DOAC Pharmacogenomics: Learning the DOs

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Disclosures

- Ryan Lewis – No financial disclosures
- Trishia E. Shaw – No financial disclosures

Objectives

At the end of this presentation, **pharmacist** participants should be able to:

1. Define the term pharmacogenomics and identify key drug metabolizing enzymes.
2. Review coagulation cascade and describe how oral anticoagulant medications work in the coagulation cascade.
3. Review current literature describing pharmacogenomic polymorphisms in the enzymes that metabolize direct oral anticoagulant medications
4. Explain recommendations for therapy management based on genetic polymorphism information.

Pre-Assessment Questions

Pre-Assessment Question #1

- **True or False**: The CPIC guidelines are a resource to guide medication therapy in patients with known genetic variants in drug metabolizing enzymes.
  A. True
  B. False

Pre-Assessment Question #2

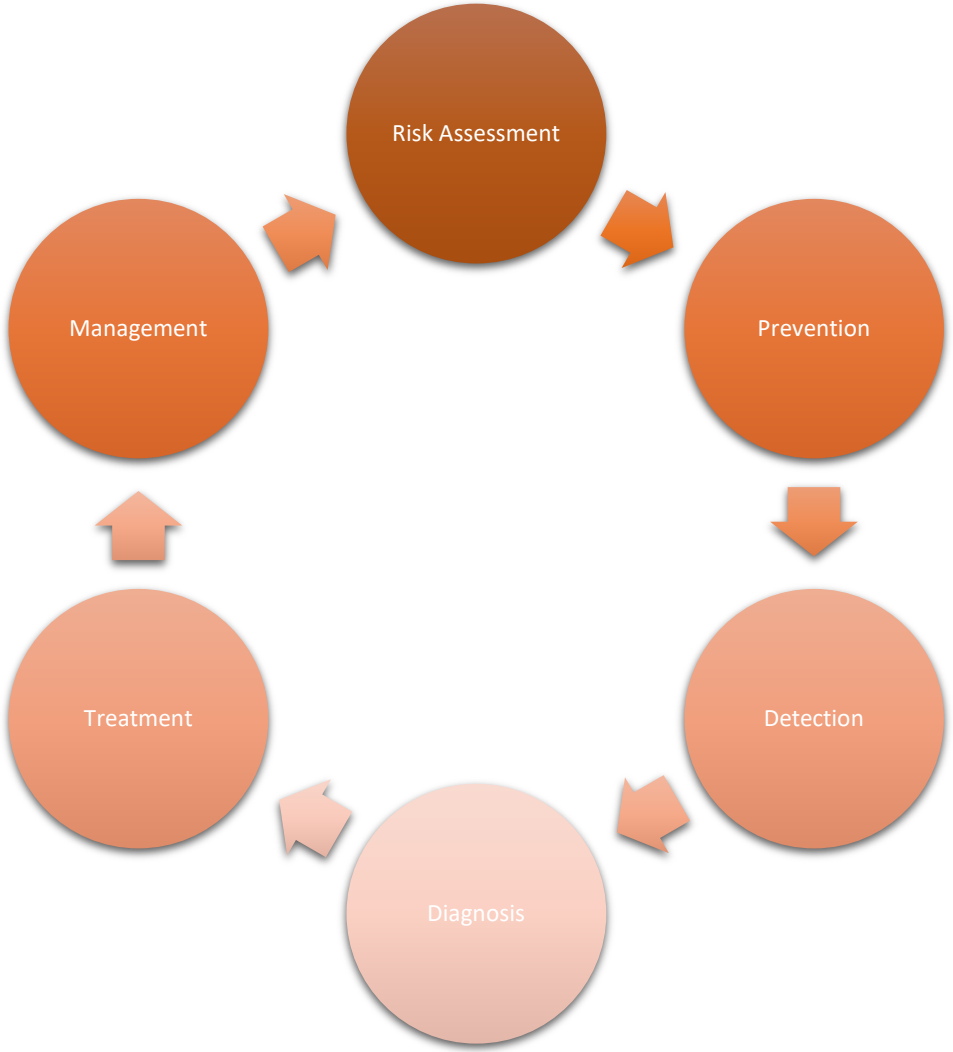
- **True or False**: All drugs with published genetic literature have guidelines to guide optimal medication use.
  A. True
  B. False

Pharmacogenomic (PGx) Basics

What is “Personalized Medicine”?

- Definition: the tailoring of medical treatment to the individual characteristics of each patient

