



# Personalized Medicine: Implications for Women's Health

Christina Aquilante, PharmD, FCCP

Professor, Department of Pharmaceutical Sciences

University of Colorado



**Skaggs** School of Pharmacy  
and Pharmaceutical Sciences

UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

# Objectives

- Identify evidence-based resources that aid in the use of personalized medicine strategies (e.g., pharmacogenomics) in clinical practice
- In the context of women's health examples, formulate patient-specific medication recommendations based on clinical guidelines, genetic test results, and other patient factors
- Educate patients about the utility of personalized medicine strategies to improve their health

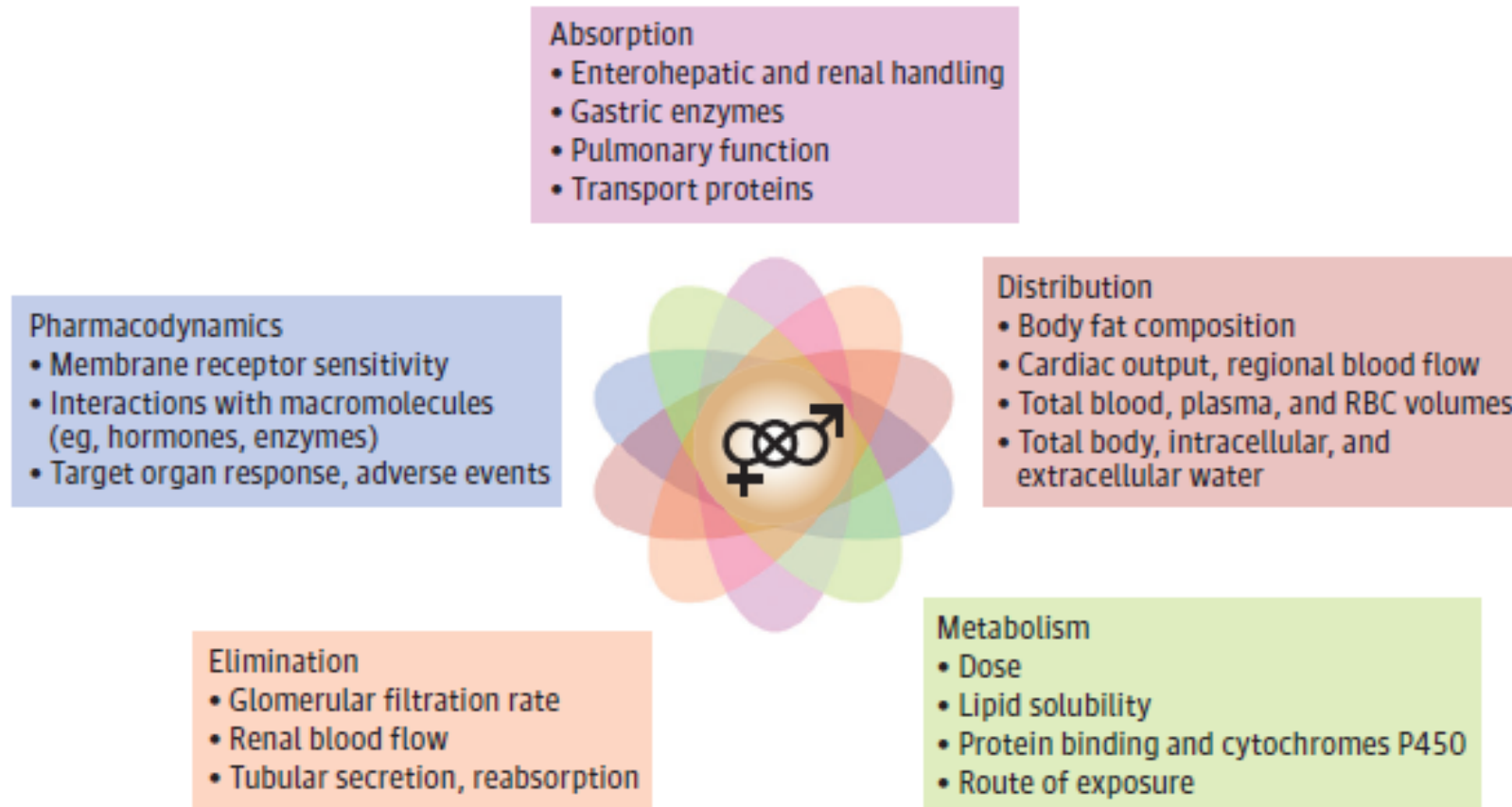
# The Era of Precision Medicine

## **Precision Medicine:**

- Approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person
