Updates in Pharmacogenetics Education on Drugs Used in Cardiovascular Conditions and Infectious Diseases

Southeastern Ohio Academies of Pharmacy (SEOPA) Spring Seminar
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WestVirginiaUniversity. SCHOOL OF PHARMACY

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"I have nothing to disclose concerning possible financial relationships with ineligible companies that may have a direct or indirect interest in the subject matter of this presentation"

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Learning Objectives

- Identify the role of pharmacogenetics in variability of patient response.
- Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel. statins, and beta-blockers pharmacogenetics.
- Summarize CPIC guidelines on abacavir, antimalarials and maraviroc.
- Apply pharmacogenetic recommendations in two patient cases.

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Objective 1:
Identify the role of pharmacogenetics in variability of patient response.

PGx can affect

Pharmacokinetics
ADME – Focus on distribution and metabolism.
Risk of therapeutic failure or adverse side reactions
Outcomes will depend on type of drug (prodrug)
Homozygous vs. heterozygous

Pharmacodynamics
Site of action, competing against binding

Hypersensitivity reactions
Mutations in HLA (human leukocyte antigen)

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Objective 1:
Identify the role of pharmacogenetics in variability of patient response.

How? **Genetic polymorphisms**

Variations in the DNA sequence. Genetic variations occurring in more than 1% of a population would be considered as useful polymorphism for genetic linkage analysis

Types: **Single Nucleotide Polymorphisms (SNPs)**
Insertions/Deletions (indels)
Variable number tandem repeats (VNTRs)
Copy Number Variants (CNVs)

From Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014)

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Objective 1:
Identify the role of pharmacogenetics in variability of patient response.

SNPs

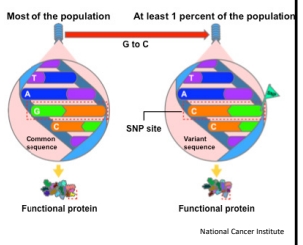
SNPs can alter transcription, and mRNA expression. They occur every 100-300 bp.

Synonymous: No change in amino acid. It was previously thought that it was silent (no effect), but currently it is thought that synonymous SNPs can alter mRNA stability

Nonsynonymous (missense): Changes amino acid. Could affect protein structure and/or function.

Nonsense: Insertion of stop codon

Indel: Disrupts codon sequence



https://www.genome.gov/genetics-glossary/Single-Nucleotide-Polymorphisms
From Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014
Lam JT, Gutierrez MA, Shah S. eds. *Pharmacogenomics: A Primer for Clinicians*. McGraw Hill; 2021.

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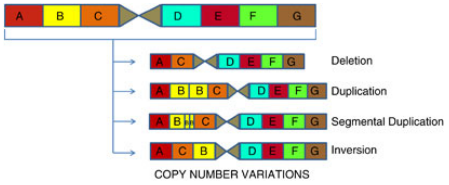
Objective 1:
Identify the role of pharmacogenetics in variability of patient response.

CNV

Alterations of the DNA that results in having abnormal number of copies of one or more sections of the DNA. It can be lower (deleted) or higher (more than normal).



Implications of gene copy-number variation in health and diseases. https://www.researchgate.net/publication/51678716_Implications_of_gene_copy-number_variation_in_health_and_diseases [accessed Sep 21, 2017]

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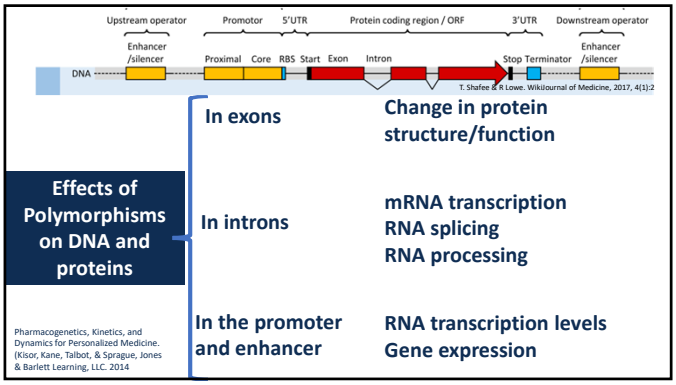

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Objective 1:
Identify the role of pharmacogenetics in variability of patient response.

- FDA – The Food and Drug Administration
- CPIC – The Clinical Pharmacogenetics Implementation Consortium
- PharmGKB – The PGx Knowledgebase
- PharmVar – The Pharmacogene Variation consortium
- NHGRI – The National Human Genome Research Institute

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Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

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Beta-blockers

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Objective 2: **Beta-blockers**
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Facts[1]:
- Beta-blockers are widely use.
- Metoprolol is top 6 most prescribed drug in USA.
- Six beta-blockers are in the top 200 Rx drugs
- In 2020, over 117,000,000 (117 M) beta-blockers were prescribed for over 26 M Americans.

Why is important?

- Even by small improvements in BB therapy, the impact in public health could be significant.

1 Fuentes et al. Pharmacia (Basel)2018 May 14;6(2):43. doi: 10.3390/pharmacy6020043.

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Beta-blockers

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Individual patient response to BB is variable:

- Some patients experience adverse effects even at the recommended dose:
  - Bradycardia
  - Hypotension
  - Fatigue
- Some patients do not obtain a therapeutic effect when provided a BB:
  - Only ~22% of heart failure patients have a marked and sustained improvement in their heart function with BB.