- Multi-faceted approach to patient care

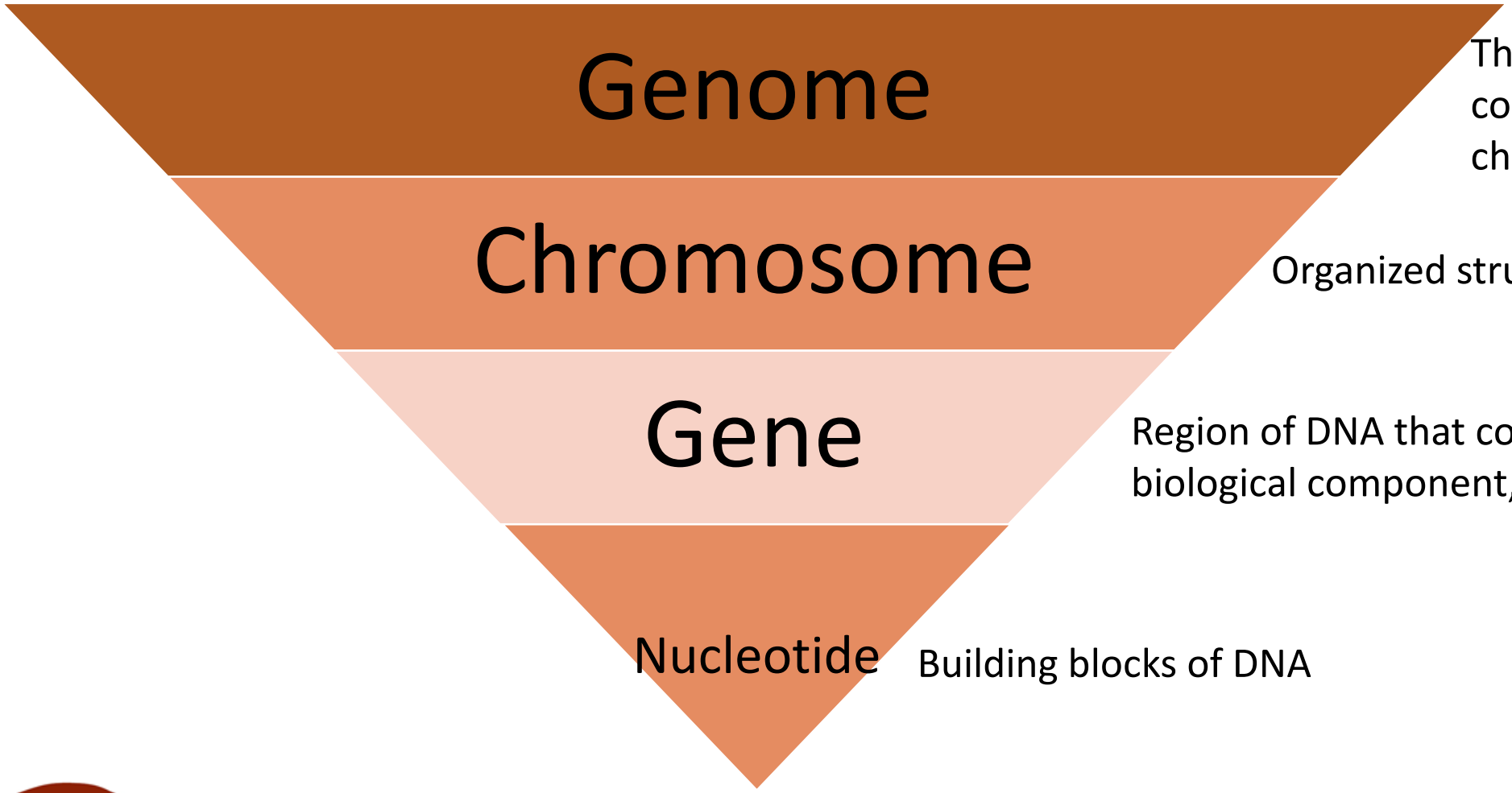


Adapted from “The Age of Personalized Medicine.” https://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_age_of_pmc_factsheet.pdf . Accessed 10/25/20.

Pharmacogenetics vs. Pharmacogenomics

Pharmaco**genetics**	Pharmaco**GENOMICS**
Study of the relationship between variations in a **single gene** and variability in drug disposition, response, and toxicity	Study of the relationship between variations in **a large collection of genes (up to the whole genome)** and variability in drug disposition, response, and toxicity

Definition of Basic Genetic Terms



The total genetic material contained within the chromosomes of an organism

Organized structures that carry the DNA

Region of DNA that contains the code for a biological component, usually a protein

Building blocks of DNA

Pharmacogenetics Terminology

- Genetic variant
  - Difference in the DNA sequence compared with a reference sequence

Polymorphism

- Genetic variant that is **common**
- Defined in 1% or more in the population

Mutation

- Genetic variant that is **rare**
- Defined in less than 1% in the population

Allele

- One or two (or more) of a DNA sequence that is located at a specific position on a specific chromosome

