PharmGenEd™
Clinical Applications of Pharmacogenomics

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Therapeutic Areas

- Infectious Diseases: abacavir
- Oncology: trastuzumab
- Anticoagulation: warfarin
- Psychiatry: SSRIs
- Neurology: carbamazepine

Discussion Format

- Gene/Allele of interest
- Functional Effect
- Population Prevalence
- Genomic Test
- Clinical Relevance
  - Dosing/selection
  - Efficacy
  - Toxicity
- Genomic Testing Recommendation

Learning Objectives

Upon completion of this program, participants will be able to

- Identify therapeutic areas in which pharmacogenomic testing can be applied in the clinical setting
- Evaluate the limitations and benefits of pharmacogenomic testing
- Summarize evidence-based recommendations for pharmacogenomic testing
- Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence
- Identify resources for obtaining current pharmacogenomic information

Therapeutic Area: Infectious Diseases

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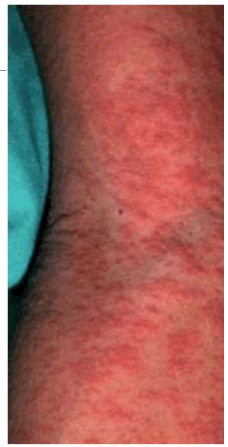
Pre-Test Question:

HIV-positive patients with the *HLA-B*5701* genetic variation and taking abacavir are at increased risk for which one of the following events?

A. Bleeding
B. Serotonin syndrome
C. Hypersensitivity reaction
D. Tumor recurrence

Patient Case

- 29-year old Caucasian male with HIV presents to clinic with fever, GI upset and skin rash on forearms and trunk
- Labs:
  - Viral load: 50,000 copies
  - CD4 count: 100/mm^3
- Allergies: no known drug allergy
- Medications (x3 months): abacavir, zidovudine, efavirenz, sulfamethoxazole-trimethoprim
- Questions:
  - Cause of rash?
  - Testing recommended?
  - Intervention?



Highleyman L, 2008. www.hivandhepatitis.com/recent/2008/101008_c.html
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Abacavir

- **A nucleoside reverse transcriptase inhibitor with activity against HIV**
- **Gene/Allele: *HLA-B*5701***
- **Functional Effect**
  - Presence of allele confers high risk of abacavir-induced hypersensitivity reaction (HSR)
    (Hetherington 2002, Mallal 2002, Cutrell 2004, Nolan 2009, Adam 2011)
  - Symptoms of HSR may include fever, rash, GI and respiratory symptoms and general malaise
  - Untreated HSR can lead to significant hypotension and possibly even death
  - Interaction of drug (or its metabolite) with MHC Class I may lead to CD8$^+$ T-cell mediated cell death
    (Chessman 2008, Nolan 2009, Yang 2009 Adam 2011)

Abacavir

- **Population Prevalence (of *HLA-B*5701)***
  - Among those initiating therapy with abacavir:
    - Caucasians: 5-8% (Hetherington 2001, Lucas 2007)
    - Asians: 0-2%
    - Hispanics: 1%
    - African-Americans: 0.5% (Chui 2007, Maiers 2007)
- **Genomic Test**
  - HLA typing: Positive test for *HLA-B*5701* confers ↑ risk for HSR
    - *HLA-B*5701* negative patients: <1% HSR
    - *HLA-B*5701* positive: >70% HSR (Hetherington 2002, Mallal 2002)

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Abacavir: Clinical Relevance

- **Dosing/Selection**
  - Dosing is not affected by pharmacogenomic testing but drug selection may be affected
- **Efficacy**
  - No literature related to how pharmacogenomics impacts drug efficacy
- **Toxicity**
  - **PREDICT-1** study showed that *HLA-B*5701* screening can accurately predict patients who may be at risk for abacavir hypersensitivity (Mallal 2008)
  - Incidence of confirmed abacavir HSR was 2.7% among unscreened patients vs. 0% among screened patients ($p<0.001$) (Mallal 2008)