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Beta-blockers

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Beta-Blocker (oral)	Metabolic enzymes
Acebutolol	CYP2D6
Atenolol	N/A (excreted unchanged)
Betaxolol	CYP1A2, CYP2D6
Bisoprolol	CYP2D6, CYP3A4
Carvedilol	CYP1A1, CYP1A2, CYP2C9, CYP2D6, CYP2E1
Esmolol	Esterases
Labetalol	UDP-Glucuronosyltransferase
Metoprolol	CYP2D6
Nadolol	N/A (excreted unchanged)
Nebivolol	CYP2D6, UDP-Glucuronosyltransferase
Pindolol	UDP-Glucuronosyltransferase, Sulfotransferases
Propranolol	CYP1A2, CYP2D6
Sotalol	N/A (excreted unchanged)

Common feature- **most** of BB are metabolized by CYP2D6

https://files.cpicpgx.org/data/guideline/publication/beta_blockers/2024/38951961.pdf

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Beta-blockers

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Current clinical practice guidelines & recommendations for BB and *CYP2D6* genetic variation

CPIC

Beta-blocker guideline

https://files.cpicpgx.org/data/guideline/publication/beta_blockers/2024/38951961.pdf

CPIC GUIDELINE

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for *CYP2D6*, *ADRB1*, *ADRB2*, *ADRA2C*, *GRK4*, and *GRK5* Genotypes and Beta-Blocker Therapy

FDA

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#about

- Higher systemic concentrations in CYP2D6 poor metabolizers treated with metoprolol, nebivolol, or propranolol.
- Potential increased risk of adverse effects (dizziness) in CYP2D6 poor metabolizers treated with carvedilol.

AHA

https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search

- Not in any guidelines. Scientific statements briefly mention FDA recommendations.

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Beta-blockers

Objective 2:
Summarize CPIC guidelines on warfarin, clopidogrel, statins, and beta-blockers

CPIC

Beta-blocker guideline

Key concept – understand the classification recommendation and how to interpret it.

(strong, moderate, no recommendation)

Activity score- assumption that each "normal" allele =1.

Table 2 Dosing recommendations for metoprolol based on CYP2D6 phenotype

Phenotype	Activity score	Implications[a]	Recommendations	Classification of recommendations[b]
CYP2D6 ultrarapid metabolizer	>2.25	Increased metabolism of metoprolol leading to decreased drug concentrations; however, it is unclear whether this results in clinically significant changes in heart rate, blood pressure, or clinical outcomes.	No recommendation for metoprolol therapy due to insufficient evidence regarding diminished metoprolol effectiveness clinically.	No recommendation
CYP2D6 normal metabolizer	1.25 ≤ x ≤ 2.25	Normal metabolism of metoprolol	Initiate standard dosing.	Strong
CYP2D6 intermediate metabolizer	0 < x < 1.25	Decreased metabolism of metoprolol leading to increased drug concentrations; however, this does not appear to translate into clinically significant changes in heart rate, blood pressure, or clinical outcomes.	Initiate standard dosing.	Moderate
CYP2D6 poor metabolizer	0	Decreased metabolism of metoprolol leading to markedly increased drug concentrations; this leads to greater heart rate and blood pressure reductions. The effect on clinical outcomes is unclear.	Initiate therapy with lowest recommended starting dose. Carefully titrate dose upward to clinical effect or guideline-recommended dose; monitor more closely for bradycardia. Alternatively, consider selecting another beta-blocker.	Moderate
CYP2D6 indeterminate	n/a	n/a	No recommendation	No recommendation

n/a, not applicable.
[a]Metoprolol has no known active metabolites via CYP2D6. [b]Rating scheme described in Supplemental Materials

https://files.cpicpgx.org/data/guideline/publication/beta_blockers/2024/38951961.pdf

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Beta-blockers

Objective 2:
Summarize CPIC guidelines on warfarin, clopidogrel, statins, and beta-blockers

FDA

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations#about

Table of Pharmacogenetic Associations

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Pharmacogenetic tests, along with other information about patients and their disease or condition, can play an important role in drug therapy. When a health care provider is considering prescribing a drug, knowledge of a patient's genotype may be used to aid in determining a therapeutic strategy, determining an appropriate dosage, or assessing the likelihood of benefit or toxicity.

On this page:

- About the Table
- Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations
- Section 2: Pharmacogenetic Associations for which the Data Indicate a Potential Impact on Safety or Response
- Section 3: Pharmacogenetic Associations for which the Data Demonstrate a Potential Impact on Pharmacokinetic Properties Only

Section 3: Pharmacogenetic associations for which data demonstrate a potential impact on pharmacokinetic properties only

Metoprolol: CYP2D6 poor metabolism may result in higher systemic concentrations

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Beta-blockers

Objective 2:
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Which of these patients could be at higher risk of having lower blood pressure?

A. Rapid metabolizer for CYP2D6 following a treatment with atenolol
B. Poor metabolizer for CYP2D6 following a treatment with esmolol
C. Normal metabolizer for CYP2D6 following a treatment with sotalol
D. Poor metabolizer for CYP2D6 initiating a treatment with metoprolol

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Clopidogrel

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Objective 2: Clopidogrel

Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

A patient developed an acute coronary syndrome (heart failure) 6 months ago and he was initiated on clopidogrel. Last week, you received a call sharing that the same patient had developed a second heart attack. While meeting with the patient, you learn that he has been compliant with all the prevention recommendations as well as adherence to the medications.

Considering that clopidogrel is a prodrug and is metabolized by *CYP2C19*. Which type of metabolizer could the patient potentially be?