- “Personalized Medicine” or “Precision Health”



# One Drug Does Not Fit All



# Pharmacogenomics (PGx)

- Component of precision and personalized medicine
- How does genetic variation contribute to variability in drug disposition, response, and toxicity?
- Use genetic information to **guide drug selection and dosing** to maximize efficacy and minimize adverse effects

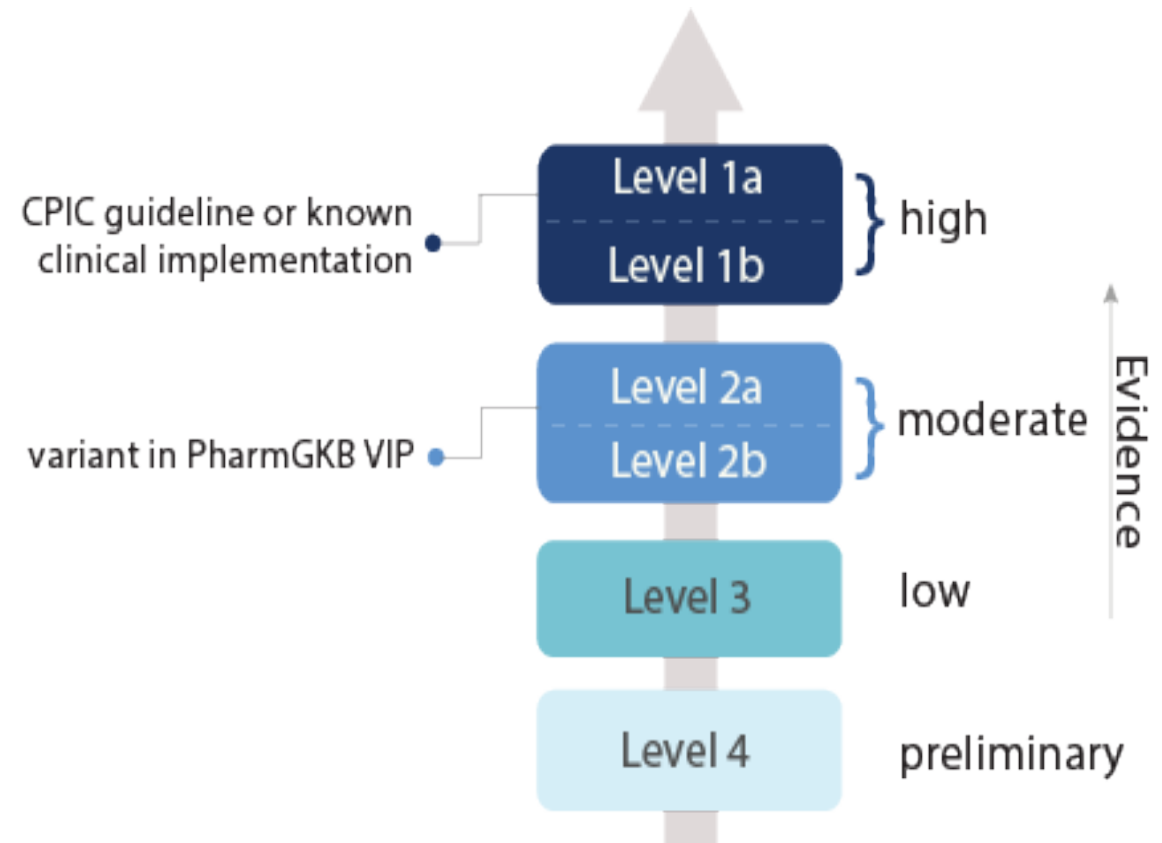


# Information Overload

- Thousands of clinical PGx studies in the literature
- **Not all PGx knowledge merits clinical implementation!**
- Need to demonstrate:
  - Clinical Validity: ability of the PGx test to predict the presence or absence of a medication-related phenotype
  - Clinical Utility (actionability): likelihood that a PGx test will alter clinical outcomes or treatment strategies
- **How do we prioritize the existing evidence?**

