Practical Pharmacogenomics: A Look at the Past, Present, and Possibilities

Jay Jackson, Pharm.D.

Assistant Dean of Student Affairs, Associate Professor of Pharmacy Practice
Palm Beach Atlantic University, Lloyd L. Gregory School of Pharmacy

Conflict of Interest Disclosure

The presenter has no relevant financial relationships with commercial interests pertaining to the content of this presentation.

Objectives

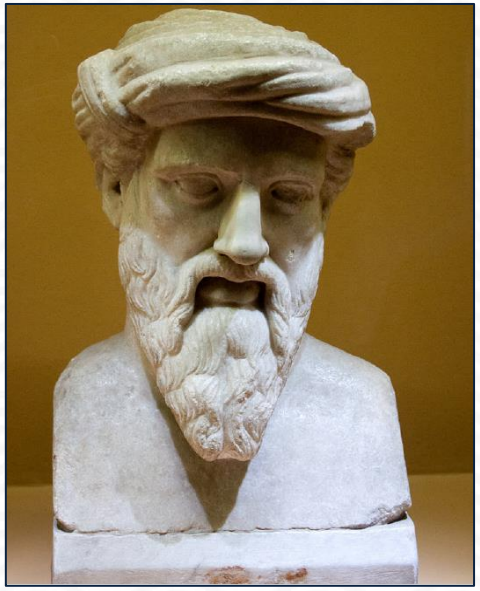
At the completion of this activity, participants will be able to:

1. Describe the origin, potential benefits, and common examples of pharmacogenomics
2. Summarize the newly updated Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline recommendations for clopidogrel and statin therapy
3. Discuss the current landscape of direct-to-consumer pharmacogenomic testing and implications for pharmacy practice
4. Display a general understanding of the major challenges and potential solutions for the implementation of pharmacogenomics in clinical practice
5. Describe the limitations of race-based pharmacogenomic decision-making

Fava beans, anyone?

- **510 B.C.**
  - Pythagoras observes that fava beans cause fatal reaction in *some* individuals (i.e. “favism”)

- **1940’s**
  - William Boyd notes differences in rates of fava bean-induced hemolytic anemia between native British and Mediterranean populations



- **1950’s**
  - Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency linked to hemolytic anemia caused by ingestion of fava beans

Pirmohamed M. *Br J Clin Pharmacol*. 2001 Oct; 52(4): 345–347.

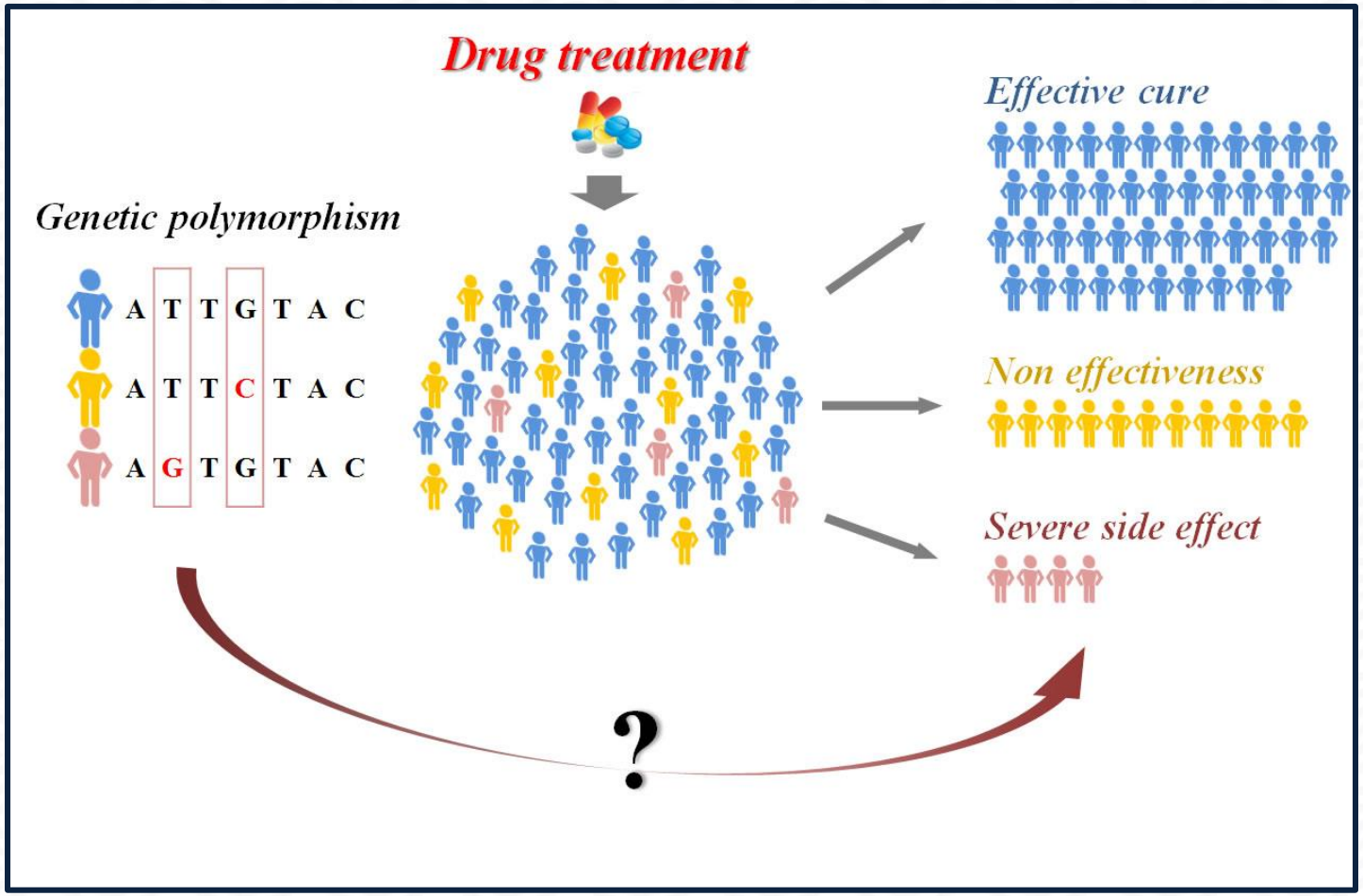
The Human Genome Project (HGP)