A. Ultrarapid Metabolizer
B. Normal Metabolizer
C. Poor Metabolizer

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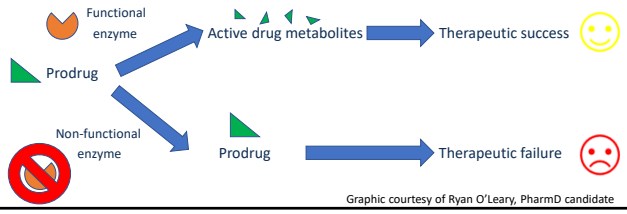
Objective 2: Clopidogrel

Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Commonly Prescribed Prodrugs: Clopidogrel, Codeine, Tramadol, Tamoxifen

- Prodrugs are non-active drugs that are metabolized into active drug metabolites by drug metabolizing enzymes. Some of them are cytochromes (CYP) (P-450)



Graphic courtesy of Ryan O'Leary, PharmD candidate

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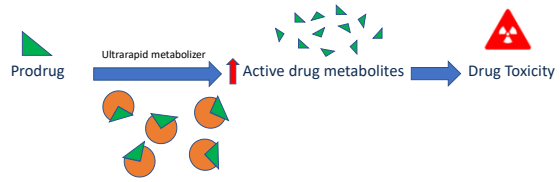
Objective 2: Clopidogrel

Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

What would happen if a person is an ultra-rapid/rapid metabolizer in this scenario?

- Prodrugs will be metabolized at a much higher rate, leading to toxic concentrations of active drug metabolites in the body



Graphic courtesy of Ryan O'Leary, PharmD candidate

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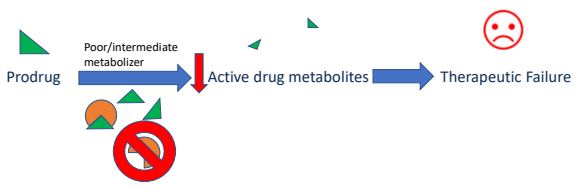
Objective 2: Clopidogrel

Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

What would happen if a person is a poor metabolizer in this scenario?

- Prodrugs will be metabolized at a much lower rate (or none), leading to there being much less active drug metabolites



Graphic courtesy of Ryan O'Leary, PharmD candidate

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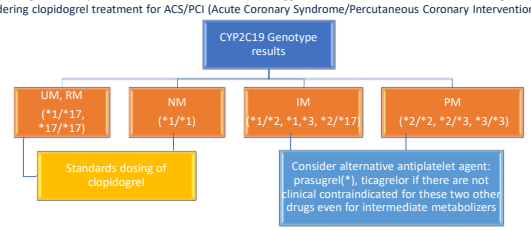
Objective 2: Clopidogrel

Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Clinical Pharmacogenetics Implementation consortium (CPIC) for suggested clinical actions based on *CYP2C19* genotype when considering clopidogrel treatment for ACS/PCI (Acute Coronary Syndrome/Percutaneous Coronary Intervention) patients.



(*) Prasugrel is not recommended in patients with BW <60 Kg, or >75 yrs old.
Ticagrelor is BID and aspirin dose should be reduced to 81 mg QD.

https://files.cpicpgx.org/data/guideline/publication/clopidogrel/2022/35034351.pdf

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Warfarin

Objective 2:
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CYP2C19 polymorphisms distribution

Population	CYP2C19 *2 Frequency (%)	CYP2C19 *3 Frequency (%)
African American/ Caribbean	18.15	0.28
American	12.14	0.04
Central/South Asian	26.99	1.57
East Asian	28.35	7.25
European	14.69	0.16
Latino	10.42	0.08
Near Eastern	11.98	1.65
Oceanian	60.95	14.64
Sub-Saharan Africa	15.68	0.27

Two admixed groups:
- African American/Afro-Caribbean (AAC)
- Latino (LAT)

Huddart et al. Clin Pharmacol Ther 2019. May 105(5):1256-1262

News - Court

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Statins

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Statins

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

A 75 yo female patient is being prescribed simvastatin 20 mg QD. Her genotype profile is SLC01B1 *1/*15. So far, the patient is taking the medication without any side effects. Due to other health complications, the patient is prescribed cyclosporine. Soon after, the patient starts complaining of severe muscular pain.

What do you think is happening?

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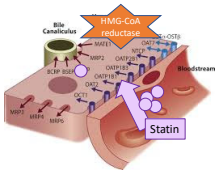
Statins

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

- Hepatocytes take up statins through **OATP1B1** transporter.
- The gene that encodes the OATP1B1 transporter is ***SLC01B1***.
- Once statins are in the hepatic cells → block HMG-CoA reductase and get cleared through bile clearance.
- There are different polymorphisms that have been associated with an **increase in statin concentrations in blood**, and secondarily to **myopathy**.
- **Several polymorphisms associated with a lower or lack of function of OATP1B1 have been associated with MARKEDLY INCREASED SEVERITY OF STATIN-ASSOCIATED MUSCULOSKELETAL SYMPTOMS (SAMS).**
- These patients will have higher AUC in blood for the statins, since there is less drug taken up by the transporter OATP1B1, and therefore, lower levels in hepatocytes.



Modified from Ho&Kim. Clinical Pharmacology & Therapeutics (2005) 78, 260–277; doi: 10.1016/j.clpt.2005.05.011

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Statins

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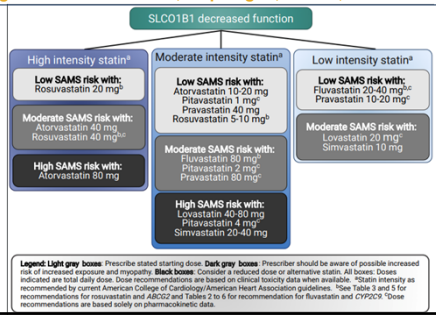

Decreased function: 1 allele is defective

SAMS = Statin Associated Muscle Symptoms

https://files.cpicpgx.org/data/guideline/publication/statins/2022/publication.pdf

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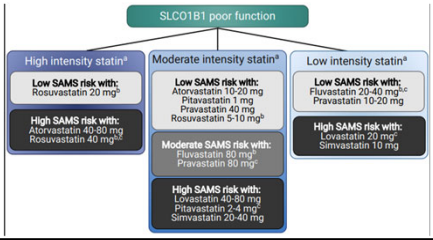
Statins