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Abacavir: Clinical Relevance

- **Toxicity** (Cont.)
  - **SHAPE** study showed similar trend in Whites and Blacks
    - *HLA-B*5701* screening accurately predicted 100% of abacavir HSR cases (confirmed by skin patch testing) (Saag 2008)
  - **ARIES** study investigated *HLA-B*5701* negative patients
    - <1% had clinically suspected HSR
    - none had positive skin patch tests at 30 weeks (Young 2008)

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Abacavir: Genomic Testing Recommendations

- Screening for *HLA-B*5701* prior to initiation of abacavir is recommended by the Department of Health and Human Services Guidelines (U.S. DHHS 2008)
- Screening for *HLA-B*5701* is included in the black box warning (Ziagen® Prescribing Information)
- Patients testing positive for the *HLA-B*5701* allele should *not* be prescribed abacavir if other options are available

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Post-Test Question:

HIV-positive patients with the *HLA-B*5701* genetic variation and taking abacavir are at increased risk for which one of the following events?

A. Bleeding
B. Serotonin syndrome
C. Hypersensitivity reaction
D. Tumor recurrence

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Patient Case Summary

- Patient was screened and tested positive for *HLA-B*5701*
- Symptoms were due to abacavir-induced HSR
- Abacavir was discontinued; other medications were continued
- Patient continued to be monitored for worsening hypersensitivity and other complications such as hepatomegaly, lactic acidosis, toxic epidermal necrolysis, Stevens-Johnson Syndrome
- Symptoms resolved with discontinuation of abacavir
- Patient was not re-challenged with abacavir

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Therapeutic Area: Oncology

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Trastuzumab

- **Trastuzumab is a monoclonal antibody used to treat breast cancer**
- **Gene: Human epidermal growth factor receptor *(HER2)*** (Dowsett 2009)
- **Functional Effect**
  - Overexpressed proto-oncogene in some breast cancers
  - *HER2* overexpression correlates with reduced disease-free time and overall survival (Slamon 1987)
  - Trastuzumab binds to HER2 protein on the surface of tumor cells (Herceptin® Prescribing Information)

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Trastuzumab

- **Population Prevalence:**
  - No evidence that *HER2* expression differs by race (Marti 2008)
  - *HER2* levels may be inversely related to body mass index among premenopausal women (Sherman 2007)
- **Genomic Tests** (Herceptin® Prescribing Information)
  - Two types of tests for *HER2* status have been approved by the Food and Drug Administration (FDA)
    - Fluorescence In Situ Hybridization (FISH): PathVysion®, *HER2* FISH pharmDx™
    - Immunohistochemistry: HercepTest®, Pathway™
  - Positive results indicate overexpression of *HER2*

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Trastuzumab: Clinical Relevance

- **Dosing/Selection**
  - Dosing is not affected by pharmacogenomic testing, but drug selection is affected
- **Efficacy**
  - Trastuzumab plus chemotherapy in patients with *HER2*-positive breast cancer are associated with
    - Increased time to disease progression
    - Longer median survival time
    - Decreased risk of death in metastatic breast cancer (Slamon 2001, Marty 2005)
  - Adjuvant trastuzumab given with paclitaxel in patients with *HER2*-positive breast cancer resulted in
    - Increased disease-free survival
    - Decreased risk of death compared to chemotherapy alone (Piccart-Gebhart 2005, Romond 2005)

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Trastuzumab: Clinical Relevance

- **Efficacy**
  - There is insufficient evidence to conclude benefit of continued treatment with trastuzumab monotherapy or with chemotherapy after progression of disease (Hudis 2007)
- **Toxicity**
  - Trastuzumab alone is associated with 5% risk of cardiomyopathy (Slamon 2001)
  - There is limited evidence of increased risk of cardiotoxicity from trastuzumab if one copy of the *Ile655Val* allele variant of *HER2* gene is present (Beauclair 2007)
  - Testing for *Ile655Val* allele is not standard of care