Wild-Type

- Most common or reference allele
- “the major allele”
- Often denoted as *1

Variant

- Polymorphic allele
- “the minor allele”
- Often denoted as *N

Genotype

- The combination of alleles a person carries at a particular location in DNA

Heterozygous

- Two different alleles

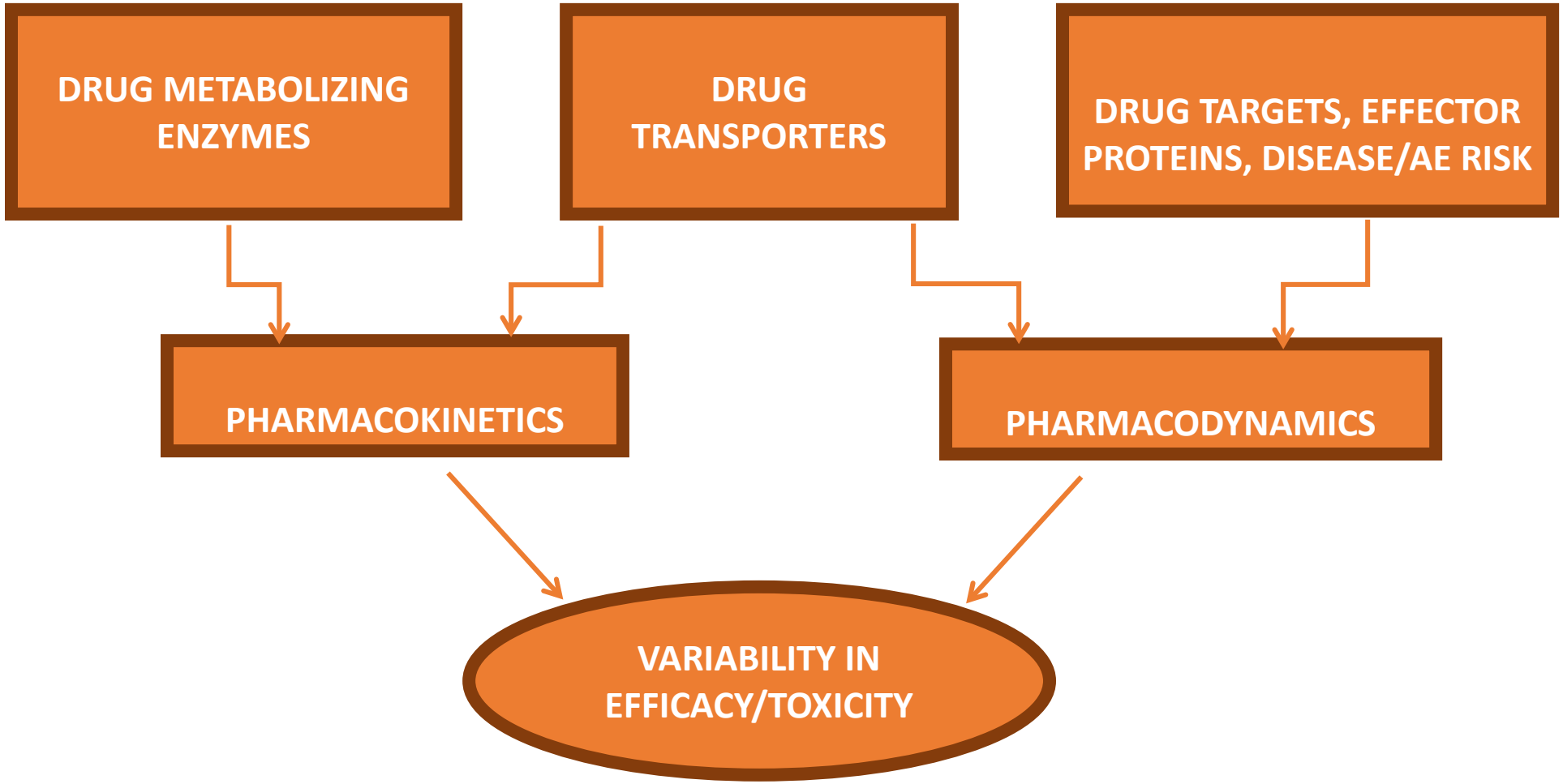
Homozygous

- Two identical alleles

Phenotype

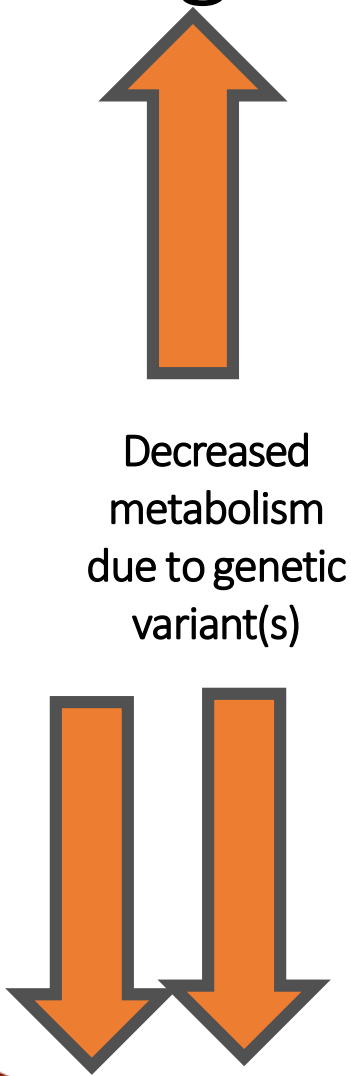
- Measurable characteristic of an organism (i.e. hair color, eye color)
- Results of genetics, environment or the combination of both
- Examples of **pharmacologic phenotypes**
  - Metabolism: ultra-rapid, extensive, intermediate, poor metabolism
  - Pharmacokinetics: plasma drug concentration, AUC, clearance, Cmax
  - Pharmacodynamics: responder vs non-responder