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Poor function: 2 alleles are defective



https://files.cpicpgx.org/data/guideline/publication/statins/2022/publication.pdf

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Statins

Objective 2:
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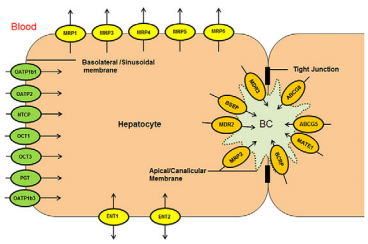

- Transporter involved in transporting (efflux, similar to p-gp, also called BCRP) the statin and some evidence in **rosuvastatin** show that **when *ABCG2* is deficient, patients have higher blood concentrations** (less is exported to the bile).

https://www.researchgate.net/publication/330416225_Review_Article_-_Blood_Bile_Barrier_Morphology_Regulation_and_Pathophysiology

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Statins

Objective 2:
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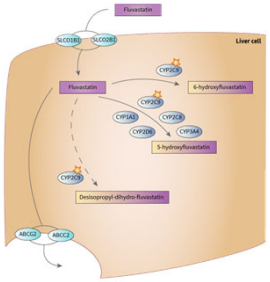

- CYP2C(Enzyme involved in drug metabolism.
- **Poor or intermediate metabolizers will have higher plasma** concentrations and higher risk for muscular adverse events.
- This is relevant only for **fluvastatin**
- **Normal metabolizers – AS 2 (it is assumed that each allele if it is normal will have activity score =1).**

https://www.pharmgkb.org/chemical/PA449688/guidelineAnnotation/PA166262341

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Statins

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

A 60 yo female patient is being prescribed with rosuvastatin 20 mg QD. The patient has received as Christmas gift a kit to get her 23 and me genetic test, and she comes to you asking about the interpretation of the results. The test states: SLC01B1 *15/*15
What would you recommend and why?

A. Keep taking rosuvastatin and monitor for side effects
B. Discontinue rosuvastatin since the patient is a poor metabolizer
C. Discontinue rosuvastatin since the transporter has poor function
D. Replace rosuvastatin with simvastatin 40 mg since it is safer for this patient.

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Statins

Objective 2:
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Would your recommendation change if you find that her BCRP (ABCG2) has poor function?

A. Yes, CPIC recommends to prescribe 10 mg and additional therapy if there was a need for a high-intensity statin.
B. No, this transporter is not involved with rosuvastatin metabolism.

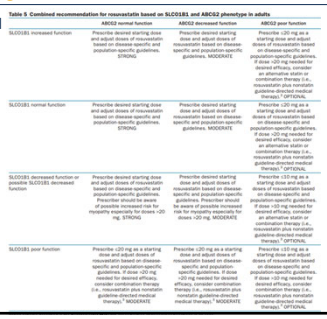
Table 5 Combined recommendation for rosuvastatin based on SLCO1B1 and ABCG2 phenotype in adults

	ABCG2 normal function	ABCG2 decreased function	ABCG2 poor function
SLCO1B1 increased function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª OPTIONAL
SLCO1B1 normal function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª OPTIONAL
SLCO1B1 decreased function or possible SLCO1B1 decreased function	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20 mg. STRONG	Prescribe desired starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. Prescriber should be aware of possible increased risk for myopathy especially for doses >20 mg. MODERATE	Prescribe ≤10 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >10 mg needed for desired efficacy, consider an alternative statin or combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª OPTIONAL
SLCO1B1 poor function	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª MODERATE	Prescribe ≤20 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >20 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª MODERATE	Prescribe ≤10 mg as a starting dose and adjust doses of rosuvastatin based on disease-specific and population-specific guidelines. If dose >10 mg needed for desired efficacy, consider combination therapy (i.e., rosuvastatin plus nonstatin guideline-directed medical therapy).ª OPTIONAL

https://files.cpicpgx.org/data/guideline/publication/statins/2022/publication.pdf

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Statins

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Back to the first question…

A 75 yo female patient is being prescribed simvastatin 20 mg QD. Her genotype profile is SLC01B1 *1/*15. So far, the patient is taking the medication without any side effects. Due to other health complications, the patient is prescribed cyclosporine. Soon after, the patient starts complaining of severe muscular pain.

What do you think is happening?

Phenoconversion Risk of having therapeutic failure due to drug-drug interactions and showing a different phenotype that the patient's genotype.

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Warfarin

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Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

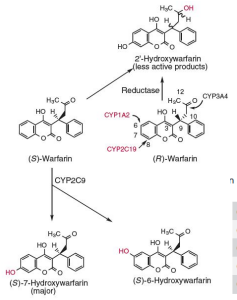
Warfarin

Warfarin Metabolism

Variants

CYP2C9*2 – reduces warfarin metabolism by **30-40%** (mutation of aminoacid (Arg-Cys)
CYP2C9*3– reduces warfarin metabolism by **80-90%** – (mutation of aminoacid ile-leu).

****5, *6, *8 and *11*** also associated with decreased function – **more prevalent in African ancestry**.



Genetic Allele	Clearance
CYP2C9*1/*2	↓ 20%
CYP2C9*1/*3	↓ 40%
CYP2C9*2/*2	↓ 50%
CYP2C9*2/*3	↓ 60%
CYP2C9*3/*3	↓ 85%

Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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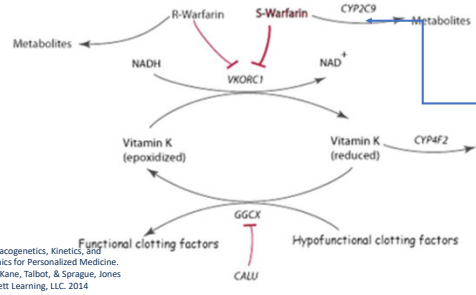
Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Warfarin



