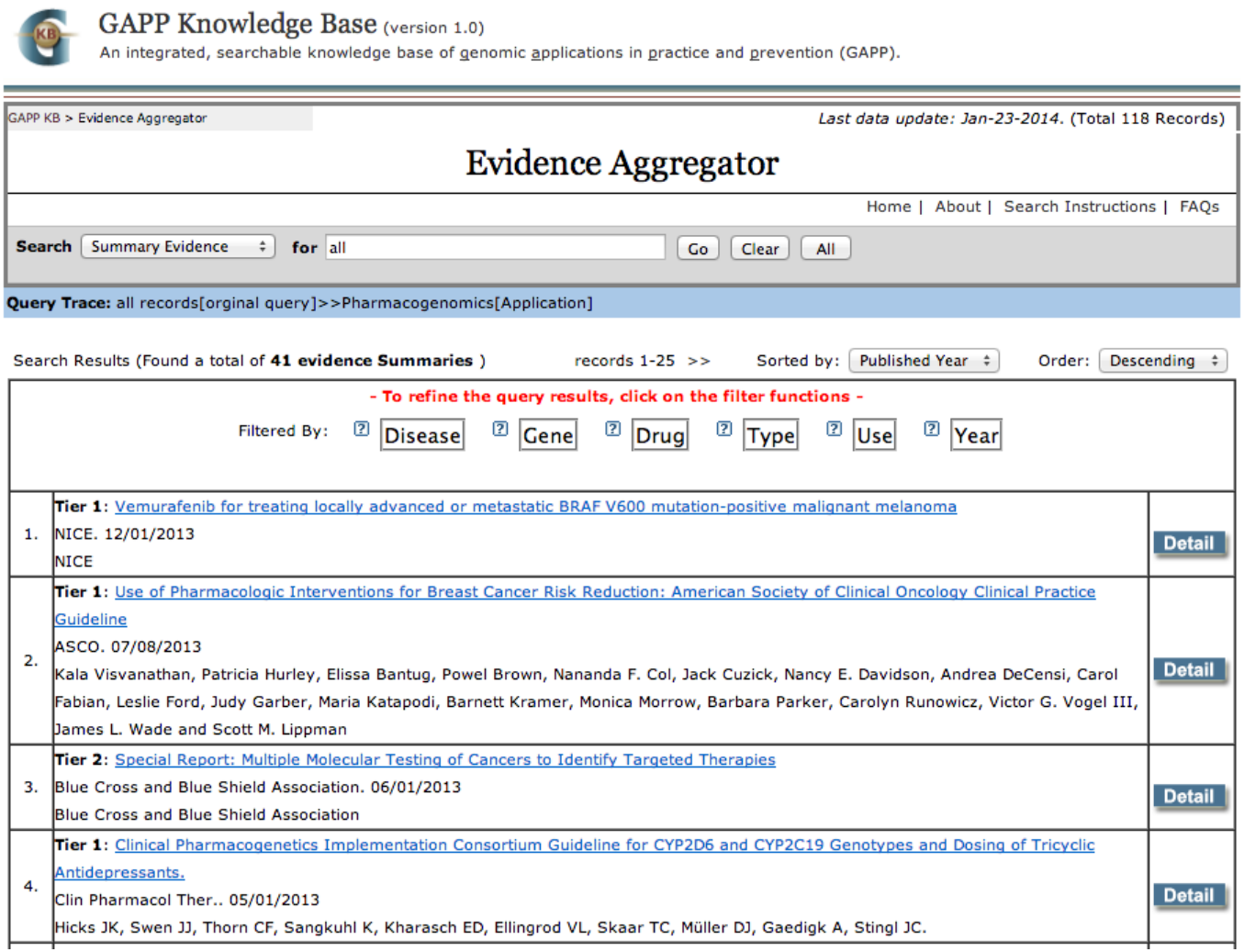
PLoS Currents example: HLA-B*5701 testing for abacavir hypersensitivity

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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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?

