PHARMACOGENETIC CASES IN PRIMARY CARE

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2021

DISCLOSURES

- Volunteer member of CPIC

OBJECTIVES

- Explain the ways that genetics plays a role in drug metabolism/response
- Understand clinical differences between metabolic phenotypes
- Utilize prescribing recommendations for specific drugs with clinical correlations to genomic variations

WHAT HAPPENED IN HAWAII

- Clopidogrel (Plavix) lawsuit filed in 2014
- Pacific Islanders
  - Genetic variant in 40 – 77% of the population that affects metabolism of Plavix
  - 23 – 45% in East Asians
  - 10 – 20% frequency in Caucasian populations

Estimated 25% of Hawaiians have reduced efficacy of Plavix

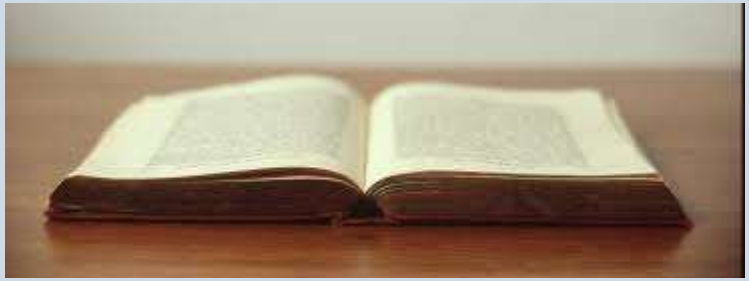
- 4.8% mortality post AMI vs 2.5% Caucasians

http://www.futuremedicine.com/doi/full/10.2217/pme.15.4

GENETICS VS GENOMICS

Pharmacogenetics: words on a page

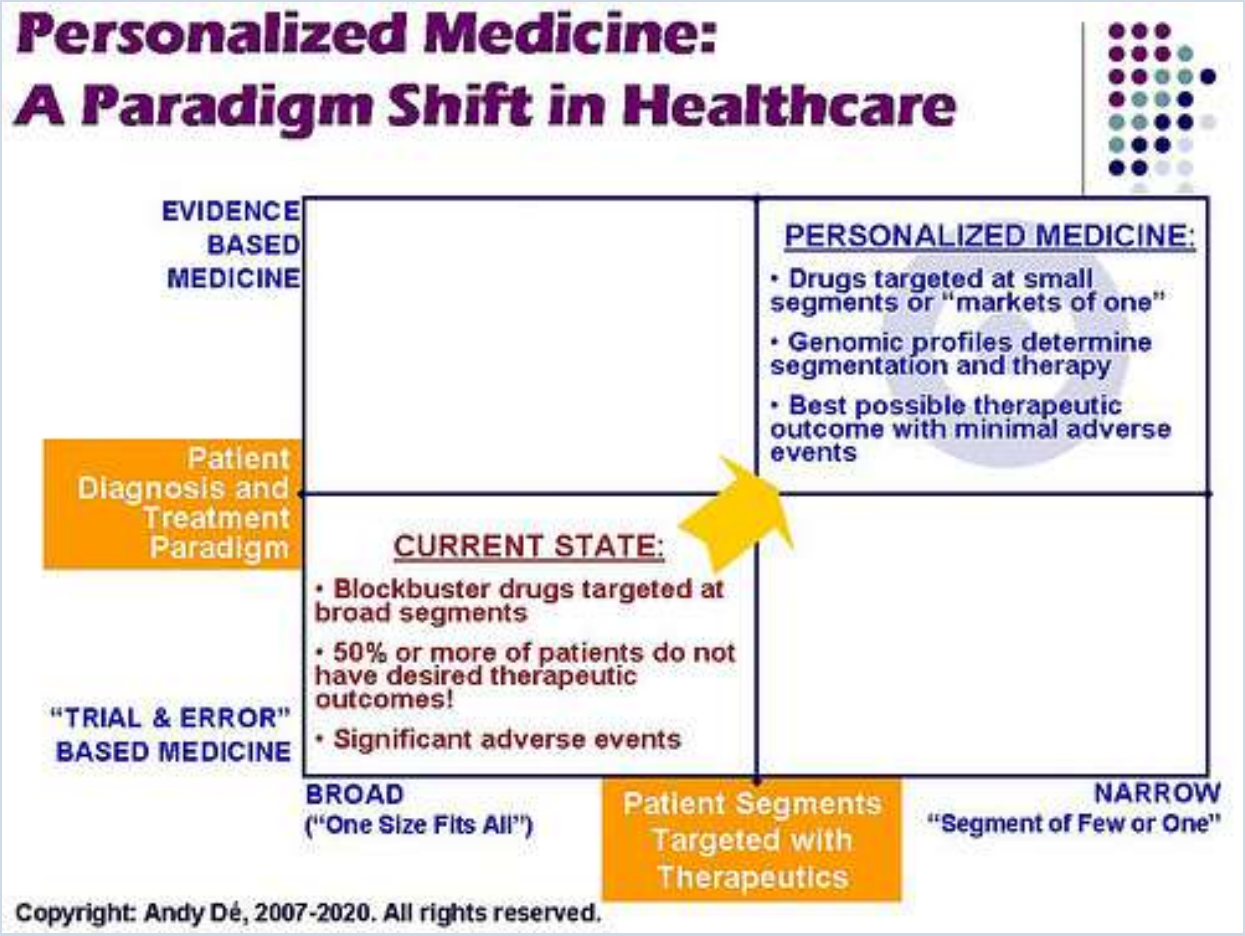
Pharmacogenomics:



ADVERSE DRUG REACTIONS (ADRS)

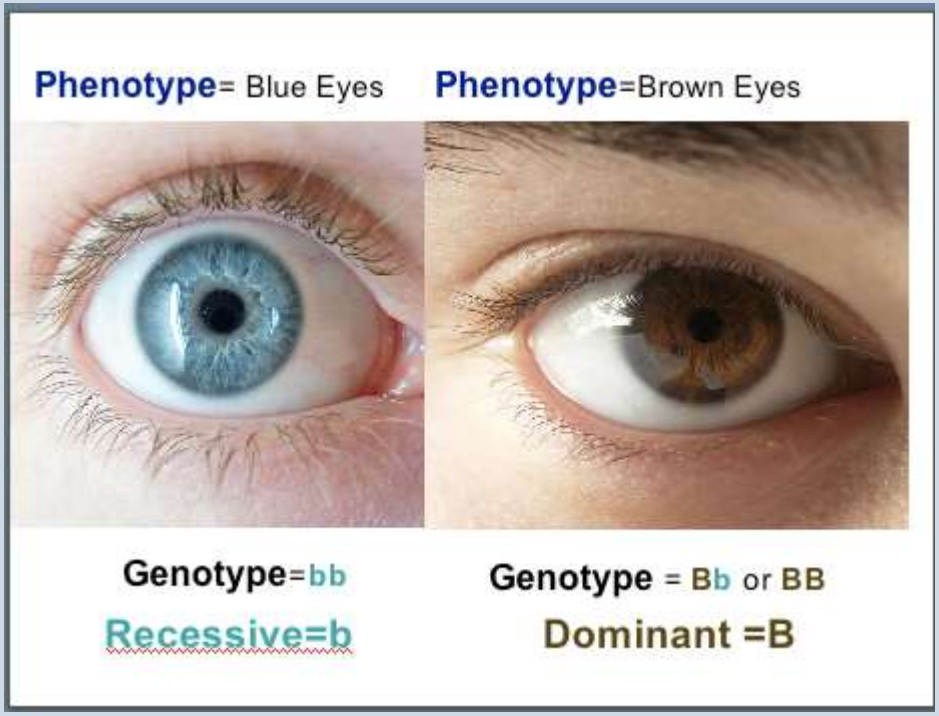
DRUG RESPONSE RATES

PERSONALIZED MEDICINE



http://atavas.com/personalized-medicine-myth-pipe-dream-or-realizable-promise/

PHARMACOGENETICS



Variation in drug responses used to be phenotype → genotype

FDA TABLE OF PHARMACOGENETIC ASSOCIATIONS

- About 50 drugs
- Pharmacogenetic associations that support therapeutic recommendations
- Evidence-based information on safety or response
- Evidence of only pharmacokinetic impact