- An international, collaborative research initiative that sought to identify and map every gene that makes up the human genome
  - Active from 1990 to 2003

- Major findings
  - The human genome contains ~3 billion nucleotide base pairs (A, T, C, and G) and contains ~20,000 genes
  - ~ 99.9% of nucleotide base pairs are the same in all humans
  - Millions of single nucleotide polymorphisms (SNPs) exist that can affect gene expression and protein function

National Human Genome Research Institute (NHGRI). https://www.genome.gov/. Accessed May 12, 2023

Potential Benefit of Pharmacogenomics (PGx)



http://twsnp.tmu.edu.tw/image/pharmacogenomics1.jpg

President Obama's 2015 "Precision Medicine Initiative"

https://obamawhitehouse.archives.gov/precision-medicine. Accessed May 12, 2023.

Common Characteristics of PGx Drugs

- *Often* metabolized by a hepatic enzyme that has shown variability due to genetic polymorphisms
  - CYP2D6, CYP2C9, and CYP2C19 are most commonly implicated
  - Primary route of elimination/activation is the polymorphic enzyme
- Narrow therapeutic index
- Severe ADR's
- Expensive
- High-risk disease state
- Therapeutic drug monitoring is not feasible/available

Common Characteristics of PGx Drugs

Enzymes	*Fraction of drug metabolism (%)*	*Genetic polymorphism**
CYP1A2	5	+
CYP2C9	10	+ + +
CYP2C19	5	+ + +
CYP2D6	20-30	+ + +
CYP2E1	2-4	+
CYP3A4	40-45	-

*The significance of polymorphism is based on the number of reports showing impact of the P450 polymorphism on the pharmacokinetics of drugs that are substrate for the enzyme in question. Increasing number of + illustrate the increasing importance of the polymorphism.

http://www.biology-online.org/kb/print.php?aid=2340. Accessed May 14, 2023.

2022 Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Update for *CYP2C19* and Clopidogrel