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Trastuzumab: Genomic Testing Recommendations

- Testing for *HER2* status is necessary prior to initiation of trastuzumab (Wolff 2007, Padzur 2011, Herceptin® Prescribing Information)
- National Comprehensive Cancer Network Task Force Report provides guidelines about IHC and FISH cutoff scores to determine *HER2* status (Carlson 2006)
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group does not yet have recommendations for the use of genomic tests for trastuzumab (http://www.egappreviews.org/)

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Therapeutic Area: Anticoagulation

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Pre-Test Question:
Which polymorphisms will most likely influence warfarin dosing?

A. *CYP2C9* and *VKORC1*
B. *CYP2C19* and *VKORC1*
C. *CYP2D6* and *VKORC9*
D. *CYP2D6* and *VKORC1*

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Warfarin

- Oral anticoagulant, widely used to prevent and treat thromboembolic disease in patients with deep vein thrombosis, pulmonary embolism, mechanical heart valves and atrial fibrillation
- Associated with significant risk of major and sometimes fatal bleeding events

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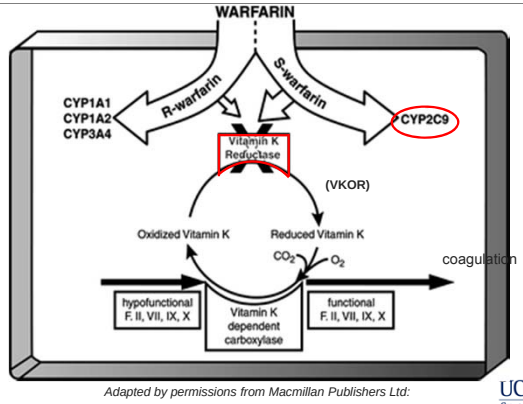
Warfarin Metabolism is Affected by *CYP2C9* and *VKORC1*



Adapted by permissions from Macmillan Publishers Ltd: [The Pharmacogenomics Journal] (V.4: Issue 4, 224-225), (pg.225), (2004)

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Warfarin and *CYP2C9*

- **Gene/alleles: *Cytochrome P450 2C9***
  - *CYP2C9*1 wild type allele*
  - *CYP2C9*2 variant allele*
  - *CYP2C9*3 variant allele*
- **Functional Effect**
  - *CYP2C9*2* and **3* alleles result in ↓ *CYP2C9* activity by 50% and 90%, respectively (Lee 2002, Schwarz 2003)
  - ↓ *CYP2C9* activity results in ↑ warfarin concentrations
- **Population Prevalence**
  - Caucasians: 3-20% (Xie 2002)
  - Asians & African-Americans: 1-4% (Lee 2002, Xie 2002)

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Warfarin and *VKORC1*

- **Gene/allele: *Vitamin K epoxide reductase complex subunit 1 (VKORC1)***
  - *VKORC1 1173 C>T*
  - *VKORC1 -1639 G>A (also known as 3673 G>A)*
  - These two SNPs, along with others, combine to form several haplotypes (Rieder 2005)
- **Functional Effect** (Rieder 2005, Gage 2008)
  - Five common haplotypes are categorized into two groups, according to their impact on warfarin dose
    - Group A haplotypes (1 and 2) are associated with requiring a lower warfarin dose
    - Group B haplotypes (7, 8, and 9) are associated with requiring a higher warfarin dose

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Warfarin and *VKORC1*

- **Population Prevalence** (Rieder 2005, Yuan 2005, Mushiroda 2006)
  - *VKORC1 1173 C>T*
    - Asians: 82-89%, Caucasians: 14%-41%, African-Americans: 9%
  - *VKORC1 -1639 G>A* (or *3673 G>A*)
    - Asians: 82%, Caucasians: 14%
  - *VKORC1* Haplotypes
    - Group A: Asians: 89%, Caucasians: 37%, African-Americans: 14%
    - Group B: Caucasians: 58%, African-Americans: 49%, Asians 10%
  - *VKORC1* Genotypes
    - Genotype AA: Caucasians 18%
    - Genotype BB: Caucasians 35%