FDA TABLE OF PHARMACOGENETIC ASSOCIATIONS

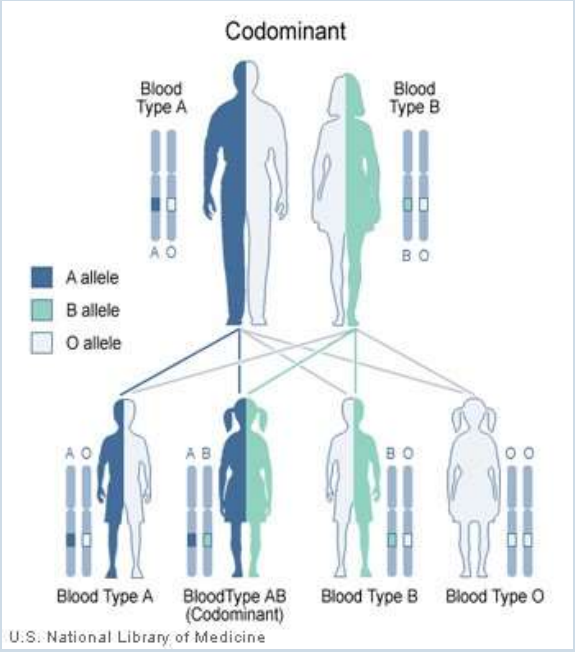
- Knowing a patient's pharmacogenetic genotype may help with:
  - Choosing an appropriate drug regimen
  - Adjusting dosage
  - Determining potential benefit
  - Determining potential for toxicity

PHARMACOGENETICS

Polymorphisms

- Genetic variation among individuals within a specific species or population
- Promotes genetic diversity
- Ex: blood types

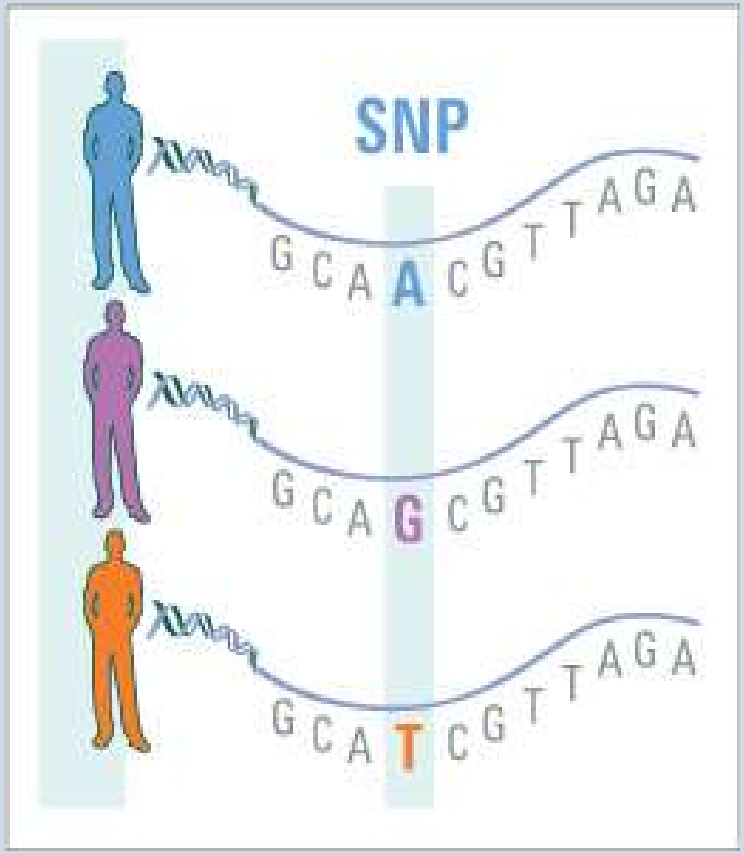
http://wikidoc.org/index.php/ABO_blood_group_system