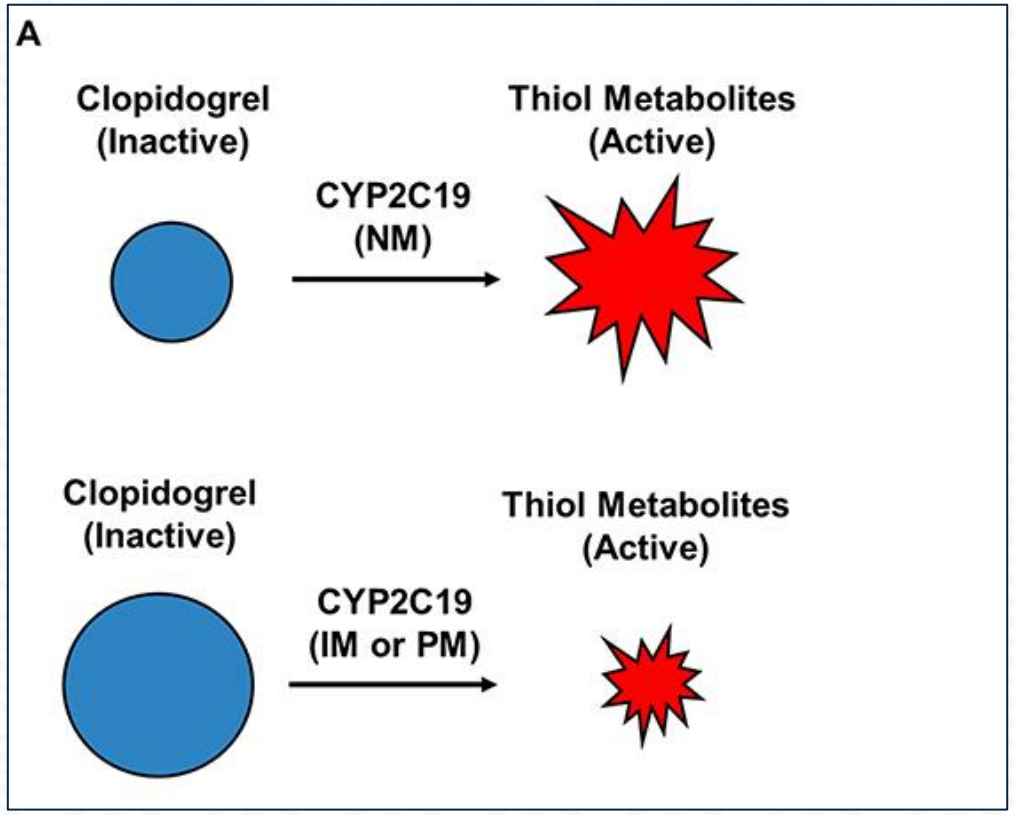
Clopidogrel

- Antiplatelet indicated to reduce the risk of major adverse cardiovascular events (MACE) in patients with hx of MI, stroke, or peripheral artery disease

- Thienopyridine prodrug that requires CYP2C19 hepatic biotransformation to active metabolite

- *CYP2C19* genetic polymorphisms contribute to variability in clopidogrel response

Clopidogrel



WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

Duarte JD, Cavallari LH. *Nat Rev Cardiol*. 2021 Sep;18(9):649-665.

Clopidogrel *Cardiovascular* Recommendations (2022 Update)

CYP2C19 Phenotype	Therapeutic Recommendation	Strength of Recommendation	
		ACS/PCI	Non-ACS/PCI
Ultra-rapid metabolizer (*17/*17)	Standard clopidogrel dose	Strong	None
Rapid metabolizer (*1/*17)	Standard clopidogrel dose	Strong	None
Normal metabolizer	Standard clopidogrel dose	Strong	Strong
Intermediate metabolizer	Avoid clopidogrel; use alternative agent	**Strong***	None
Poor metabolizer	Avoid clopidogrel; use alternative agent	Strong	None

Standard clopidogrel dose: 75 mg/day
*Upgraded strength of recommendation from 2013 guidelines

Lee CR, et al. CPIC Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther*. 2022 Nov;112(5):959-967.

Clopidogrel for ***Neurovascular*** Indications

- The CHANCE-2 trial evaluated **6,412** patients with a history of acute ischemic stroke/TIA
  - Key inclusion criteria: *CYP2C19* IM's and PM's
  - Ticagrelor vs. Clopidogrel
    - All patients received aspirin
  - Better outcomes seen with ticagrelor
    - Lower rate of stroke (HR 0.77; 95%CI 0.64-0.94, P=0.008)
    - No difference in bleeding

Yang W, et al. *N Engl J Med* 2021; 385:2520-2530.

Clopidogrel *Neurovascular* Recommendations (2022 Update)

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Ultra-rapid metabolizer (*17/*17)	Standard clopidogrel dose	None
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Normal metabolizer	Standard clopidogrel dose	Strong
Intermediate metabolizer	Consider alternative agent as clinically indicated	Strong
Poor metabolizer	Consider alternative agent as clinically indicated	Strong
Standard clopidogrel dose: 75 mg/day		

Lee CR, et al. CPIC Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clin Pharmacol Ther*. 2022 Nov;112(5):959-967.