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Warfarin: Genomic Tests

- **Systematic review found that:**
  - More analytic validity data exist for *CYP2C9* than for *VKORC1*
  - Sensitivity and specificity for *CYP2C9* genotyping >98%; unknown for *VKORC1* (McClain 2008)
- Turn-around time is less than 6 hours, but may take longer depending on transport and lab specifics
- There is limited evidence on specific variants of *CYP2C9/VKORC1* that should be included in the current tests, long-term performance of tests, and consistency between laboratories

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Warfarin: Clinical Relevance

- **Dosing/Selection**
  - Variability in warfarin dosing among Caucasians & Asians can be explained by *VKORC1* (23%), *CYP2C9* (17%), and other factors (60%) (McClain 2009)
  - *CYP2C9* variant alleles lead to lower warfarin dose requirements
    - Gene-dose relationship exists; having 2 copies of a variant allele results in lower dose requirements than having only 1 copy of a variant allele (Higashi 2002, Takahashi 2003, Borgiani 2007)
  - *VKORC1* alleles influence dosing
    - Genotype AA is associated with requiring a lower warfarin dose (2.9-3.0 mg/day)
    - Genotype BB is associated with requiring a higher warfarin dose (5.5-6.0 mg/day) (Rieder 2005)

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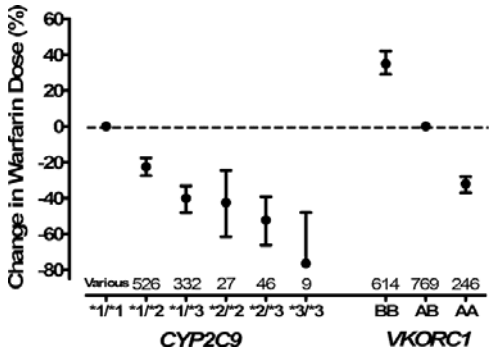
Clinical Relevance: *CYP2C9* & *VKORC1* Alleles Influence Warfarin Dose



Reprinted by permission of Wolters Kluwer. McClain MR et al. A Rapid-ACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Genet Med 2008:10(2):89–98.

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Clinical Relevance: Genotype-Guided Warfarin Dosing

- A multicenter trial of 4,043 patients, requiring target International Normalized Ratios (INR) between 2-3, compared three dosing algorithms for warfarin
  (Int. Warfarin Pharmacogentics Consortium 2009)
  - Pharmacogenetic algorithm
  - Fixed dose approach (35mg/week)
  - Clinical algorithm
- The pharmacogenetic algorithm combined both clinical information and genetic information to make dose recommendations

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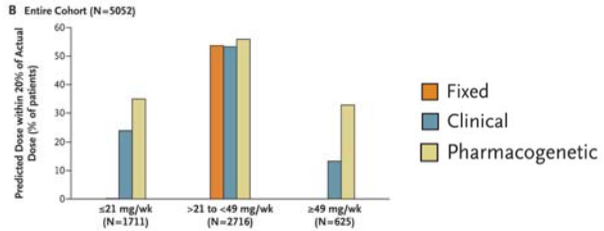
Comparison of Pharmacogenetic, Fixed, & Clinical Algorithm Dosing

- Pharmacogenetic algorithm was the most accurate method at predicting dose for patients requiring:
  - ≤ 21 mg/week of warfarin (35% vs. 24%, p<0.001)
  - ≥49 mg/week of warfarin (32.8% vs. 13.3%, p<0.001)



Int. Warfarin Pharmacogent. Consort. 2009. NEJM 2009; 360(8):753-64.
Estimation of the warfarin dose with clinical and pharmacogenetic data.