SNPS

Single Nucleotide Polymorphisms

- Single nucleotide exchanged for another at a point on the individual's genome
- Normal genetic variation
- Some cause change in amino acid or protein code
- Some have NO effect
- SNP = genotype



http://www.broadinstitute.org/education/glossary/snp

PHARMACOGENETICS

Drug response determined by

- Genetic factors
- Environmental factors

Twin studies

- 75 – 85% of variation in $t_{1/2}$ due to genetics

Question

- Which genetic variants are clinically relevant?

PHARMACOGENETIC PHENOTYPES

- Kinetic
  - Variability in genes that encode kinetic determinants
    - Metabolizing enzymes
    - Determine therapeutic response and ADRs
    - Some are monogenic
      - Ex: fast vs slow acetylation
    - Some are multigenic
      - Ex: CYP 450 Extensive vs poor metabolizers

CYP450

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
clozapine	artemisinin	paclitaxel	**NSAIDs:**	**PPIs:**	**Beta Blockers:**	**Anesthetics:**	**Macrolide antibiotics:**
cyclobenzaprine	bupropion[1]	torsemide	diclofenac	esomeprazole	carvedilol	enflurane	clarithromycin
duloxetine	cyclophosphamide	amodiaquine[2]	ibuprofen	lansoprazole	S-metoprolol	halothane	erythromycin (not 3A5)
fluvoxamine	efavirenz[1]	cerivastatin	naproxen	omeprazole	propafenone	isoflurane	NOT azithromycin
haloperidol	ifosfamide	repaglinide	piroxicam	pantoprazole	timolol	methoxyflurane	telithromycin
imipramine	ketamine					sevoflurane	
mexiletine	meperidine		**Oral Hypoglycemics:**	**Anti-epileptics:**	**Antidepressants:**		**Anti-arrhythmics:**
nabumetone	methadone		tolbutamide	diazepam	amitriptyline	**Others:**	quinidine→3-OH (not 3A5)
naproxen	nevirapine		glipizide	phenytoin	clomipramine	acetaminophen→NAPQI	
olanzapine	propofol		glyburide	phenobarbitone	desipramine	aniline	**Benzodiazepines:**
riluzole	selegiline				duloxetine	benzene	alprazolam
tacrine[2]			**Angiotensin II Blockers:**	**Others:**	fluoxetine	chlorzoxazone	diazepam→3OH
theophylline			losartan	amitriptyline	imipramine	ethanol	midazolam
tizanidine			irbesartan	carisoprodol	paroxetine	N,N-dimethyl formamide	triazolam
triamterene				citalopram		theophylline→8-OH	
zileuton			**Others:**	clomipramine	**Antipsychotics:**		**Immune Modulators:**
zolmitriptan			celecoxib	clopidogrel	haloperidol		cyclosporine
			fluvastatin	cyclophosphamide	risperidone		tacrolimus (FK506)
			phenytoin	imipramine	thioridazine		sirolimus
			rosiglitazone	labetalol			
			torsemide	proguanil	**Others:**		**HIV Antivirals:**
			valproic acid	voriconazole	aripiprazole		indinavir
			warfarin		atomoxetine		ritonavir
			zafirlukast		codeine		saquinavir
					dextromethorphan		nevirapine
					doxepine		
					flecainide		**Prokinetics:**
					mexiletine		cisapride
					ondansetron		
					oxycodone		**Antihistamines:**
					risperidone		astemizole
					tamoxifen		chlorpheniramine
					TAMOXIFEN GUIDE		
					tramadol		**Calcium Channel Blockers:**
					venlafaxine		amlodipine

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed March 23, 2017.