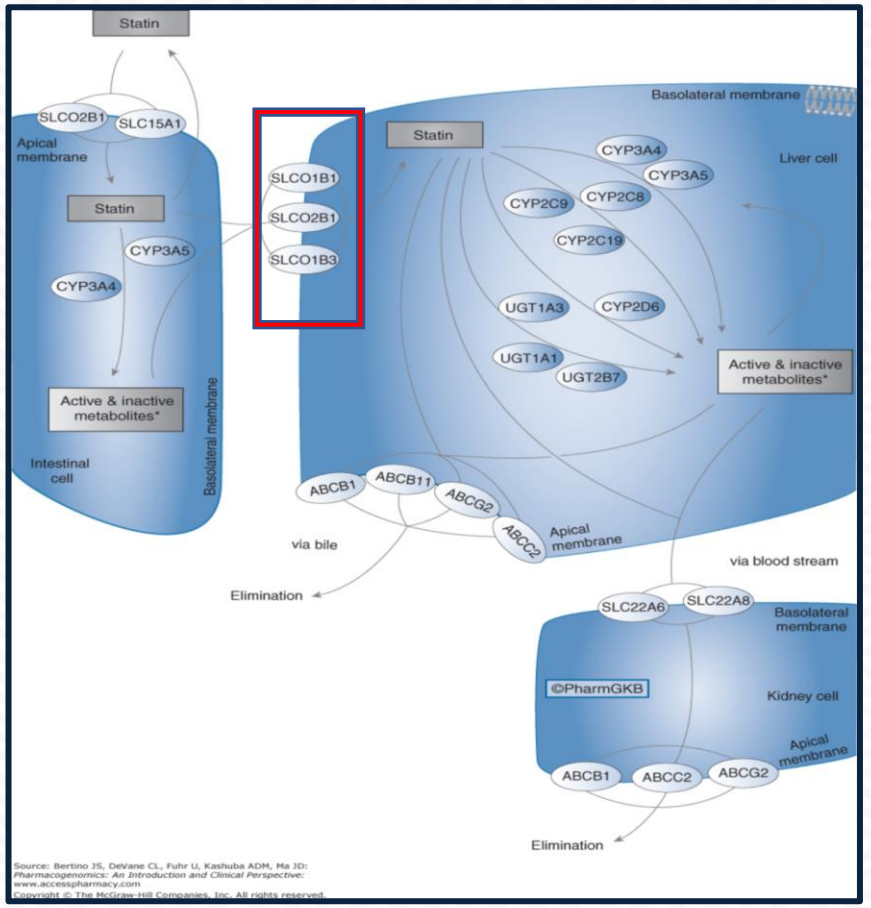
2022 CPIC Guideline Update for *SLCO1B1*, *ABCG2*, and Statin Therapy

Statins

- Most commonly prescribed drugs for dyslipidemia
  - Reduce CV morbidity & mortality in high-risk patient populations
  - Most common ADR is statin-associated musculoskeletal symptoms (SAMS)
- Genetic variations in *SLCO1B1*, *ABCG2*, and *CYP2C9* contribute to the risk of SAMS

Statins & *SLCO1B1*

- The SLCO1B1 transporter facilitates statin* uptake into hepatocytes for metabolism
- Polymorphisms in the *SLCO1B1* gene lead to decreased transporter activity
  - Increases statin plasma concentrations
  - Increased risk of SAMS
  - Strongest association with simvastatin



*Except Fluvastatin

Bertino JS, et al. *Pharmacogenomics: An Introduction and Clinical Perspective.* www.accesspharmacy.com. Accessed: April 12, 2022.