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Warfarin: Clinical Relevance

- **Dosing/Selection**
  - Genetic testing may guide initial warfarin dose, but utility may be limited once the therapeutic dose is achieved (Gage 2008)
  - Genetic testing may decrease time to stabilization of dose; but long-term impact on safety is unknown
  - No literature suggests that testing would affect selection of the drug

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Warfarin: Clinical Relevance

- **Efficacy**
  - Testing may improve prediction of stable doses, resulting in smaller and fewer dosing changes (Anderson 2008)
- **Toxicity**
  - Clinical sensitivity of *CYP2C9* testing to identify serious bleeding events is 46%
  - Clinical specificity of *CYP2C9* testing is 69%
  - Relative risk for serious bleeding in variant versus wild-type individuals is 1.7 (95% CI: 0.8-3.6)
  - *CYP2C9* testing may ↓ risk of serious bleeding events but may ↑ risk of clotting events (Anderson 2008, McClain 2008)

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Warfarin: Genomic Testing Recommendations

- Prescribing information contains pharmacogenomic testing information relevant to warfarin dosing (Coumadin Prescribing Information)
- Pharmacogenomic testing is not required for patients currently on warfarin therapy
- Centers for Medicare and Medicaid Services (CMS) will pay for pharmacogenomic testing for those who are enrolled in clinical studies, have not been previously tested and have received fewer than 5 days of warfarin (CMS 2009)

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Post-Test Question:
Which polymorphisms will most likely influence warfarin dosing?

A. *CYP2C9* and *VKORC1*
B. *CYP2C19* and *VKORC1*
C. *CYP2D6* and *VKORC9*
D. *CYP2D6* and *VKORC1*

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Therapeutic Area: Psychiatry

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Patient Case

- 45-year old Asian man recently diagnosed with recurrent major depression
- The patient needs a recommendation for a new antidepressant
- Past medical history:
  - Has tried paroxetine, but has had significant nausea and diarrhea
  - Despite lowering the dose, patient still experienced adverse effects
  - No improvement in depressive symptoms
- Question:
  - Should pharmacogenomic testing be used to predict response and minimize potential SSRI toxicity?

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Selective Serotonin Reuptake Inhibitors (SSRIs)

- **Genes for Cytochrome P450 (CYP) enzymes:**
  - *CYP2C9, CYP2D6, CYP1A2, CYP3A4,* and others (EGAPP Working Group 2007)
- **Functional Effect**
  - Null or ↓ CYP activity confers poor metabolizer phenotype
  - ↑ CYP activity activity confers ultra-rapid metabolizer phenotype
  - Multiple enzymes are involved in SSRI metabolism, but CYP2D6 is the most important enzyme for this class of drugs

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SSRI: Functional Effect of *CYP2D6*

CYP2D6 Genotypes	Phenotype (Metabolizer Status)	Expected Effects from Usual SSRI Doses
>2 copies of wild-type allele	Ultra-rapid Metabolizer (UM)	Sub-therapeutic drug concentrations → no response
2 copies of wild-type allele	Extensive Metabolizer (EM)	Expected drug concentrations and response
1 inactive and 1 reduced activity allele or 2 reduced activity alleles	Intermediate Metabolizer (IM)	Drug effects between those of EMs and PMs
2 copies of inactive alleles	Poor Metabolizer (PM)	Higher than expected drug concentrations → adverse reactions

EGAPP Working Group 2007

SSRI: Population Prevalence

Major variant allele	Caucasians (%)	Asians (%)	African-Americans (%)
*CYP2C9*2*	8-12	<3	<3
*CYP2C9*3*	6-10	4-7	1-2
*CYP2D6*4*	12-21	1	2
*CYP2D6*5*	27	6	4
*CYP2D6*10*	1-2	51	6
*CYP2D6*17*	0	0	20-35
*CYP2D6*41*	8-10	0-2	11-14
*CYP3A4*1B*	4	0	67
*CYP3A5*3*	92-94	55-75	29-35
*CYP1A2*1F*	68	32	46