# Pharmacogenomics Knowledgebase (PharmGKB)

- Collects, curates and disseminates knowledge about PGx
  - Annotate genetic variants and gene-drug-disease relationships via literature review
  - Curate FDA drug labels containing PGx information
- Create clinical annotations for drug-gene pairs based on curated literature
  - Assign “Levels of Evidence” based on criteria such as replication, statistical significance, and study size



# Clinical Pharmacogenetics Implementation Consortium (CPIC)



- Established in 2009 to address the need for guidelines to instruct clinicians on how to modify drug therapy based on genetic information
- Provide peer-reviewed, evidence-based clinical guidelines for select gene-drug pairs
- Designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy
  - Key assumption: Clinical high-throughput and pre-emptive genotyping will become widespread



# Over 40 Medications with CPIC Guidelines

Cardiology	
Clopidogrel	CYP2C19
Simvastatin	SLCO1B1
Warfarin	CYP2C9, VKORC1, CYP4F2
Infectious Disease	
Abacavir	HLA-B
Atazanavir	UGT1A1
Efavirenz	CYP2B6
Voriconazole	CYP2C19
Rheumatology	
Allopurinol	HLA-B
Thiopurines	TPMT
Pain Management	
Codeine	CYP2D6
Tramadol	CYP2D6

Psychiatry	
SSRIs	CYP2D6, CYP2C19
TCAs	CYP2D6, CYP2C19
Atomoxetine	CYP2D6
Neurology	
Carbamazepine	HLA-B, HLA-A
Oxcarbazepine	HLA-B
Phenytoin	HLA-B, CYP2C9
Oncology/Supportive Care	
Thiopurines	TPMT
Fluoropyrimidines	DPYD
Tamoxifen	CYP2D6
Ondansetron	CYP2D6
Surgery	
Volatile anesthetics & Succinylcholine	RYR1, CACNA1S

# Clinically-Actionable PGx Examples: Women's Health

- **Clopidogrel:** CYP2C19

- Variants associated with increased risk of major adverse CV effects

- **Simvastatin:** SLCO1B1

- Variants associated with increased risk of myopathy

- **Tamoxifen:** CYP2D6

- Variants associated with decreased efficacy in some studies

- **Codeine:** CYP2D6

- Variants associated with decreased response or increased risk of adverse effects

- **SSRIs/TCAs:** CYP2C19 and CYP2D6

- Variants associated with altered dose requirements, response, and risk of adverse effects

# Case Study – Mrs. B

- Mrs. B is a 74-year-old woman who presents to her PCP with complaints of fatigue, decreased appetite, and a change in sleep habits over the past few months.
- Her medical history is significant for hyperlipidemia (atorvastatin), hypertension (hydrochlorothiazide), and overactive bladder (oxybutynin). She performs well on cognitive tests and physical exam reveals no underlying illness.
- She used to be active with her church fellowship group, but now spends much of her time at home watching television. She no longer enjoys the weekly visits from her grandchildren.
- Mrs. B had symptoms like this about 8 months ago and was treated with citalopram. She stopped taking the medication after 2 months because “it didn’t do a darn thing.”