Key Clinical Pharmacologic Components in Pharmacogenomics

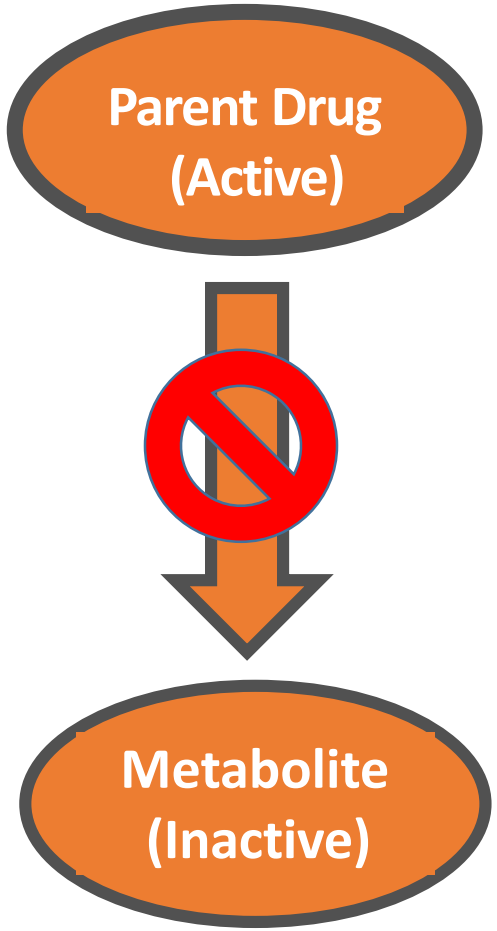


Trends in Genetics. 2003: 660-666

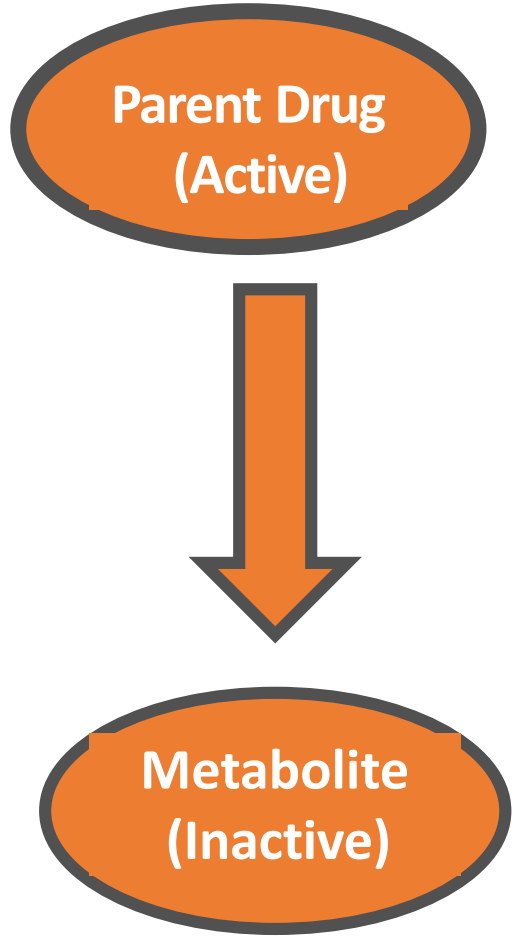
Drug Metabolism – Active Parent Drug



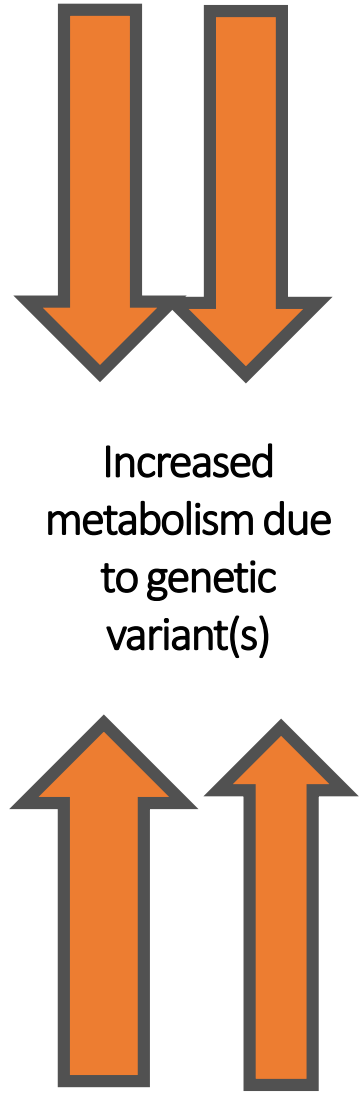
Decreased metabolism due to genetic variant(s)



Decreased metabolism due to genetic variant(s) = Increased plasma exposure of the active parent drug; increased pharmacologic effect and/or risk of toxicity



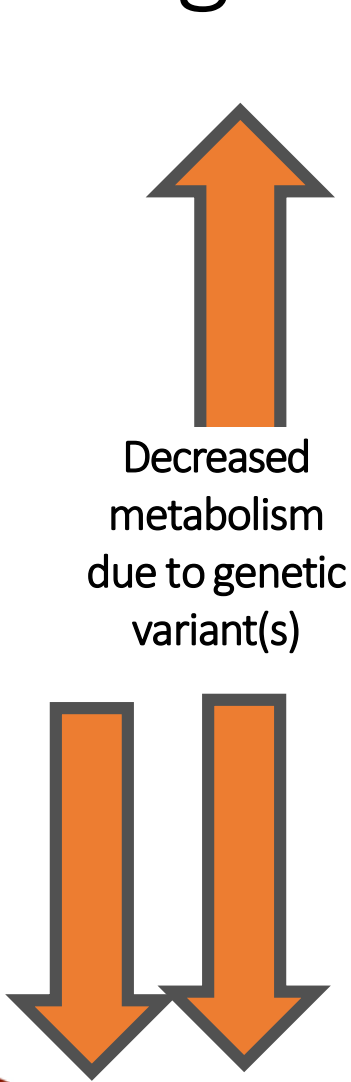
Increased metabolism due to genetic variant(s) = Decreased plasma exposure of the active parent drug; decreased pharmacologic effect



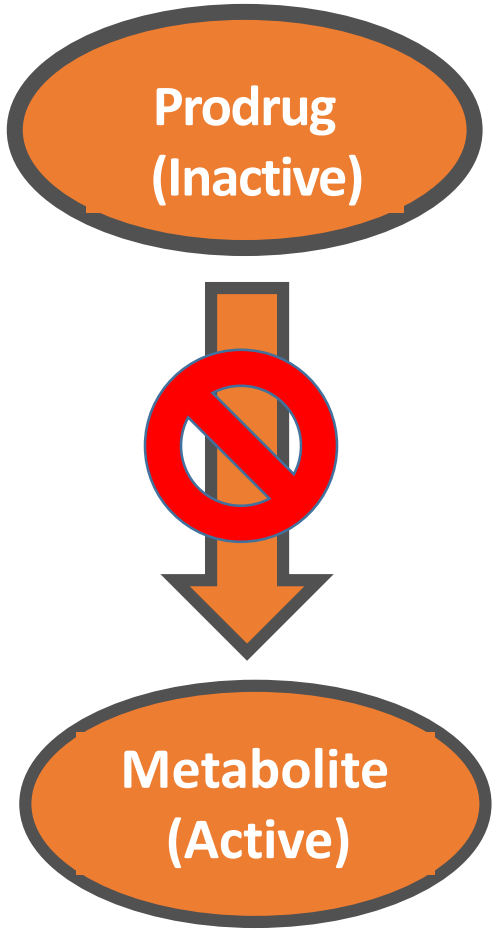
Increased metabolism due to genetic variant(s)