WARFARIN (COUMADIN)

2 genomic enzyme polymorphisms

Metabolic

- CYP2C9
  - Frequency in Caucasians approx 10%

Mechanistic

- VKORC1
  - Variable efficacy of warfarin vitamin K activation inhibition

Dosing Recommendations without Consideration of Genotype

If the patient's CYP2C9 and VKORC1 genotypes are not known, the initial dose of COUMADIN is usually 2 to 5 mg once daily. Determine each patient's dosing needs by close monitoring of the INR response and consideration of the indication being treated. Typical maintenance doses are 2 to 10 mg once daily.

Dosing Recommendations with Consideration of Genotype

Table 1 displays three ranges of expected maintenance COUMADIN doses observed in subgroups of patients having different combinations of CYP2C9 and VKORC1 gene variants *[see Clinical Pharmacology (12.5)]*. If the patient's CYP2C9 and/or VKORC1 genotype are known, consider these ranges in choosing the initial dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen than patients without these CYP variants.

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

†Ranges are derived from multiple published clinical studies. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.

METABOLIC PHENOTYPES

- **Ultrarapid metabolizer**
  - More efficient metabolism
- **Extensive (normal) metabolizer**
  - Metabolism proceeds as expected
- **Intermediate metabolizer**
  - Diminished or normal metabolism
- **Poor metabolizer**
  - Metabolism significantly decreased

ACTIVITY SCORES

- 0
  - Enzyme with no function
- 0.5
  - Enzyme with reduced function
- 1
  - Enzyme with ‘normal’ activity
- Add both genes together for phenotype activity score

MOST DRUGS

- **Ultrarapid metabolizer**
  - Drug may be rendered ineffective
  - Activity score > 2
- **Extensive (normal) metabolizer**
  - Metabolism proceeds as expected
  - Activity score 1 - 2
- **Intermediate metabolizer**
  - Diminished or normal metabolism
  - Activity score 0.5
- **Poor metabolizer**
  - Drug may become toxic
  - Prodrug may be ineffective
  - Activity score 0

CLOPIDOGREL (PLAVIX)

- Prodrug
  - efficacy dependent on activation to an active metabolite by CYP2C19
- Poor metabolizers forms less active metabolite
  - lesser effect on platelet function
- ACS or PCI at recommended doses exhibit higher CVE rates than patients with ‘normal’ CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

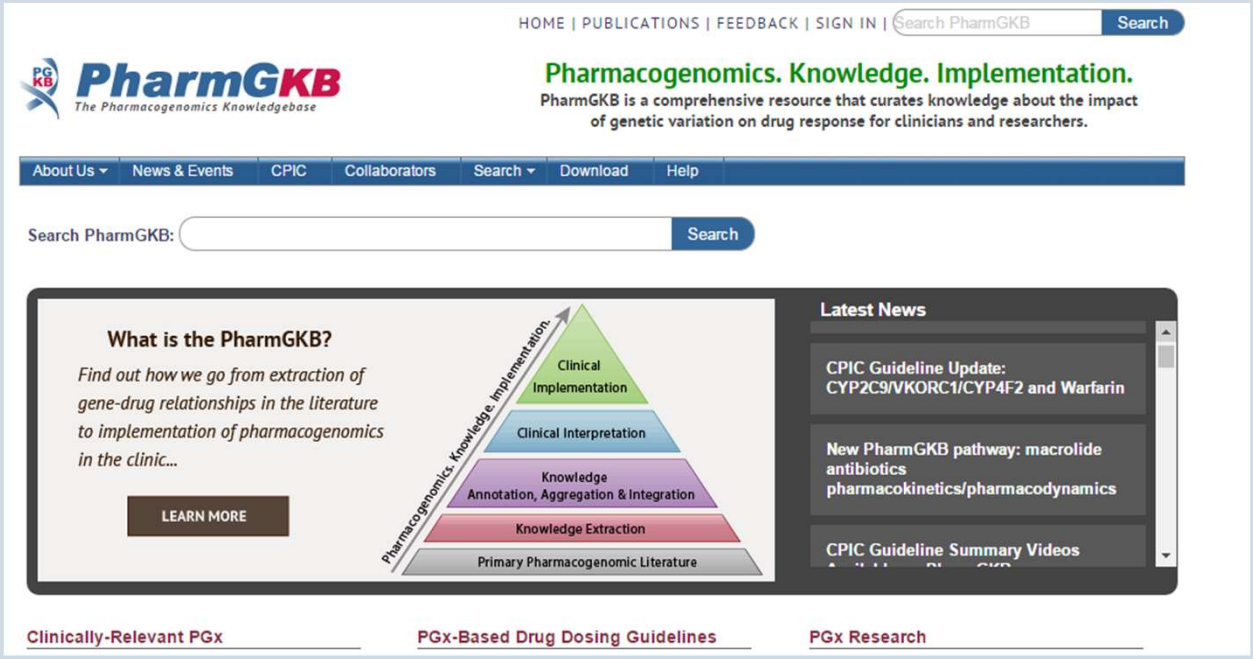
CLOPIDOGREL (PLAVIX)