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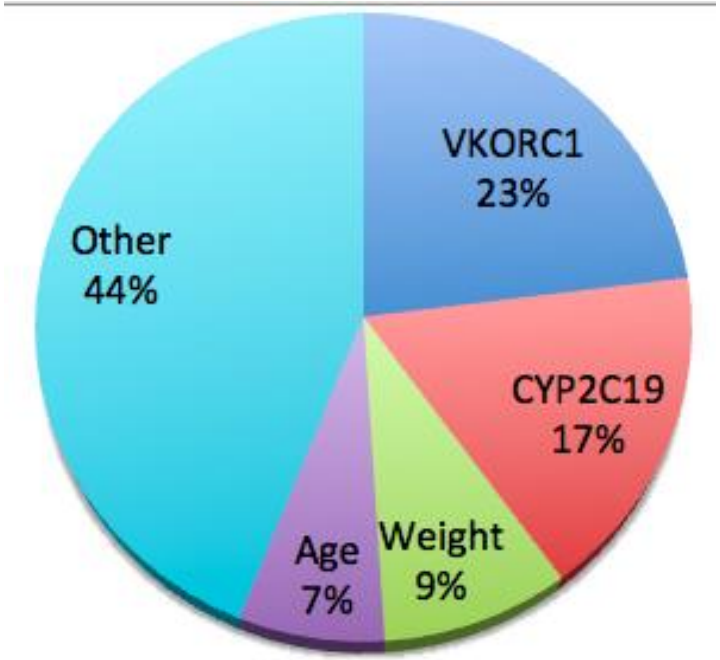
Factors affecting inter-individual variability in drug response

- 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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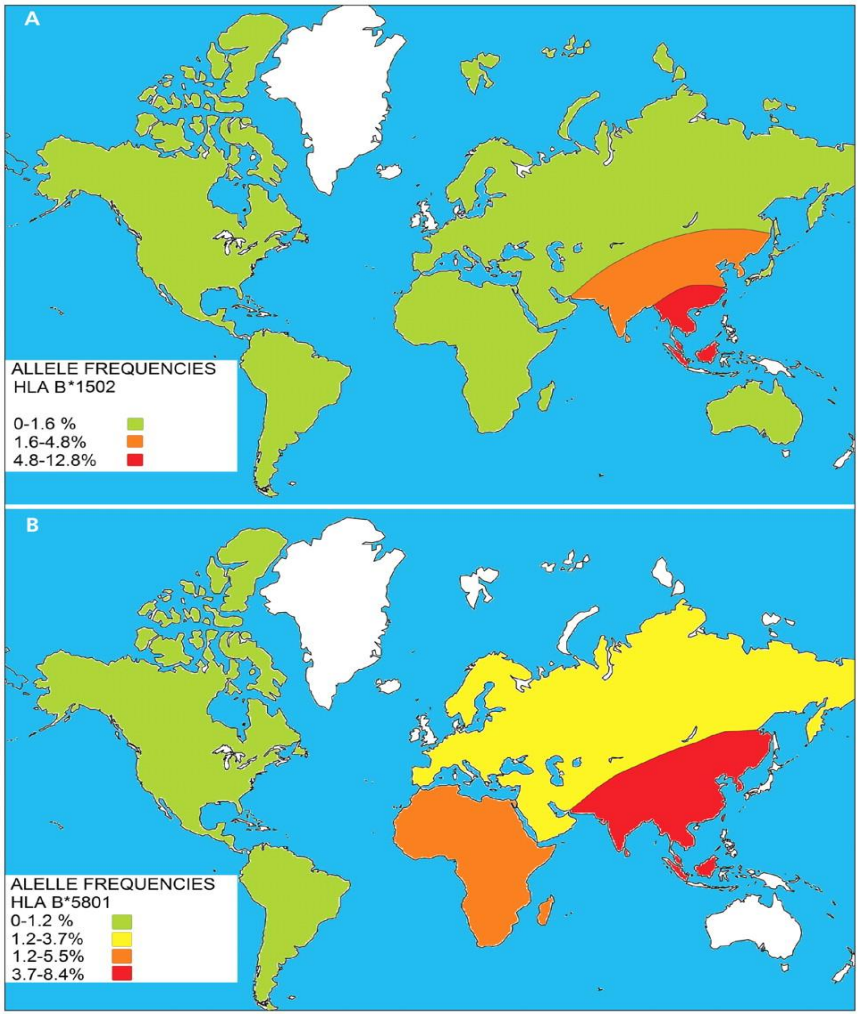
Is test appropriate in patient's ethnic group?

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

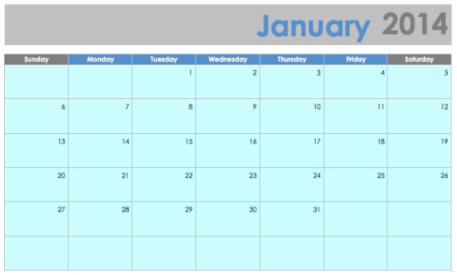
Fernando S L , and Broadfoot A J CMAJ 2010;182:476-480

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