Trends in Genetics. 2003: 660-666

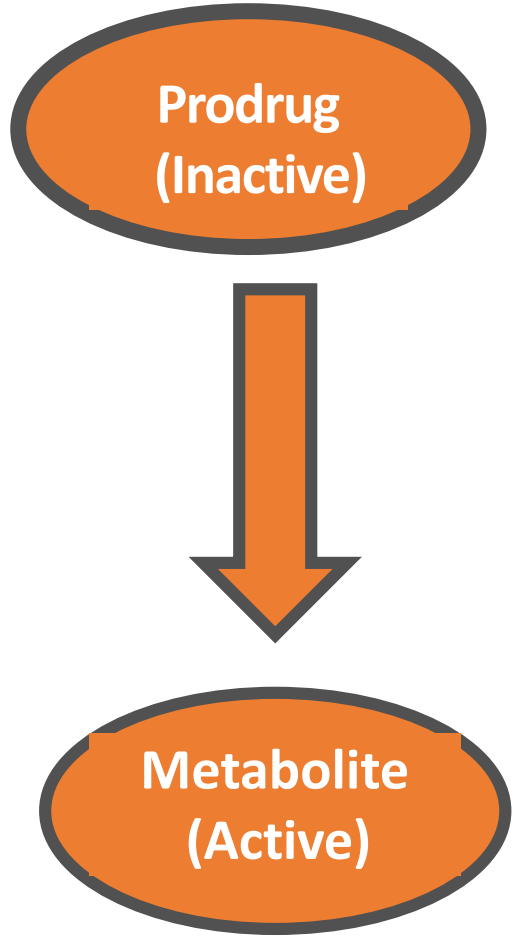
Drug Metabolism – Prodrugs



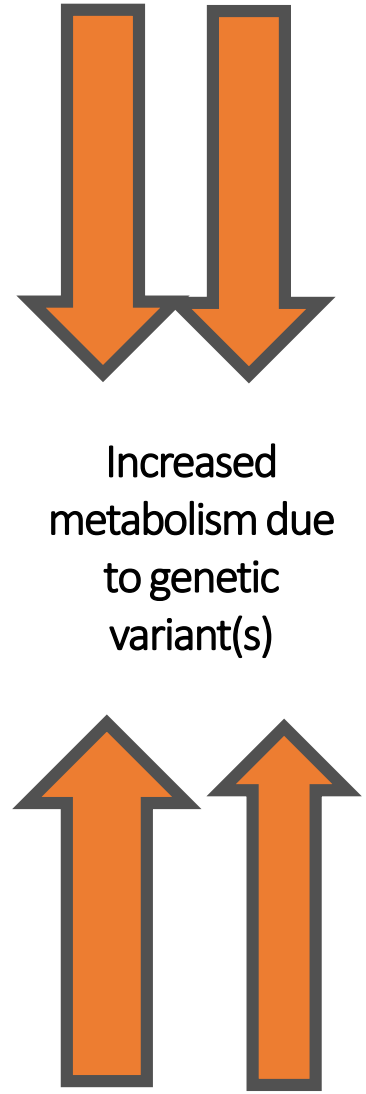
Decreased metabolism due to genetic variant(s)



Decreased metabolism due to genetic variant(s) = Decreased plasma exposure of the active metabolite i.e Decreased pharmacologic effect



Increased metabolism due to genetic variant(s) = Increased plasma exposure of the active metabolite i.e. Increased pharmacologic effect and/or risk of toxicity

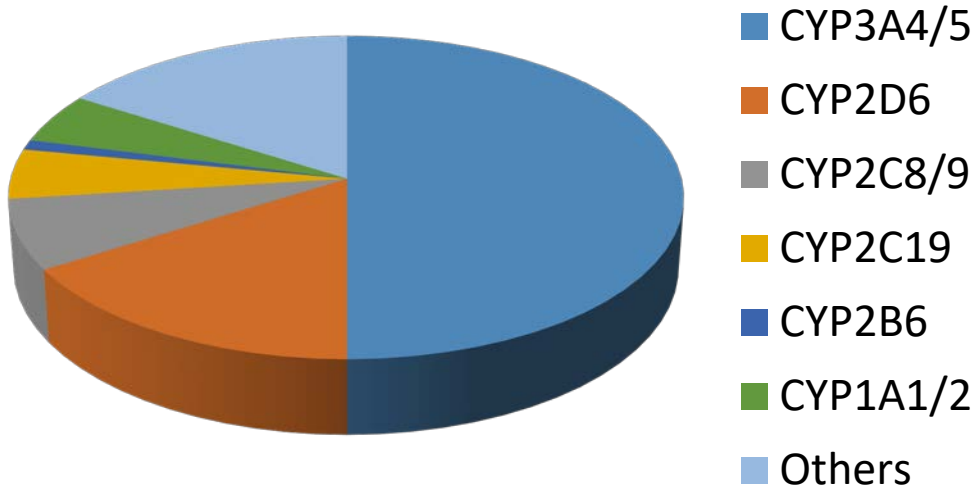


Increased metabolism due to genetic variant(s)

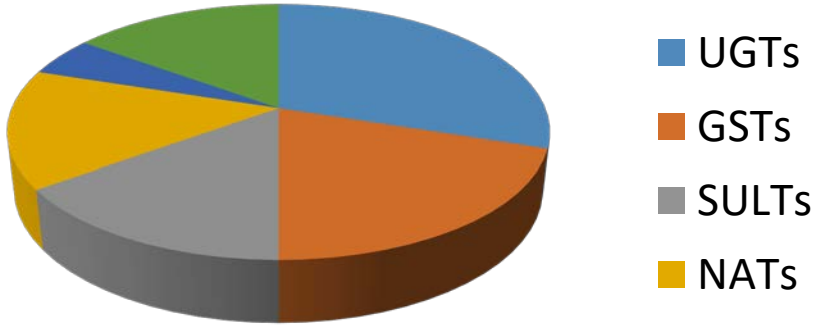
Trends in Genetics. 2003: 660-666

CYP Enzymes

- CYP = Cytochrome P450
- CYP1, CYP2 and CYP3 families play a major role in drug metabolism
  - Primarily in the liver, although distribution may be found in the intestine, lung, kidney and brain
- For each CYP gene, the wild-type allele is denoted at *1
  - SNPs are then sequentially numbers as they are identified (i.e. *2, *3, *4)