# Citalopram and CYP2C19

- Citalopram is administered in its active form and is metabolized by CYP2C19

- DNA variants in the CYP2C19 gene affect how quickly the body metabolizes citalopram

- Ultrarapid metabolizers (UMs)
- Rapid metabolizers (RMs)
- Normal metabolizers (NMs)
- Intermediate metabolizers (IMs)
- Poor metabolizers (PMs)

- Rapidly convert citalopram to less active metabolites. Low citalopram concentrations in the blood
- Decreased citalopram efficacy and increased chance for treatment failure

- Slowly convert citalopram to its less active form. High citalopram concentrations in the blood
- Increased citalopram efficacy, but also an increased chance for side effects

**TRUE OR FALSE:**

PGx testing must be conducted with an FDA-approved genetic test










# Clinical Laboratory Improvement Amendments (CLIA)

- Regulations governing all laboratory testing (except research) performed on humans in the United States
  - Objective: ensure quality laboratory testing
- Per CLIA, genetic testing is a high-complexity and non-waived test
  - Laboratories that perform this type of testing must meet CLIA requirements for high-complexity, non-waived tests

# Scope of Testing

- **Single gene/few variants:** genotype a few variants in (usually) a single gene related to the medication of interest
  - Example: CYP2C19\*2, \*3, \*17 genotyping for clopidogrel
- **Multi-gene/multi-variant panel:** genotype many variants in many pharmacogenes, not necessarily related to the medication(s) of interest
  - Example: panel that interrogates 120 variants covering 30 pharmacogenes
- There are an increasing number of commercial panel-based PGx tests

## Mrs. B's PCP orders a commercially-available multi-gene/variant PGx testing panel

Gene	Genotype		Phenotype summary / Metabolic status
CYP1A2	*1A/*1F		Rapid Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.
CYP2B6	*1/*5		Intermediate to Normal Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.
CYP2C9	*1/*3		Intermediate Decreased activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.
CYP2C19	*17/*17		Ultrarapid Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.
CYP2C Cluster	rs12777823 GG		Normal Normal warfarin clearance associated with CYP2C rs12777823, independent of CYP2C9*2 and *3. CYP2C rs12777823, together with CYP4F2, CYP2C9, and VKORC1, influences response to warfarin therapy.
CYP2D6	*1/*1		Normal Normal level of activity. Drugs metabolized at a normal rate.
CYP3A4	*1/*1		Normal Normal level of activity. Drugs metabolized at a normal rate.
CYP3A5	*3/*3		Poor Normal dosing may be required because original dosing guidelines for drugs have been established on patients with poor metabolizer phenotype.
CYP4F2	*1/*1		Normal activity Normal activity of the CYP4F2 enzyme, which catalyzes the metabolism of vitamin K, in counterpoint to the activity of VKORC1. CYP4F2, together with CYP2C9, VKORC1, and a variant in CYP2C Cluster, influences response to warfarin therapy.



# Case Study – Mrs. B

- PGx test results indicate Mrs. B is a **CYP2C19 ultrarapid metabolizer**

Table 3 Dosing recommendations for CYP2C19 and SSRIs

Table 3a Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation <sup>a</sup>
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19. <sup>b</sup>	Moderate
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended dose.	
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction <sup>c,d</sup> of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. <sup>b</sup>	Moderate

Potential therapeutic options:

- Paroxetine, Venlafaxine

# Commercially Available PGx Tests

- Not all PGx tests are created equally – buyer be aware!
- Ask questions!
- Genetics does not guarantee that a medication will work, but it may help minimize the trial-and-error process

Table 1. Four Domains for Evaluating Pharmacogenomic Laboratories

Domain	Key questions
Pharmacogene selection	<ol style="list-style-type: none"><li>1 What gene(s) is/are applicable to my clinical setting?</li><li>2 How are the genes aggregated for testing? (single gene, disease-specific panel, broad panel testing)</li><li>3 Can the laboratory provide a customized panel of genes?</li><li>4 What variants for each gene are interrogated, and are they representative of my patient population?</li></ol>
Logistics	<ol style="list-style-type: none"><li>1 What type of sample is required?</li><li>2 What is the turnaround time?</li><li>3 Are samples stored for future testing?</li><li>4 Are samples used for research purposes?</li><li>5 What information is included on the consent form, if required?</li></ol>
Reporting of results	<ol style="list-style-type: none"><li>1 How are the results returned to a provider/patient?</li><li>2 Are the results easy to interpret for a provider/patient?</li><li>3 Is the evidence for each recommendation available?</li><li>4 Does the evidence support the recommendations?</li><li>5 What educational materials are available to aid in discussion of the results?</li></ol>
Test cost and reimbursement	<ol style="list-style-type: none"><li>1 Does the laboratory bill patient insurance directly?</li><li>2 What patient financial assistance programs does the laboratory provide?</li><li>3 Does the laboratory provide a maximum cost for the patient?</li></ol>