Statins & *SLCO1B1*

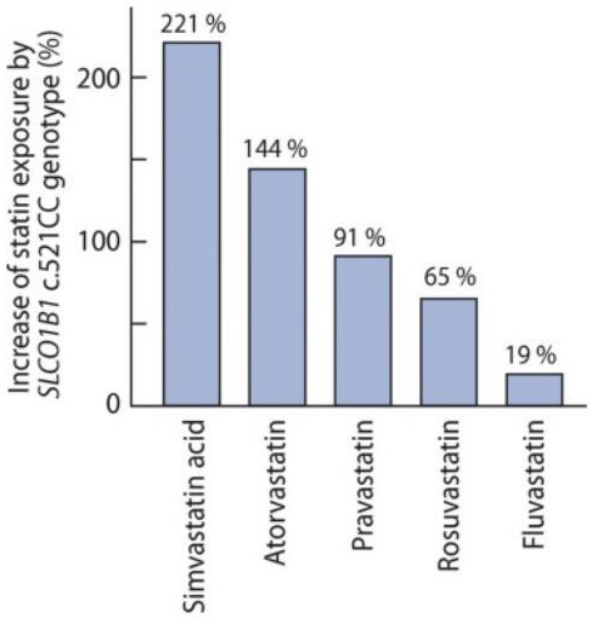
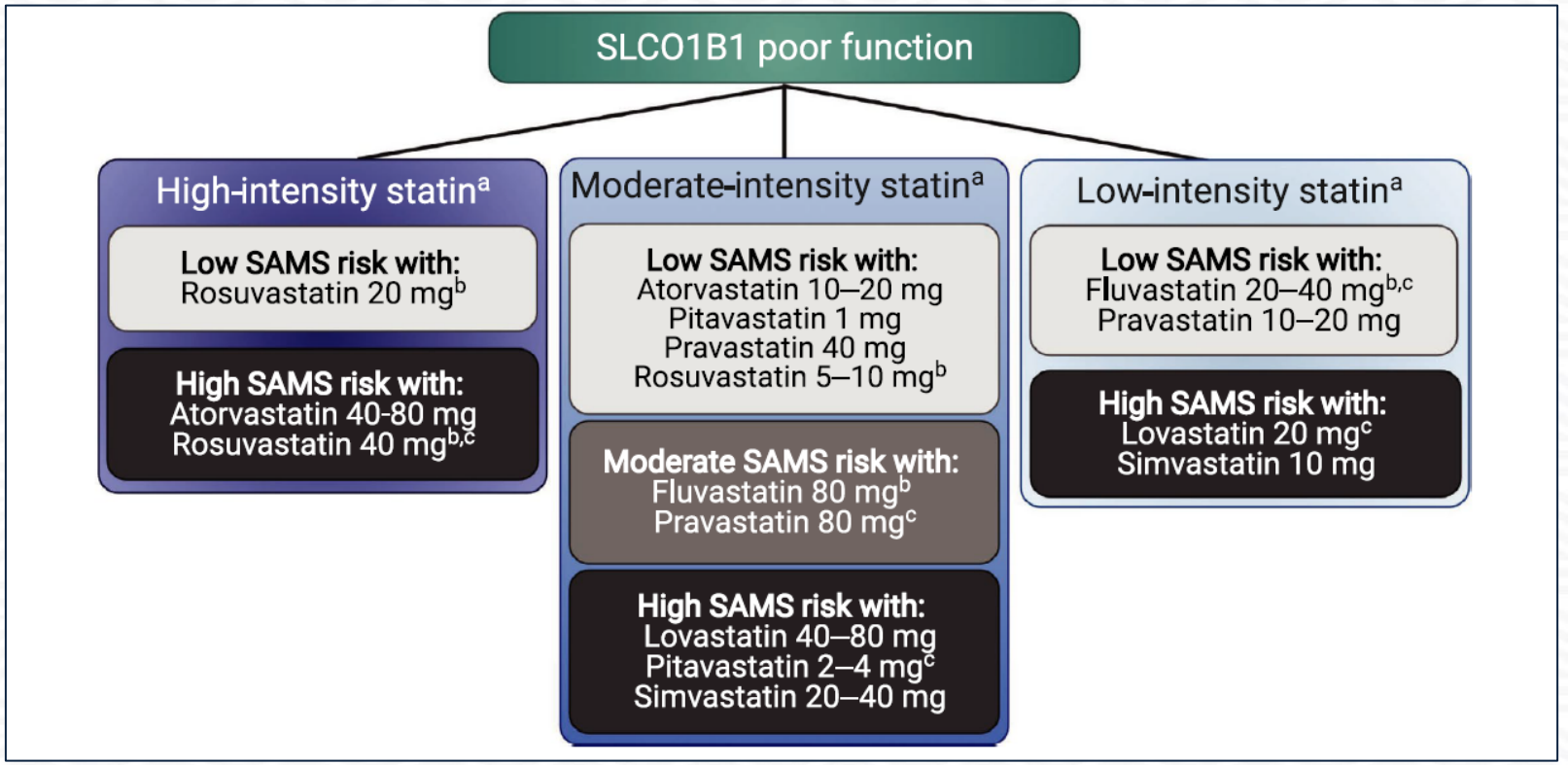


FIG. 5. Effects of the *SLCO1B1* c.521T>C variant on the exposure (area under the plasma statin concentration-time curve) to different statins. The data are from Niemi et al. (2006b) and Pasanen et al. (2006b, 2007).

Niemi M, et al. *Pharmacol Rev*. 2011 Mar;63(1):157-81.