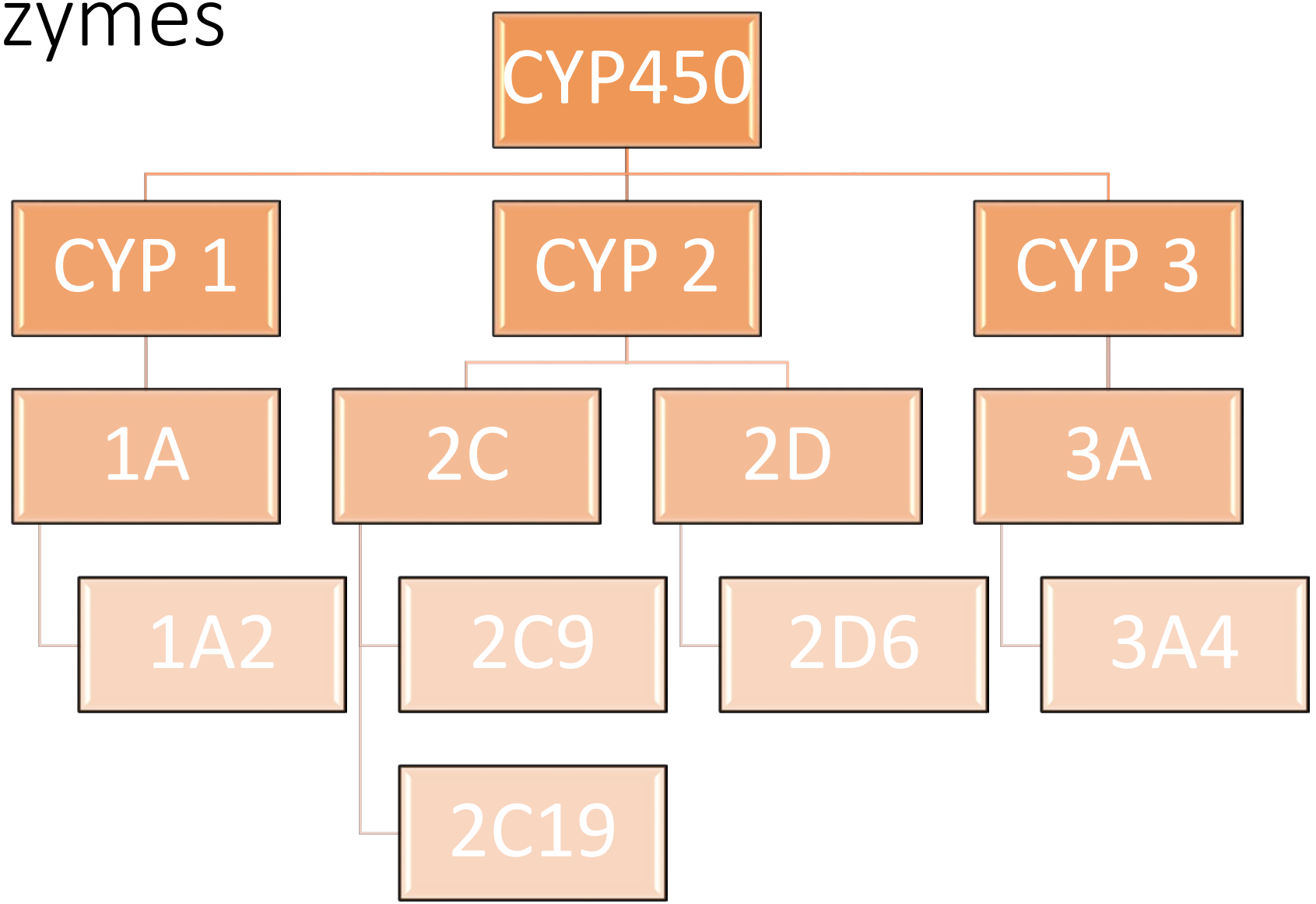


Percent of Other Metabolizing Enzymes



Adapted from Katzung B. Basic and Clinical Pharmacology, 14th Edition

CYP Enzymes



Key Drug Metabolizing Enzymes – Phenotypes

Phenotype	Description of genotype
Ultrarapid Metabolizer	An individual carrying duplications of functional alleles.
Extensive Metabolizer	An individual carrying: •two functional alleles, or •two reduced function alleles, or •one functional and nonfunctional allele, or •one functional and reduced function allele
Intermediate Metabolizer	An individual carrying one reduced function and one nonfunctional allele.
Poor Metabolizer	An individual carrying two nonfunctional alleles.