Modified from Sata 2000, Takahashi 2001, Lee 2002, Xie 2004, Ingelman-Sundberg 2005, Soyama 2005

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SSRI: Genomic Test

- Various *CYP450* genotype platforms exist that have been approved for *CYP2D6* and *CYP2CI9* by the FDA
- Sensitivity and specificity of available pharmacogenomic tests for *CYP2D6, CYP2C9, CYP2C19* are high (>95%)
- Evidence for *CYP2D6* genotyping is most compelling (Matchar 2007)

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SSRI: Clinical Relevance

- **Dosing/Selection**
  - Single-dose SSRI studies in healthy volunteers showed that poor metabolizer genotype (*CYP2D6, CYP2C19*) correlates with ↑ SSRI concentrations and ↓ clearance (Yoon 2000, Liu 2001, Wang 2001, Yu 2003)
- **Efficacy**
  - Conflicting evidence from cross-sectional studies regarding clinical response and *CYP450* genotypes *(CYP2D6, CYP2C9, CYP2C19)* (Gerstenberg 2003, Murphy 2003, Grasmader 2004, Kawanishi 2004, Rau 2004)
  - No conclusion can be made about relationship between *CYP450* genotypes and efficacy of SSRI treatment in non-psychotic depression (Matchar 2007)

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SSRI: Clinical Relevance

- **Toxicity**
  - Conflicting evidence for *CYP2D6* polymorphisms and rates of SSRI adverse effects (mostly GI effects) (Chen 1996, Gerstenberg 2003, Murphy 2003, Rau 2004, Roberts 2004, Suzuki 2006)
  - None of the studies were prospective randomized trials
  - No conclusions may be drawn about relationship between *CYP* genotypes and adverse effects of SSRIs (Matchar 2007)

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SSRI: Genomic Testing Recommendations

- Insufficient evidence to support recommendation *for or against* testing prior to initiating treatment with SSRIs for non-psychotic depression (EGAPP Working Group 2007)
- No specific recommendations for testing CYP enzyme activity

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Therapeutic Area: Neurology

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Pre-Test Question:
What is the current pharmacogenomic testing recommendation for carbamazepine?

A. Test all patients prior to starting carbamazepine
B. Test high risk patients only prior to starting carbamazepine
C. Test patients only if they have a history of hypersensitivity reactions
D. Test patients only if they develop a hypersensitivity reaction

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Carbamazepine

- **Anticonvulsant indicated for partial and generalized seizures, trigeminal neuralgia, and bipolar disorder**
- **Gene/Allele**
  - *HLA-B*1502, HLA-A*3101, HLA-B*1511*
- **Functional Effect**
  - *HLA-B*1502* ↑ risk of carbamazepine-induced, life-threatening hypersensitivity reactions Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (Chung 2004, Yip 2012)
  - *HLA-A*3101* and *HLA-B*1511* ↑ risk of carbamazepine-induced, cutaneous hypersensitivity (both mild and severe) (McCormack 2011, Ozeki 2011, Niihara 2012, Yip 2012, Kaniwa N 2010)
  - Interaction between drug and MHC Class I may lead to CD8+ T-cell mediated cell death (Yang 2007, Adam 2011, Pichler 2011, Chung 2012, Ko 2012)

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Carbamazepine

- **Population Prevalence**
  - *HLA-B*1502* frequency (Chung 2010, Aihara 2011, Kim 2011, www.allelefrequencies.net, www.ihwg.org)
    - East Asians: Han Chinese 2-12%, Thai 6-8%
    - South Asians: Indians 1-6%, Singapore, Malaysians 8.4-11.6%, Thai, Filipino: 5.3-6.1%
    - North Asians: Japanese 0.1%, Koreans: 0.2-0.4%
    - Caucasians, Europeans, Hispanics 0%
    - African-Americans 0.2%
  - *HLA-A*3101* frequency (Wen 2008, Schmidt 2009, Gonzalez-Galarza 2011, McCormack 2011, Ozeki 2011, Yip 2012)
    - North European: 2-5%, Han Chinese: 2-3%, Japanese: 7-12%
  - *HLA-B*1511* frequency (www.allelefrequencies.net; Kim 2011)
    - Singaporeans: 2%, Koreans: 3-4%, Taiwanese: 1-2%, Caucasians and African-Americans: 0%
- **Genomic Test**
  - *HLA* typing: Patients are positive if either one or two copies of a relevant allele is present