Statins & *SLCO1B1*

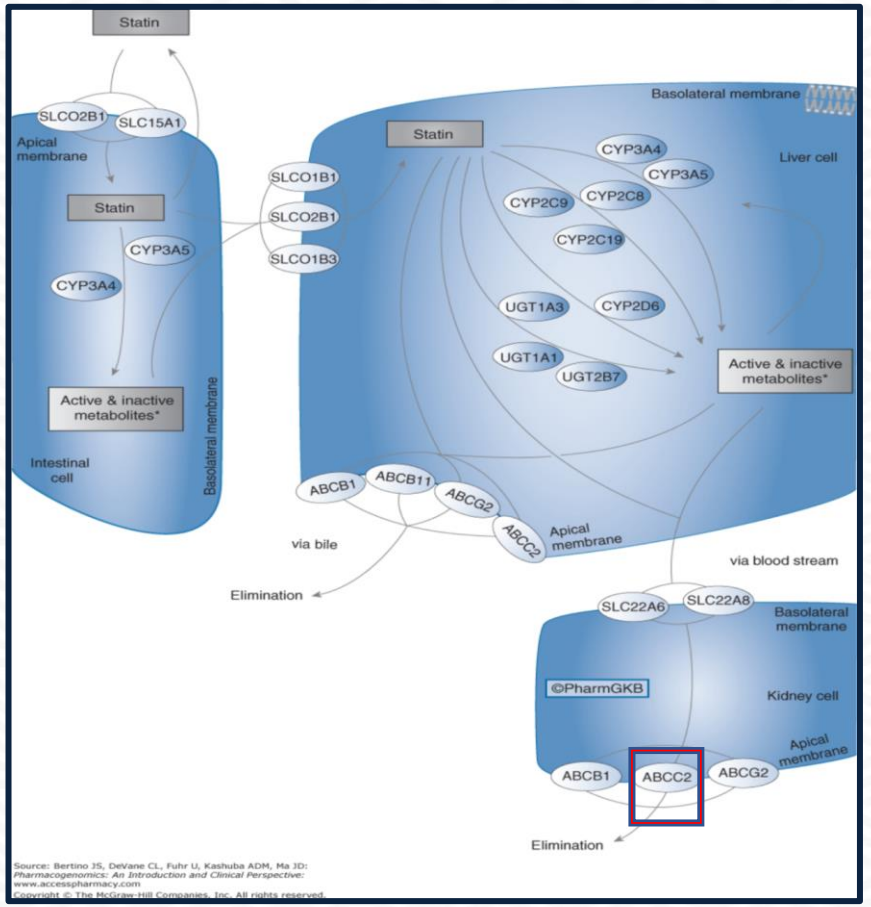


Legend: Light gray boxes: Prescribe stated starting dose. **Dark gray boxes**: Prescriber should be aware of possible increased risk of increased exposure and myopathy. **Black boxes**: Consider a reduced dose or alternative statin. **All boxes**: Doses indicated are total daily dose. Dose recommendations are based on clinical toxicity data when available. [a]Statin intensity as recommended by current American College of Cardiology / American Heart Association guidelines. [b]See Tables 3 and 5 for recommendations for rosuvastatin and *ABCG2* and Tables 2–6 for recommendation for fluvastatin and *CYP2C9*. [c]Dose recommendations are based solely on pharmacokinetic data.

Cooper-DeHoff RM, et al. CPIC Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. *Clin Pharmacol Ther*. 2022 May;111(5):1007-1021.

Rosuvastatin & *ABCG2*

- *ABCG2* codes for an efflux transporter protein
  - Involved in elimination of **rosuvastatin** via bile excretion
- *ABCG2* genetic variations may lead to reduced efflux activity
  - Increases rosuvastatin plasma concentrations
  - Increases risk of SAMS



Bertino JS, et al. *Pharmacogenomics: An Introduction and Clinical Perspective.* www.accesspharmacy.com. Accessed: April 12, 2022.

Rosuvastatin & *ABCG2*

ABCG2 Phenotype	Implications	Dosing Recommendation	Strength of Recommendation
Normal function	Typical myopathy risk and rosuvastatin exposure	Standard rosuvastatin dose	Strong
Decreased function	• Increased rosuvastatin exposure as compared with normal function • Unknown risk for myopathy • Increased lipid-lowering effects	Standard rosuvastatin dose	Moderate
Poor function	• Increased rosuvastatin exposure as compared with normal and decreased function • Unknown risk for myopathy • Increased lipid-lowering effects	Prescribe ≤20 mg as a starting dose; if higher dose needed, consider alternative statin or combination therapy	Moderate

Cooper-DeHoff RM, et al. CPIC Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 2022 May;111(5):1007-1021.

Direct-to-Consumer PGx Testing, Implementation Challenges, and Race-Based PGx

Challenges of Direct-to-Consumer (DTC) Genetic Testing

- DTC genetic testing provides individuals with information regarding their ancestry, genetic makeup, and potential health risks
  - No involvement of healthcare professionals necessary

- Convenient *but* challenges exist:
  - Interpretation and accuracy
  - Privacy and data security
  - Limited regulation and oversight
  - Ethical dilemmas

Direct-To-Consumer PGx Options

PGx Implementation: Challenges & Solutions

- **Lack of education and awareness**
  - Provide educational initiatives (CE programming, integration into pharmacy/med school curricula)
  - Offer point-of-care decision support tools
- **Difficulty integrating into existing systems and practices**
  - Strategically integrate PGx data with electronic health records
  - Use linked drug-gene pairs that flag providers during order entry
  - Promote interprofessional collaboration

PGx Implementation: Challenges & Solutions

- **High cost and low reimbursement rates**
  - Advocate for insurance coverage, negotiate with payers, and demonstrate clinical/economic benefits of PGx-guided care
  - Provide preemptive PGx testing to reduce time delays increase cost-effectiveness
- **Limited, poor quality evidence**
  - Conduct quality studies that show improved clinical outcomes with PGx-guided care
  - Promote collaborative research efforts and data sharing

Race-based Medicine: Case Example

https://scalawagmagazine.org/2015/10/black-pill-white-pill/. Accessed May 16, 2023.