CYP2C9*2 and *3 are slow metabolizers, and they will require lower doses to avoid bleeding effects
****5, *6, *8 and *11*** *will also require reduced dosing*

Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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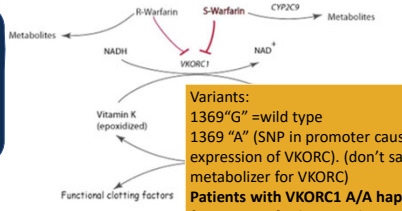
Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Warfarin

VKORC1 is responsible for producing the reduced form of Vitamin K, which is essential for vitamin K–dependent clotting factors (II, VII, IX, and X)



Variants:
1369"G" =wild type
1369 "A" (SNP in promoter causing lower expression of VKORC). (don't say poor metabolizer for VKORC)
Patients with VKORC1 A/A haplotype had 2.4 faster rate of achieving therapeutic INR since they have less enzyme → need lower dose
Ancestral frequency is different (e.g. East Asia is highly prevalent)

Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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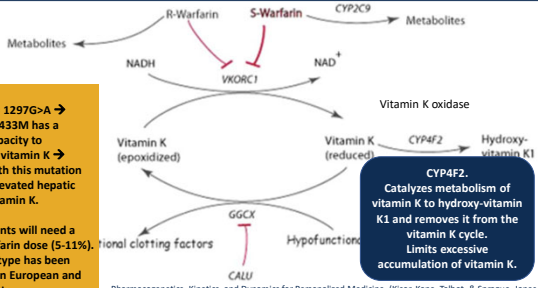
Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Warfarin

Variant:
CYP4F2*3 **= 1297G>A → mutation V433M has a reduced capacity to metabolize vitamin K → patients with this mutation will have elevated hepatic levels of vitamin K.**

These patients will need a higher warfarin dose (5-11%). This phenotype has been confirmed in European and Asian ancestry



CYP4F2.
Catalyzes metabolism of vitamin K to hydroxy-vitamin K1 and removes it from the vitamin K cycle.
Limits excessive accumulation of vitamin K.

Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014. CPIC guideline on warfarin

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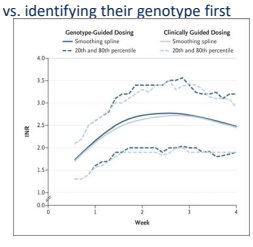
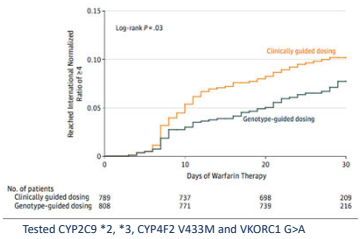
Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Warfarin

Comparison of patients INR when their warfarin dose was given following clinical guided-dosed vs. identifying their genotype first





Tested CYP2C9 *2, *3 and VKORC1 G>A. Different diseases
N Engl J Med 2013;369:2283-2293 DOI: 10.1056/NEJMoa1310669

Tested CYP2C9 *2, *3, CYP4F2 V433M and VKORC1 G>A
Hip surgery – prevention of DVT
JAMA *September 26, 2017 Volume 318, Number 12*
Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty: The GIFT Randomized Clinical Trial | Orthopedics | JAMA | JAMA Network

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Objective 2: **FDA RECOMMENDATIONS**
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Warfarin

Table 10-2

Range of Expected Therapeutic Warfarin Maintenance Doses Based on CYP2C9 and VKORC1 Genotypes

	Cytochrome P450 CYP2C9 Genotypes					
VKORC1 Genotypes	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**
G/G	5–7 mg/d	5–7 mg/d	3–4 mg/d	3–4 mg/d	3–4 mg/d	0.5–2 mg/d
A/G	5–7 mg/d	3–4 mg/d	3–4 mg/d	3–4 mg/d	0.5–2 mg/d	0.5–2 mg/d
A/A	3–4 mg/d	3–4 mg/d	0.5–2 mg/d	0.5–2 mg/d	0.5–2 mg/d	0.5–2 mg/d

Source: Coumadin tablets (warfarin sodium tablets, USP) crystalline Coumadin for injection (warfarin sodium for injection, USP). Package labeling can be found at http://packageinserts.bms.com/ pi/pi_coumadin.pdf. Accessed October 17, 2011.

FDA package insert does not include polymorphisms for CYP2F4 but some treatment algorithms include it.

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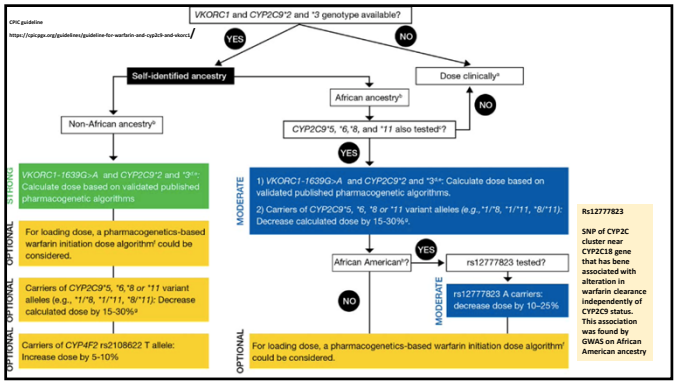

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Warfarin

Objective 2:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on warfarin, clopidogrel, statins, and beta-blockers.

Incidental findings

Homozygosity for rare coding mutations in VKORC1 can cause a combined deficiency of vitamin K-depending clotting factors 2- fatal bleeding disorder.