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Carbamazepine: Clinical Relevance

- **Dosing/Selection**
  - Dosing is not affected by pharmacogenomic testing, but selection of drug is affected
- **Efficacy**
  - *HLA* status is not known to affect clinical efficacy of carbamazepine
- **Toxicity**
  - Incidence of SJS/TEN is <2 patients per million per year. Rate of death with these conditions (in absence of carbamazepine) range from 5% and 35% for SJS and TEN, respectively
  - Carbamazepine toxicity is associated with the *HLA-B*1502 and HLA-A*3101* alleles (Gomes 2005, Yip 2012)

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Carbamazepine: Clinical Relevance

- **Toxicity associated with *HLA-B*1502***
  - *HLA-B*1502* allele was present in 98-100% of carbamazepine-induced SJS cases in Han Chinese subjects (Chung 2004, Hung 2006, Chung 2010)
  - Among Han Chinese, testing for *HLA-B*1502* provides 96% sensitivity and 88% specificity for predicting SJS/TEN (Yip 2012)
  - *HLA-B*1502* status is not associated with SJS/TEN among Japanese or Caucasians (Alfirevic 2006, Lonjou 2006, Kaniwa 2008, Ikeda 2010)

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Carbamazepine: Clinical Relevance

- **Toxicity associated with *HLA-A*3101***
  - *HLA-A*3101* is associated with carbamazepine hypersensitivity different populations (Yip 2012)
  - Among Japanese
    - Testing for *HLA-A*3101* provides 58% sensitivity and 87% specificity for predicting hypersensitivity (Yip 2012)
  - Among Caucasians
    - The test for *HLA-A*3101* provides 26% sensitivity and 96% specificity (Yip 2012)

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Carbamazepine: Genomic Testing Recommendations

- ***HLA-B*1502***
  - The FDA recommends testing prior to initiation of carbamazepine therapy in patients with at-risk Asian ancestry (FDA alert 2007)
  - Black box warning for carbamazepine includes this information (Tegretol® Prescribing Information)
  - Thai study suggests that *HLA-B*1502* testing may be cost-effective for prevention of carbamazepine-induced SJS/TEN (Locharernkul 2010)
- ***HLA-A*3101***
  - Currently the FDA does not provide any recommendation regarding testing for *HLA-A*3101*

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CPIC: Carbamazepine (CBZ) Dosing Recommendations

Genotype	Implications	Recommendations	Classification
Noncarrier of *HLA-B*15:02*	Normal or reduced risk of CBZ-induced SJS/TEN	Use CBZ per standard dosing guidelines	Strong
Carrier of *HLA-B*15:02*	Increased risk of CBZ-induced SJS/TEN	Do not use CBZ if naïve	Strong
		Use with caution if previously used CBZ > 3 months without ADR	Optional

CBZ=carbamazepine, SJS/TEN=Stevens Johnson Syndrome/Toxic Epidermal Necrolysis

ADR=adverse drug reaction

Label Section: Boxed Warning, Warnings and Precautions

Adapted from Leckband SG et al. Clinical Pharmacology & Therapeutics 2013;94(3):324.

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Post-Test Question:

What is the current pharmacogenomic testing recommendation for carbamazepine?

A. Test in all patients prior to starting carbamazepine
B. Test in high risk patients only prior to starting carbamazepine
C. Test in patients only if they have a history of hypersensitivity reactions
D. Test in patients only if they develop a hypersensitivity reaction

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Thank you!

Where discoveries are delivered.℠

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