# Case Study

- *For the sake of this example - let's say the previous PGx report showed that Mrs. B was a CYP2C19 poor metabolizer*
- One year later, Mrs. B presents to the ED (at the same health system) with an acute coronary syndrome and she undergoes PCI with stenting
- The cardiologist starts clopidogrel. The cardiologist has no knowledge that Mrs. B. had PGx testing done or that she is a CYP2C19 poor metabolizer.
- **Problem: Panel-based PGx tests are being ordered, but they aren't being integrated in the patient's health record in a way that benefits the patient over time or that communicates the information to other providers**

# Integration with the Electronic Health Record

- Enter PGx data into the EHR in a patient-centric and time-independent fashion
- Integrate PGx data into the EHR in a discrete and structured way
- Build clinical decision support tools
  - Surface genetic information and recommendations at the point-of-prescribing



# Emerging Area of PGx Research: Hormonal Contraceptives

## Influence of Genetic Variants on Steady-State Etonogestrel Concentrations Among Contraceptive Implant Users

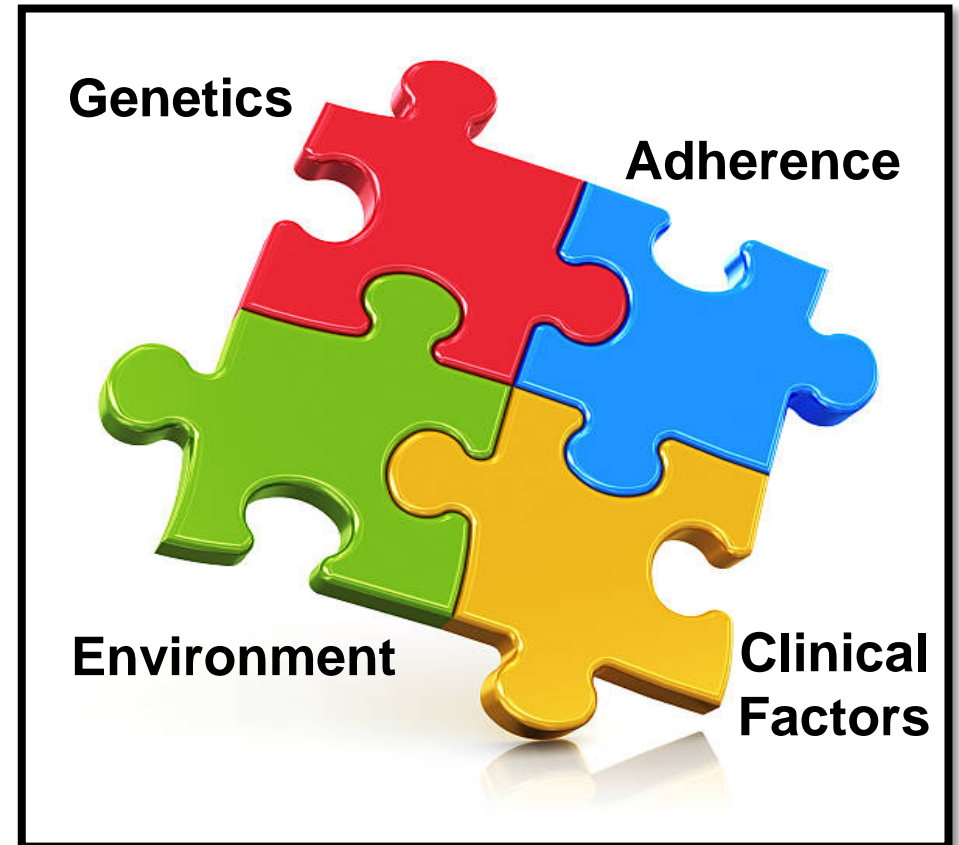
*Aaron Lazorwitz, MD, MSCS, Christina L. Aquilante, PharmD, Kris Oreschak, BS, Jeanelle Sheeder, PhD,  
Maryam Guiahi, MD, MSc, and Stephanie Teal, MD, MPH*

*CYP3A7\*1C* variant causes adult expression of CYP3A7 protein  
and can increase steroid hormone metabolism.