- **PI Black Box Warning**
- Plavix efficacy depends on conversion to active metabolite by CYP2C19
- Poor metabolizers exhibit higher CVE rates than patients with ‘normal’ CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

CPIC GUIDELINES

- Clinical implementation of pharmacogenetics
- From perspective of gene and/or drug
- Recommendations for PGx testing
- Recommendations for actionable medication prescribing based on PGx testing

PHARMGKB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PGx-Based Drug Dosing Guidelines
PGx Research

PGX LAB TESTING OPTIONS

- LabCorp
  - Blood or buccal swab
  - $456

Quest

  - Blood
- Point of care
  - Spartan Rx
    - Buccal swab
  - Luminex

CASE #1

- GA is a 34 yo female (gender identity and gender assigned at birth) who presents today with 6 month history of fatigue, weight gain, and depressed mood. She has history of allergic rhinitis and migraine disorder and has been treated in the past for depression with paroxetine (Paxil) but had some problems with it.
- Genetic testing for CYP2D6 and 2C19 enzymes are ordered. The patient's genotypes are 2D6*5*6 and 2C19*1*1.

METABOLISM AT CYP2D6

- 20 – 25% of all drugs are metabolized at least partially by 2D6
- CYP2D6 is highly polymorphic
  - Over 100 allele variants currently identified
- Can have as much as a 200-fold effect on drug metabolism

http://www.nature.com/tpj/journal/v5/n1/full/6500285a.html

SSRI AND CYP450

- SSRI metabolism occurs via CYP2D6 and CYP2C19
- Variants in 2D6 and 2C19 have some association with depression or suicide
- Normal function: CYP2D6*1 or CYP2D6*2
- Decreased function CYP2D6*9,*10,*41
- No function: CYP2D6*3-*6
- CPIC guidelines for citalopram, escitalopram, fluvoxamine, paroxetine, sertraline
- ADRs higher with longer treatment duration in poor metabolizers
- Cost of treatment in poor or ultrarapid metabolizers $4K - $6K higher annually

https://www.pharmgkb.org/chemical/PA450801#tabview=tab0&subtab=31

Table 1 Assignment of likely phenotypes based on diplotypes

Table 1a Assignment of CYP2D6 predicted phenotypes

Likely phenotype	Activity score	Genotypes	Examples of *CYP2D6* diplotypes
Ultrarapid metabolizer (~1–2% of patients)[a]	> 2.0	An individual carrying duplications of functional alleles	**1/*1xN, *1/*2xN, *2/*2xN*[b]
Extensive metabolizer (~77–92% of patients)	2.0-1.0[c]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele	**1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41*
Intermediate metabolizer (~2–11% of patients)	0.5	An individual carrying one decreased function and one no function allele	**4/*10, *4/*41, *5/*9*
Poor metabolizers (~5–10% of patients)	0	An individual carrying only no functional alleles	**3/*4, *4/*4, *5/*5, *5/*6*