Clin Pharmacol Ther 2013; 93:402-408
Clin Pharmacol Ther 2014; PMID: 25099164

Coagulation Basics

Coagulation Cascade – Anticoagulants

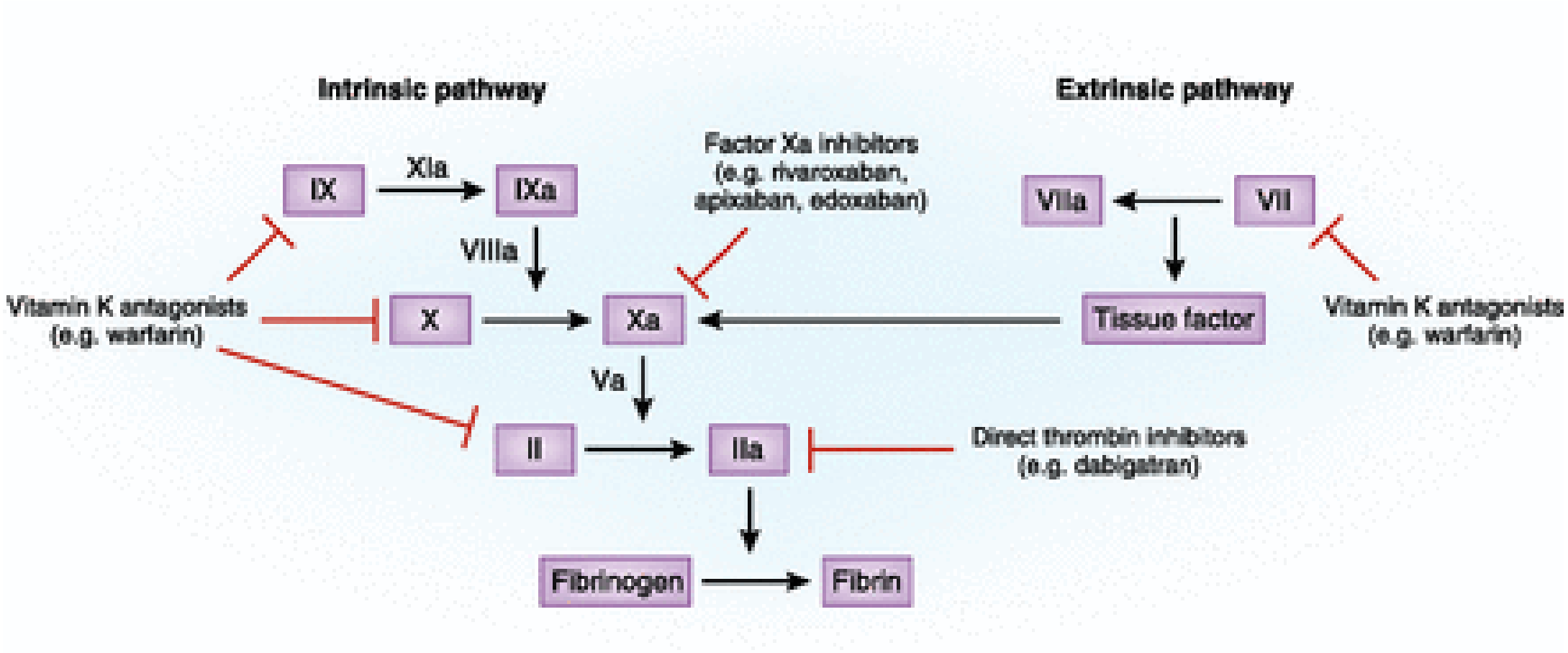


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TABLE 1. SUMMARY OF CURRENTLY AVAILABLE DIRECT ORAL ANTICOAGULANTS								
Drug and FDA Approval	**Target**	**FDA-approved indications**	**Available Strengths[a]**	**Half-life[b]**	**Dosing Frequency**	**Renal Dosing Adjustments**	**Drug Interactions**	**Reversal Agent**
Dabigatran Approved Oct 2010	Thrombin	NVAF, treatment Secondary prevention of DVT and PE VTE prevention after hip replacement	75 mg 100 mg 150 mg	12-17 hr	Twice Daily	Contraindicated if CrCl < 30 mL/min	PPI, antacids, dronedarone, P-gp inhibitors	Praxabind
Rivaroxaban Approved July 2011	Factor Xa	NVAF, treatment and secondary prevention of DVT and PE, VTE prevention after hip and knee replacement	10 mg 15 mg 20 mg	9 hr	Once Daily[c]	Avoid use if CrCl < 30 mL/min	CYP3A4 inhibitors, P-gp inhibitors	AndexXa
Apixaban Approved Dec 2012	Factor Xa	NVAF, treatment and secondary prevention of DVT and PE, VTE prevention after hip and knee replacement	2.5 mg 5 mg	12 hr	Twice Daily[c]	Limited data for serum creatinine > 2.5 mg/dL and CrCl < 25 mL/min	CYP3A4 inhibitors, P-gp inhibitors	AndexXa
Edoxaban Approved Jan 2015	Factor Xa	NVAF, treatment of DVT and PE	15 mg 30 mg 60 mg	10-14 hr	Once Daily	CrCl < 15-50mL/min: 30 mg once daily CrCl < 15 mL/min: not recommended	CYP3A4 inhibitors, P-gp inhibitors	Under development. PCC for emergencies
Betrixaban June 2017	Factor Xa	Prevention of DVT and PE in hospitalized, medically-ill patients	40 mg 80 mg	20 hr	Once Daily[c]	Not reported	Not reported	Under development. PCC for emergencies

[a] Recommended strength varies on indication, [b] Assuming normal renal function, [c] May require higher, more frequency dosing at initiation based on indication.
Abbreviations: CrCl, creatinine clearance calculated by the Cockcroft-Gault formula; CYP, cytochrome P450; DVT, deep vein thrombosis; NVAF: nonvalvular atrial fibrillation; PCC, prothrombin complex concentrate; PE, pulmonary embolism, P-gp, P-Glycoprotein; PPI, proton pump inhibitors; VTE: venous thromboembolism.

https://practicalneurology.com/articles/2019-jan/direct-oral-anticoagulants-for-secondary-stroke-prevention