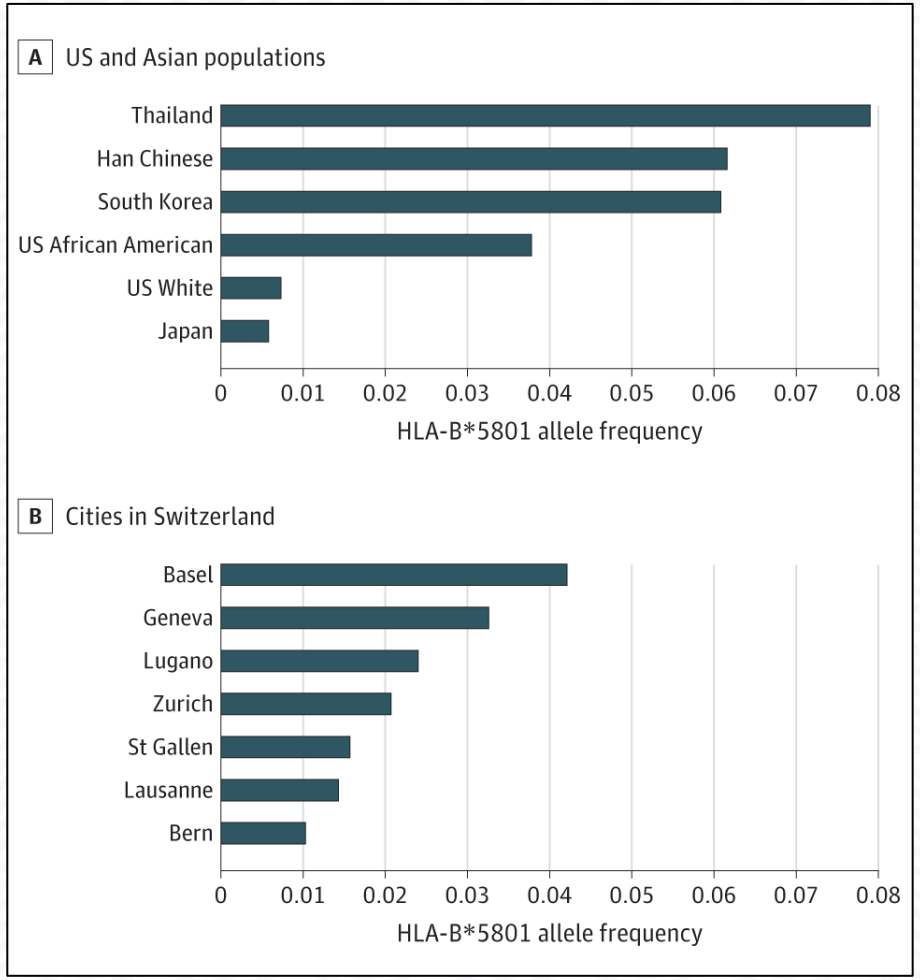
Example of Race-based PGx Decision Making

Table 4. Recommendations for patients taking specific urate-lowering therapy (ULT) medications*

Recommendation	PICO question	Certainty of evidence
Allopurinol		
We conditionally recommend testing HLA–B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA–B*5801.	12	Very low
We conditionally recommend *against* HLA–B*5801 testing in all others.		
For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we conditionally recommend using allopurinol desensitization.	23	Very low

FitzGerald JD, et al. 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Rheumatol*. 2020;72(6):879-895.

Race-based PGx Decision Making



Race and Pharmacogenomics—Personalized Medicine or Misguided Practice. *JAMA*. 2021;325(7):625-626.