Table 1b Assignment of CYP2C19 predicted phenotypes

Likely phenotype	Genotypes	Examples of *CYP2C19* diplotypes
Ultrarapid metabolizer (~5–30% of patients)[d]	An individual carrying two increased function alleles or one normal function allele and one increased function allele	**17/*17, *1/*17*
Extensive metabolizer (~35–50% of patients)	An individual carrying two normal function alleles	**1/*1*
Intermediate metabolizer (~18–45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	**1/*2, *1/*3, *2/*17*[e]
Poor metabolizer (~2–15% of patients)	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

[a]CYP2D6 metabolizer status frequencies are based on data from Caucasians and may differ from other ethnicities. See **Supplemental Tables S3** and **S6** note for information on the chances of observing specific diplotypes in different major race/ethnic groups. [b]Where *xN* represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see **Supplemental Data** for additional information on how to translate diplotypes into phenotypes. [c]Patients with an activity score of 1.0 may be classified as intermediate metabolizers by some reference laboratories. [d]CYP2C19 metabolizer status frequencies are based on average multiethnic frequency. [e]The predicted metabolizer phenotype for the*2/*17 diplotypes is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP2C19*2* allele.[36] See **Supplemental Materials** for a more comprehensive list of predicted metabolizer phenotypes.

PAROXETINE (PAXIL)

Table 1: Dosing recommendations for paroxetine based on CYP2D6 phenotype:

Adapted from Tables 1 and 2a of the 2015 guideline manuscript.

Likely phenotype	Activity Score	Genotypes	Examples of CYP2D6 diplotypes	Implications for paroxetine metabolism	Therapeutic Recommendations	Classification of recommendations [a]
Ultrarapid metabolizer (~1-2% of patients)[b]	> 2.0	An individual carrying duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN [c]	Increased metabolism to less active compounds when compared to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.	Select alternative drug not predominantly metabolized by CYP2D6.[d]	Strong
Extensive metabolizer (~77-92% of patients)	2.0-1.0 [e]	An individual carrying two normal function alleles or two decreased function alleles or one normal function and one no function allele or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*4, *1/*5, *1/*9, *1/*41, *2/*2,*41/*41	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
Intermediate metabolizer (~2-11% of patients)	0.5	An individual carrying one decreased function and one no function allele	*4/*10,*4/*41, *5/*9	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
Poor metabolizers (~5-10% of patients)	0	An individual carrying only no functional alleles	*3/*4,*4/*4, *5/*5, *5/*6	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Select alternative drug not predominantly metabolized by CYP2D6 [d] or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response	Optional

https://www.pharmgkb.org/chemical/PA450801#tabview=tab0&subtab=31

SERTRALINE (ZOLOFT)

Table 1: Dosing recommendations for sertraline based on CYP2C19 phenotype:

Adapted from Tables 1 and 3b of the 2015 guideline manuscript.

Likely phenotype	Genotypes	Examples of CYP2C19 diplotypes	Implications for sertraline metabolism	Therapeutic Recommendations	Classification of recommendations [a]
Ultrarapid metabolizer (~5-30% of patients) [b]	An individual carrying two increased function alleles or one normal function allele and one increased function allele	*17/*17, *1/*17	Increased metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.[c]	Optional
Extensive metabolizer (~35-50% of patients)	An individual carrying two normal function alleles	*1/*1	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
Intermediate metabolizer (~18-45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	*1/*2, *1/*3, *2/*17 [d]	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
Poor metabolizer (~2-15% of patients)	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction [e] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[c]	Optional

[a] Rating scheme described in Supplement.

[b] CYP2C19 metabolizer status frequencies are based on average multi-ethnic frequency.

[c] Drug-drug interactions and other patient characteristics (e.g., age, renal function, liver function) should be considered when selecting an alternative therapy.

https://www.pharmgkb.org/guideline/PA166127639

CASE #1

- GA is a 34 yo female (gender identity and gender assigned at birth) who presents today with 6 month history of fatigue, weight gain, and depressed mood. She has history of allergic rhinitis and migraine disorder and has been treated in the past for depression with paroxetine (Paxil) but had some problems with it.
- Genetic testing for CYP2D6 and 2C19 enzymes are ordered. The patient's genotypes are 2D6*5*6 and 2C19*1*1.