28% of *CYP3A7\*1C* carriers had etonogestrel levels that fell  
below the threshold for consistent ovulatory suppression.

# Summary

- Genetic variation contributes to interindividual variability in drug disposition, response, and toxicity
- Resources exist to determine if a drug-gene pair has sufficient clinical validity and utility for implementation into practice
- Genetics is only one piece of the clinical pharmacology puzzle





# Questions?

- [Christina.Aquilante@cuanschutz.edu](mailto:Christina.Aquilante@cuanschutz.edu)



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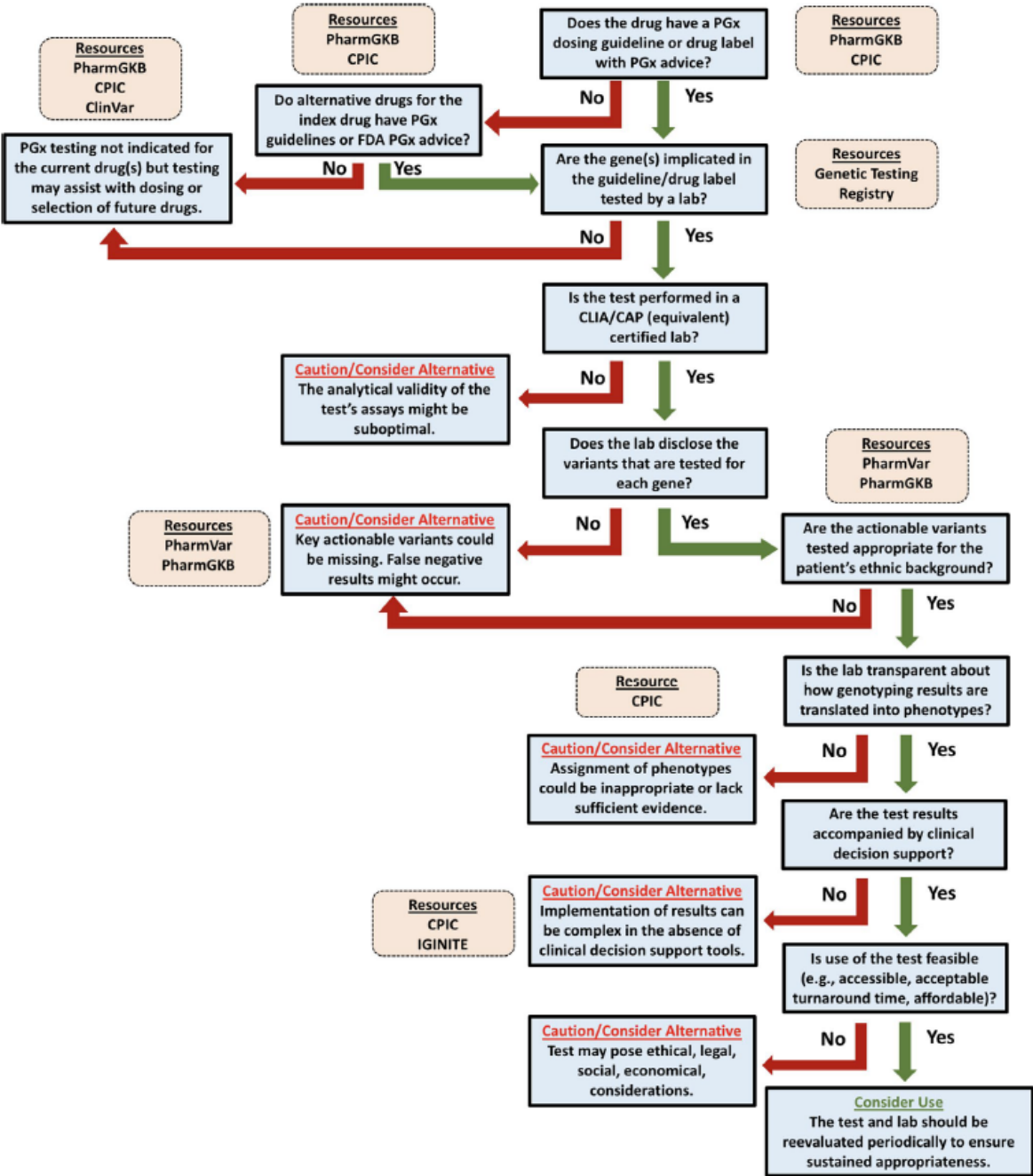
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# Navigating the Labyrinth of Pharmacogenetic Testing: A Guide to Test Selection