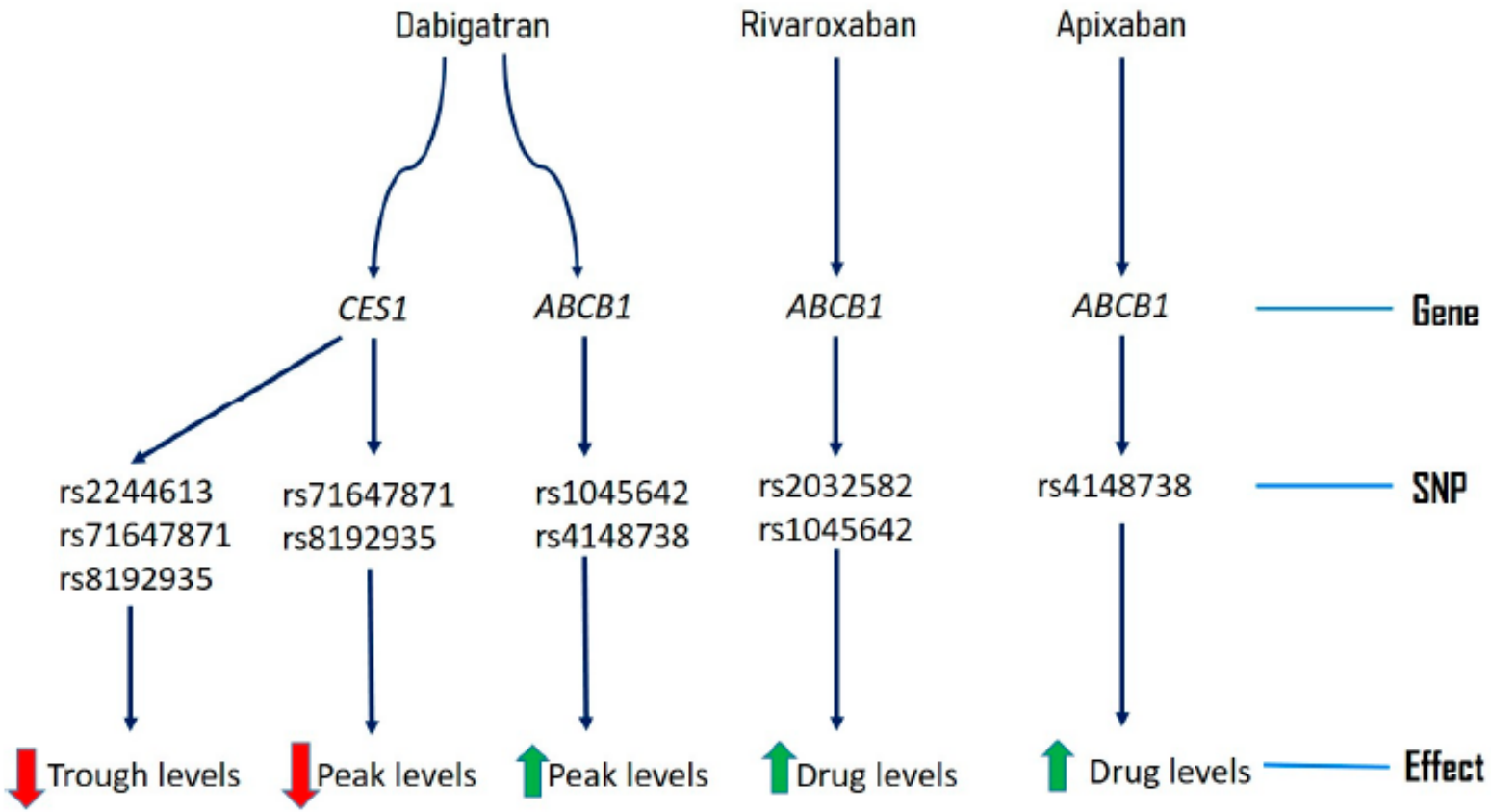
DOAC Pharmacogenomics

Key Genes that Encode the Enzymes that Metabolize DOACs

CYP 3A4/5	CES1	ABCB1	CYP 2J2	SULT1A1

• Metabolize
  • Dabigatran
  • Apixaban
  • Rivaroxaban
	• Carboxylesterase 1
	
	• Metabolize
	  • Dabigatran
		• Also known as P-Glycoprotein (Pgp)
		
		• Metabolize
		  • Dabigatran
		  • Rivaroxaban
		  • Apixaban
			• Metabolize
			  • Apixaban
			  • Rivaroxaban
				• Sulfotransferases
				
				• Metabolize
				  • Apixaban

Key Genes that Encode the Enzymes that Metabolize DOACs



DOAC PGx Literature Review

- Ing Lorenzi K, et al. *Rivaroxaban-Induced Hemorrhage Associated with ABCB1 Genetic Defect*. Front. Pharmacol. 2016;7:494.

- Nakagawa J, et al. *Impact of gene polymorphisms in drug-metabolizing enzymes and transporters on trough concentrations of rivaroxaban in patients with atrial fibrillation.* Basic Clin Pharmacol. Toxicol. 2021; 128:297-304.

- Sychev DA, et al. *The impact of ABCB1 (rs1045642 and rs4148738) and CES1 (rs2244613) gene polymorphisms on dabigatran equilibrium peak concentration in patients after total knee arthroplasty.* Pharmacogenomics and Personalized Medicine. 2018;11:127-137.

- Rosian AN, et al. *An Exploratory Association Analysis of ABCB1 rs1045642 and ABCB1 rs4148738 with Non-Major Bleeding Risk in Atrial Fibrillation Patients treated with Dabigatran or Apixaban.* J. Pers. Med. 2020,10,133; doi:10.3390/jpm10030133.

Clinical PGx Recommendations for the DOACs

- Clinical review conducted by Tseng and colleagues determined the following:

Dabigatran	• Large body of evidence suggesting role of pharmacogenomic testing to determine risk of minor bleeding in patients • Caution with CYP 3A4 inducers and inhibitors
Rivaroxaban	• NO strong evidence for use of pharmacogenomic testing in patients • Caution with CYP 3A4 inducers and inhibitors
Apixaban	• NO strong evidence for use of pharmacogenomic testing in patients • Caution with CYP 3A4 inducers and inhibitors

Cardiovasc Drugs Ther. 2018: 32;121-126

Assessment Questions

Question #1

- **<u>True or False</u>**: Pharmacogenetic information is widely available for all oral anticoagulants and is used to guide clinical decision-making.
  A. True
  B. False

Question #2

- Direct oral anticoagulants exerts their pharmacologic effects on which of the following targets in the coagulation cascade? (Select all that apply)
  A. Factor VII
  B. Factor Xa
  C. Factor Va
  D. Factor IIa
  E. B and D

Question #3

- Genetic variations in which of the following enzymes are responsible for variability in dabigatran metabolism?
  A. CYP2C19
  B. CYP2C9
  C. CYP2J2
  D. CYP3A5

Question #4

- Which of the following enzymes are not involved in the metabolism of the direct oral anticoagulants?
  A. CYP1A2
  B. CYP3A5
  C. ABCB1
  D. CYP2J2

Question #5

- HM is a 45 y/o old male who has recently undergone genotyping testing as a part of a comprehensive medical examination. His results indicate that he has a variant allele (SNP = rs41487348) at the gene for the ABCB1 enzyme. Which of the following is true for HM and dabigatran dosing?
  A. HM may experience a decreased risk of bleeding
  B. HM may experience an increased risk gastrointestinal effects
  C. HM may experience a decreased risk of gastrointestinal effects
  D. HM may experience an increased risk of bleeding

Questions?