Race-based PGx Decision Making

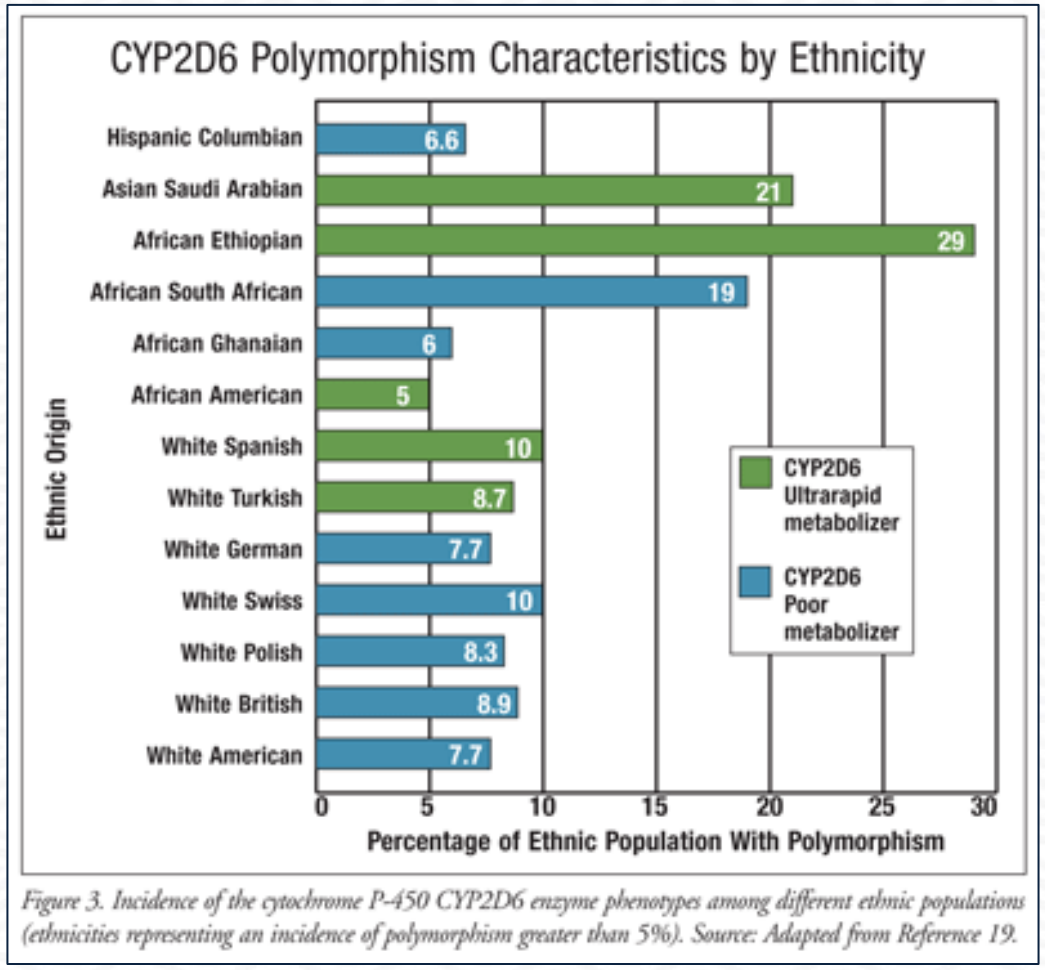


Figure 3. Incidence of the cytochrome P-450 CYP2D6 enzyme phenotypes among different ethnic populations (ethnicities representing an incidence of polymorphism greater than 5%). Source: Adapted from Reference 19.

Race and Pharmacogenomics—Personalized Medicine or Misguided Practice. *JAMA*. 2021;325(7):625-626.

Limitations of Race-based PGx Decision Making

The FDA statement acknowledges that clinicians encounter practical issues in applying race-based screening recommendations. Clinical research, and the clinical guidelines derived from it, cannot provide consistent and coherent definitions of racial categories because such categories are fluid, socially constructed concepts.

Clinicians are asked to focus on certain races or ethnicities for screening, but definitions (eg, "Southeast Asian descent" in the ACR guideline) vary across authors and over time, and mixed ancestry is rarely addressed and likely increasing in frequency. Given this uncertainty, clinicians are left to rely on their own intuitions.

Goodman CW, et al. Race and Pharmacogenomics—Personalized Medicine or Misguided Practice? JAMA. 2021;325(7):625-626.
Cooper RS, et al. Race, ancestry, and reporting in medical journals. *JAMA*. 2018;320(15):1531-1532.

Limitations of Race-based PGx Decision Making

- Race is a social construct
  - Fluidity of “race” definitions
  - PGx studies often use self-reported race to approximate the continental ancestry of individuals
  - Intrapopulation genetic variation is common
  - Constant shifts in ethnicity and increased prevalence of “mixed-races”
- Potential solution: universal screening for genetic variations (e.g. abacavir)
- **Bottom line:** biological or genetic differences cannot be **assumed** by any social construct…including “race”

Goodman CW, et al. Race and Pharmacogenomics—Personalized Medicine or Misguided Practice? JAMA. 2021;325(7):625-626.
Cooper RS, et al. Race, ancestry, and reporting in medical journals. *JAMA*. 2018;320(15):1531-1532.

Test Your Knowledge!

Which of the following would be most likely to have PGx implications?

A. Drug A that is solely metabolized by CYP3A4, has a narrow therapeutic index, and TDM

B. Drug B that is metabolized by multiple CYP enzymes

C. Drug C that is 90% excreted unchanged in the urine

D. Drug D that is solely metabolized by CYP2C19, has a narrow therapeutic index, and no TDM

TDM: therapeutic drug monitoring

True or False: *CYP2C19* poor metabolizers should receive an alternative antiplatelet for secondary prevention of an ischemic stroke or TIA?

A. True

B. False

Which of the following is NOT a potential solution for overcoming challenges associated with implementing PGx?

A. Provide point-of-care decision support tools

B. Administer preemptive PGx testing

C. Conduct quality studies that show non-inferiority of PGx-guided care

D. Integrate PGx data with electronic health records

Which of the following is TRUE regarding race-based PGx decision making?

A. Race is a concrete, objective reality

B. Race definitions and categories vary amongst researchers

C. There is a decrease in prevalence of mixed-races

D. Vast genetic differences exist across races with only ~ 50% of the genetic makeup being the same in all humans