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Objective 4:
Apply pharmacogenetic recommendations in two patient cases

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Patient Case

TR is a 66year-old African American male who was referred by his PCP to initiate anticoagulation. DOACs are cost-prohibitive at this time

PMH: Atrial fibrillation, DM2, HTN

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

Medications
Amlodipine 10mg by mouth daily
Metformin 1000mg by mouth twice daily
Metoprolol ER 100mg by mouth daily
Lisinopril 30mg by mouth daily
Vitamin D 1000 U by mouth daily

Vital/Labs	
Ht	180.3 cm (5'11")
Wt	104.5 kg (230 lbs)
HR	104 bpm
BP	123/78 mmHg
Temp	37C (98.6F)
O2	99%
Na	137 mEq/L [135-145 mEq/L]
Cl	105 mEq/L [98-110 mEq/L]
BUN	14 mg/dL [6-24 mg/dL]
K	4.2 mEq/L [3.6-5.1 mEq/L]
CO2	25 mEq/L [22-32 mEq/L]
sCr	0.87 mg/dL [0.44-1.03 mg/dL]
Glucose	94 mg/dL [67-99 mg/dL]
Mg	1.7 mEq/L [1.3-1.9 mEq/L]
TC	189 mg/dL
LDL	107 mg/dL
HDL	54 mg/dL
TG	141 mg/dL
A1C	6.7% [<5.7%]
INR	1.0 [0.8-1.2]
Hgb	13.1 g/dL [11-15 g/dL]
Hct	37.6% [32-45%]
PLT	185 x10^3/L [150-400 x10^3/L]

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Patient Case

Is there any gene that is relevant for warfarin? (select all that apply)

A. CYP2C9
B. VKORC1
C. CYP2D6
D. CYP4F2

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Patient Case

Is there any gene that is relevant for any other medication the patient is taking? (select all that apply) (Amlodipine, Metformin, Metoprolol ER, Lisinopril, Vitamin D)

A. CYP2C9
B. VKORC1
C. CYP2D6
D. CYP2C19

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Patient Case

Is there any other medication you should suggest to initiate?

A. Ezetimibe
B. High intensity statin
C. Insulin
D. HCTZ

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Patient Case

Which genes are relevant for statins? (select all that apply)

A. SLC01B1
B. CYP2C19
C. CYP2C9
D. ABCG2

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Patient Case

Connecting all pieces together, what would you recommend?

A. Initiate warfarin at lower dose and follow CPIC guidelines- Few examples: 2.5 mg QD for 7 days. , 5 mg MT, 2.5 mg for 4 days…
B. Initiate rosuvastatin 20 mg
C. Initiate simvastatin 20 mg
D. Initiate warfarin at a normal dose and monitor for sign and symptoms of blood clots

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

A 43-year-old African-American man is planning to travel to the Amazon and spend 3 months of service.
As prophylactic measurement, he starts primaquine treatment as antimalarial agent.

Few days later, he "starts feeling really sick" and goes to the emergency room. Laboratory findings show low hemoglobin (Hb), increased reticulocytosis, increased unconjugated bilirubin, and decreased haptoglobin. These results are suggestive of hemolytic anemia.

Three days after admission, the patient exhibited persistent hyperbilirubinemia with additional signs of hypoxemia, as evidenced by low hemoglobin (Hb). These laboratory findings provided evidence of acute hemolytic anemia.

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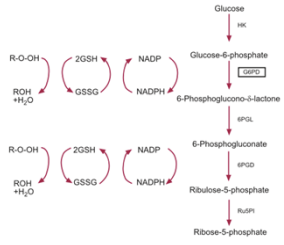
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

The patient exhibited **abnormal G6PD (glucose6-phosphate dehydrogenase) enzyme activity** (4.1 U/g Hb; reference interval 8.6 –18.6 U/g Hb)



Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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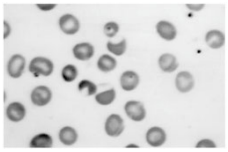
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

- Hemolysis:
- Deficiency of G6PD in red cells result from an increased susceptibility to oxidative damage, since they are unable to reduce NADP+ to NADPH. **This failure increases the generation of free radicals and oxidizes hemoglobin (Hb)** which precipitate as insoluble membrane inclusions known as Heinz bodies.
- The presence of inclusions acts as a signal for erythrocyte removal by macrophages, leading to premature lysis.
- G6PD deficiency is **X-linked-recessive trait**.
- **PRIMAQUIN AND OTHER ANTIMALARIAL DRUGS COULD CAUSE THIS HEMOLITIC ANEMIA. (Higher risks in African-American)**
- **VERY HIGH DOSES OF ACETAMINOPHEN can also trigger this complication**



Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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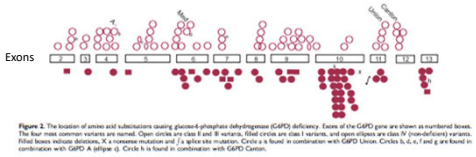
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

Many variants can be responsible of G6PD deficiency



Since it is X-linked recessive….females could experience "mosaic" due to X-chromosome inactivation

Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014

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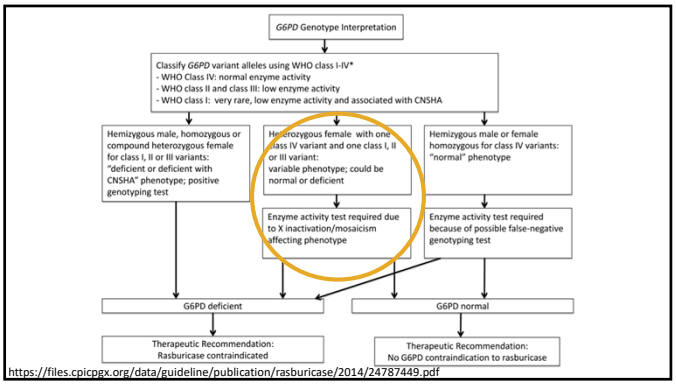

https://files.cpicpgx.org/data/guideline/publication/rasburicase/2014/24787449.pdf