Chad A. Bousman<sup>1,2,3,\*</sup>, Heather Zierhut<sup>4</sup> and Daniel J. Müller<sup>5,6</sup>

Clin Pharmacol Ther. 2019 Aug;106(2):309-312

PMID: 31004441



**Figure 1** Decision tree for the selection of a clinical pharmacogenetic (PGx) test. CAP, College of American Pathologists; CLIA, Clinical Laboratory Improvement Amendments; CPIC, Clinical Pharmacogenetics Implementation Consortium; FDA, US Food and Drug Administration; IGINITE, Implementing Genomics in Practice; PharmGKB, Pharmacogenomics Knowledgebase; PharmVar, Pharmacogene Variation Consortium.





# “Traffic Light” PGx Reports

Color-coded categories on efficacy and tolerability:

**Green:** Medications may be used as directed

**Yellow:** Use medications with caution

**Red:** Use medications with increased caution and more frequent monitoring

		<b>GeneSight Psychotropic Results</b>			
<b>Patient, Sample</b> DOB: 7/22/1984					
Reference: Clinician:	1456CIP Sample Clinician			Order Number:	9299
				Report Date:	4/03/2014
		<b>Antidepressants</b>			
		<b>USE AS DIRECTED</b>		<b>USE WITH CAUTION</b>	
		desvenlafaxine (Pristiq®) levomilnacipran (Fetzima®)		bupropion (Wellbutrin®) [1,6] selegiline (Emsam®) [1] sertraline (Zoloft®) [1,4] trazodone (Desyrel®) [1] vilazodone (Viibryd®) [1]	
				<b>USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING</b>	
				amitriptyline (Elavil®) [1,6,8] citalopram (Celexa®) [1,4,6] clomipramine (Anafranil®) [1,6,8] desipramine (Norpramin®) [1,6,8] doxepin (Sinequan®) [1,6,8] duloxetine (Cymbalta®) [1,6,8] escitalopram (Lexapro®) [1,4,6] fluoxetine (Prozac®) [1,4,6] fluvoxamine (Luvox®) [1,4,6,8] imipramine (Tofranil®) [1,6,8] mirtazapine (Remeron®) [1,6] nortriptyline (Pamelor®) [1,6,8] paroxetine (Paxil®) [1,4,6,8] venlafaxine (Effexor®) [1,6] vortioxetine (Brintellix®) [1,6,8]	

# Challenges of Relying on Traffic Light Reports to Make Clinical Decisions

- Somewhat of a “black box”
- To what extent do the algorithms incorporate evidence-based information and what are the evidence thresholds?
- To what extent do the algorithms include drug-drug-gene or drug-gene-gene interactions?
- Just because a medication might be in yellow or red bucket, does not necessarily mean you cannot use it
  - E.g., the patient may already be taking a “red” medication and doing just fine!
- **Need to evaluate the genotype and phenotype data yourself!**
- **Need to look at the patient as a whole and take into account their current and past medical and medication history**