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

- Package insert/recommendations vary from antimalarial to antimalarial. For example, for primaquine, the mutation is listed as contraindication, and dose adjustment is listed.
- For hydroxychloroquine, it is just as precaution.
- CPIC guideline is for all drugs that could affect G6PD:

https://files.cpicpgx.org/data/guideline/publication/G6PD/2022/36049896.pdf

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Voriconazole

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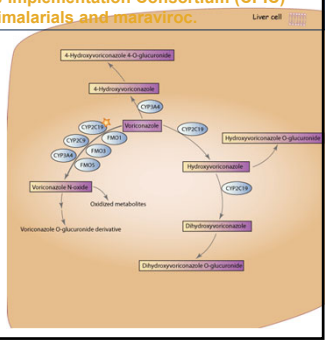
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

- Second-generation triazole antifungal agent.
- Spectrum: Aspergillus and Candida.
- MOA: Disrupt synthesis of ergosterol (required for fungal membrane).
- It is both fungistatic (for yeasts) and fungicidal (for mold)
- Use: Tx invasive aspergillosis and fungal infections in immunocompromised patients.
- It is metabolized by CYP2C19 (mainly), CYP2C9, and CYP3A4.
- Voriconazole is also an inhibitor of CYP2C19, CYP2C9, and CYP3A4 substrates.
- High concentrations in plasma → hepatotoxic, visual disturbances hallucinations.



https://www.pharmgkb.org/pathway/PA166160640

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

CYP2C19 phenotype	Implications for Voriconazole	Recommendations	Classification of recommendation
Ultrarapid metabolizer (*17/*17)	Probability of attainment of therapeutic concentration is small	Choose an alternative agent not dependent on CYP2C19 (amphotericin B, posaconazole)	Moderate
Rapid metabolizer (*1/*17)	The probability of attainment of therapeutic concentrations is variable	Initiate therapy with recommended standard of care dosing. Use therapeutic drug monitoring to titrate dose to therapeutic trough concentrations	Moderate
Normal metabolizer (*1/*1)	Normal voriconazole plasma levels	Initiate therapy with recommended standard-of-care dosing	Strong
Intermediate metabolizer	Higher-dose adjusted trough concentrations compared with normal metabolizers	Initiate therapy with recommended standard-of-care dosing	Moderate
Poor metabolizer	Higher dose-adjusted trough concentrations and may increase probability of adverse events	Choose an alternative not dependent on CYP2C19 (amphotericin B, posaconazole). If voriconazole is considered most appropriate, administer preferable lower-than-standard dosage and careful therapeutic drug monitoring	Moderate

Moriyama B, Owusu Obeng A, Barbarino J et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for *CYP2C19* and Voriconazole Therapy. Clinical Pharmacology & Therapeutics. 102, 1: 45-51, 2017

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Abacavir

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

OM is a 37-year-old Caucasian male with a six-week history of muscle soreness, swollen lymph nodes in the neck, night sweats, and a three-week history of a slight rash, with small dark raised bumps on his abdomen and back. He is also experiencing gastrointestinal discomfort and right lower quadrant pain.

OM is started a medication which contains **abacavir sulfate** (300 mg), lamivudine (150 mg), and zidovudine (300 mg) twice a day.

Three weeks after initiation of the triple drug combination, OM presents to the emergency department with **nausea, diarrhea, mild rash, headache, fever, and other constitutional symptoms including severe fatigue and myalgia**.

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

While the symptoms appear to be similar to her original presentation prior to the HIV diagnosis, **OM states that the current symptoms seem to "get worse" after each dose of his HIV medication**.

OM states the that symptoms continue to become more severe as time progresses. **With this information, OM is now diagnosed with abacavir hypersensitivity reaction**.

Pharmacogenetic testing is utilized to determine if OM expresses the *HLA-B*5701* allele. **Individuals with the *HLA-B*5701* allele (i.e. positive to *HLA-B*5701*) are at risk of hypersensitivity reaction to abacavir.** Testing reveals OM expresses the *HLA-B*5701* allele.

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

HLA-B*5701
(HLA are own's antigens to recognize self from non-self)

Abacavir is taken up into the cytoplasm of antigen-presenting cells. Once in the cytosol, it is transformed and then, binds to cytosolic protein. When patients have the variant HLA-B*5701, the interaction between the complex of drug-HLA will activate **CD8(+) T-lymphocytes.**

T-cell Lymphocytes will secrete IFN-gamma and TNF alpha.
TNF-alpha is responsible for fever, and organ failure.

Patients with this HLA variant are at higher risk of hypersensitivity and severe toxicity (not just a mild "allergic" reaction)

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

The re-challenge of a patient with abacavir:

- Fever, rash, gastrointestinal problems, bronchoconstriction, hypotension, and resultant renal failure.
- Occurs in up to 20% of patients
- **Abacavir rechallenge is not appropriate**.

Higher frequency: Caucasians (7-8%)

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

The US DHHS panel (Department of Health and Human Services) on Antiretroviral Guidelines for Adult and Adolescents, recommends preforming this screening before starting in any abacavir-naïve patient.

Patients with HLA-B*5701

- Avoid abacavir

This does not mean that patients with HLA-B*5701 have no risk of hypersensitivity reaction, but their risk is lower than those that are positive.

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Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

Details	Testing required	FDA	Annotation of FDA Label for carbamazepine and HLA-B
Details	Testing required	Swissmedic	Annotation of Swissmedic Label for carbamazepine and HLA-B
Details	Testing recommended	HCSC	Annotation of HCSC Label for carbamazepine and HLA-A, HLA-B
Details	Testing recommended	Swissmedic	Annotation of Swissmedic Label for carbamazepine and HLA-A
Details	Actionable PGx	FDA	Annotation of FDA Label for carbamazepine and HLA-A
Details	Actionable PGx	PMDA	Annotation of PMDA Label for carbamazepine and HLA-A, HLA-B

https://www.pharmgkb.org/chemical/PA448785/labelAnnotation

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Maraviroc

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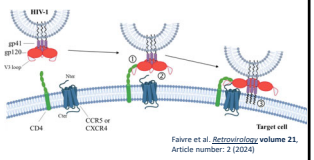
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

- CCR5 and CXCR4 are the major chemokine receptors involved in HIV infection.
- HIV utilizes CD4 as the receptor on host cells, but the presence of chemokines is needed for the virus to "cleave" in the CD4 receptor.
- CCR5 receptor is expressed on macrophages and some T-cells.
- M-tropic HIV isolates use CCR5 as co-receptor.
- **Maraviroc** is a selective, reversible, small molecule CCR5 receptor antagonist that blocks the entry of CCR5- tropic HIV into host cells.
- Only patients whose isolates show CCR5 tropism qualify for treatment with maraviroc.



Fäivre et al. *Retrovirology* **volume 21**, Article number: 2 (2024)

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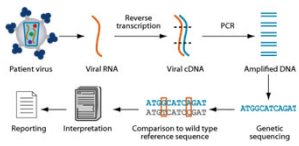
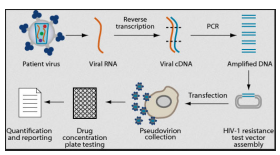
Objective 3:
Summarize Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines on abacavir, antimalarials and maraviroc.

Patient's "HIV viruses, not patient's DNA are tested at the genomic level and phenotypic level, to assure that the phenotype matches the genotype

Genotypic Assay



Phenotypic Assay



https://monograbio.labcorp.com/resources/phenotyping

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Objective 4:
Apply pharmacogenetic recommendations in two patient cases

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Patient Case

TR is a 66year-old African American male who was referred by his PCP to initiate anticoagulation. DOACs are cost-prohibitive at this time.
the patient is admitted to the hospital with positive for aspergillosis after an event of cough dyspnea and fever and voriconazole treatment is initiated.
PMH: Atrial fibrillation, DM2, HTN

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

Medications
Amlodipine 10mg by mouth daily
Metformin 1000mg by mouth twice daily
Metoprolol ER 100mg by mouth daily
Lisinopril 30mg by mouth daily
Vitamin D 1000 U by mouth daily
Rosuvastatin 20 mgQD
Warfarin

Vital/Labs	
Ht	180.3 cm (5'11")
Wt	104.5 kg (230 lbs)
HR	104 bpm
BP	123/78 mmHg
Temp	37C (98.6F)
O2	99%
Na	137 mEq/L [135-145 mEq/L]
Cl	105 mEq/L [98-110 mEq/L]
BUN	14 mg/dL [6-24 mg/dL]
K	4.2 mEq/L [3.6-5.1 mEq/L]
CO2	25 mEq/L [22-32 mEq/L]
sCr	0.87 mg/dL [0.44-1.03 mg/dL]
Glucose	94 mg/dL [67-99 mg/dL]
Mg	1.7 mEq/L [1.3-1.9 mEq/L]
TC	189 mg/dL
LDL	107 mg/dL
HDL	54 mg/dL
TG	141 mg/dL
A1C	6.7% [<5.7%]
INR	1.0 [0.8-1.2]
Hgb	13.1 g/dL [11-15 g/dL]
Hct	37.6% [32-45%]
PLT	185 x10^9/L [150-400 x10^9/L]

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Patient Case

What would you suggest based on patient's genotype?

A. Voriconazole is metabolized by *CYP2C19* and it is not affected.

B. Voriconazole is metabolized by *CYP2C9* and we need to substitute with a drug that is not metabolized by *CYP2C9*

PGx	
CYP1A2	*1A/*1F
CYP2C9	*1/*3
CYP2C19	*1/*1
CYP2D6	*1/*10
CYP3A5	*1/*3
CYP4F2	*1/*3
ABCG2	CC
SLCO1B1	*1/*5
UGT1A1	*1/*28
VKORC1	TT
CYP2C cluster	GA

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Questions?

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Guidelines:
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- **Maraviroc:**
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  - To learn about overall maraviroc: Dean L. Maraviroc Therapy and CCR5 Genotype. In Medical Genetics Summaries. 2017 Pratt VM, Scot SA, Pirmnohamed M et al. (eds) National Center for Biotechnology Information. https://www.ncbi.nlm.nih.gov/books/NBK279895/. Accessed on 3/6/2025

Textbooks:
- Pharmacogenetics, Kinetics, and Dynamics for Personalized Medicine. (Kisor, Kane, Talbot, & Sprague, Jones & Barlett Learning, LLC. 2014
- Pharmacogenomics,: An Introduction and Clinical Perspective. (Bertino, Devane, Fuhr, Kashuba, Ma, McGraw-Hill 2013)
- Pharmacogenomics: A Primer for Clinicians (Kam, Gutierrez, Shah, McGraw-Hill, 2021)
- Fun way of reviewing genetics: https://www.genome.gov/About-Genomics/Educational-Resources
- From National Library Medicine: https://medlineplus.gov/genetics/understanding/
- https://www.nigms.nih.gov
- US National Library of Medicine. http://ghr.nlm.nih.gov/handbook.pdf
- PharmGKB: https://www.pharmgkb.org/
- FDA PGx associations: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

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CE Evaluation Access Code

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Capital Letters, No spaces, complete by March 16, 2025

Note: CE credit will be reported to NABP CPE Monitor within 4-6 weeks

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Updates in Pharmacogenetics Education on Drugs Used in Cardiovascular Conditions and Infectious Diseases

Southeastern Ohio Academies of Pharmacy (SEOPA) Spring Seminar
March 9, 2025
Marina Galvez Peralta, PharmD, PhD, FCP
Associate Professor, Assistant Chair and Director of Professional Development WVU School of Pharmacy

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