ANALGESICS

CLINICAL CORRELATION

FDA NEWS RELEASE

For Immediate Release: Aug. 15, 2012
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA warns of risk of death from codeine use in some children following surgeries

- The U.S. Food and Drug Administration today issued a Drug Safety Communication concerning three children who died and one child who experienced a non-fatal but life-threatening case of respiratory depression after taking the pain reliever codeine following surgery to remove tonsils (tonsillectomy) and/or adenoids (adenoidectomy).
- The surgeries were performed to treat obstructive sleep apnea syndrome, a condition that results in repeated episodes of complete or partial blockage of the upper airway during sleep. The children received doses of codeine that were within the typical dose range.
- Health care professionals and parents should be aware of the risks of using codeine in children who have had their tonsils and/or adenoids removed to treat obstructive sleep apnea syndrome. When prescribing codeine-containing drugs, health care providers should use the lowest effective dose for the shortest time on an as-needed basis. If parents or caregivers notice signs of overdose in a child, such as unusual sleepiness, difficulty being aroused or awakened, confusion, or noisy and difficult breathing, they should stop giving the child codeine and seek medical attention immediately.
- "The FDA is currently conducting a review of adverse event reports and other information to determine if there are additional cases of inadvertent overdose or death in children taking codeine, and if these adverse events occur during treatment of other kinds of pain, such as post-operative pain following other types of surgery or procedures," said Bob Rappaport, M.D., director of the Division of Anesthesia, Analgesia and Addiction Products in FDA's Center for Drug Evaluation and Research. "The FDA will update the public when more information is available."
- Codeine is an ingredient found in prescription medicines used to relieve pain or cough. Once in the body, codeine is converted to morphine in the liver by an enzyme called cytochrome P450 isoenyme 2D6 (CYP2D6).
- Some people metabolize codeine much faster and more completely than others. These people, known as ultra-rapid metabolizers, are likely to have higher-than-normal levels of morphine in their blood after taking codeine. These high levels can lead to overdose and death. The three children who died after taking codeine exhibited evidence of being ultra-rapid metabolizers.
- The estimated frequency of ultra-rapid metabolizers is generally 1 to 7 out of every 100 people. However, in certain ethnic groups, the frequency may be as high as 28 out of every 100 people. The only way to know if someone is an ultra-rapid metabolizer is to do a genetic test. There are FDA-cleared tests to check for ultra-rapid metabolism.

CODEINE

Likely phenotype.[a]	Activity score	Genotypes	Examples of diplotypes	Implications for codeine metabolism	Recommendations for codeine therapy.[b]	Classification of recommendation for codeine therapy	Considerations for alternative opioids
Ultrarapid metabolizer (~1-2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity.[d,e]
Extensive metabolizer (~77-92% of patients)	1.0-2.0.[c]	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Normal morphine formation	Use label recommended age- or weight-specific dosing.	Strong	
Intermediate metabolizer (~2-11% of patients)	0.5.[c]	An individual carrying one reduced and one nonfunctional allele	*4/*10, *5/*41	Reduced morphine formation	Use label recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a non-opioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer (~5-10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[d,e]

https://www.pharmgkb.org/guideline/PA166104996

CASE #1 (CONT)

- GA asks what she can take for her migraines. She doesn't have them frequently but would like to know what is best for when she does have one. She has tried OTC Tylenol with no relief and states that Advil upsets her stomach.
- Genetic testing for CYP2D6, 2C9, and 2C19 enzymes are ordered.
- The patient's genotypes are:
- 2D6*5*6
- 2C9*3*3
- 2C19*1*1

2020 CPIC GUIDELINE: NSAIDS

- CYP2C9
- *3/*3
  - Two non functional alleles
  - Activity score = 0
  - Poor metabolizer
- Recommendation:
  - Starting dose 25% - 50% lower than normal
  - Alternative: naproxen

CASE #2

- RH is a 58 yo male (gender identity and gender assigned at birth) who presents to family practice clinic for followup of newly diagnosed hyperlipidemia and chronic gout currently controlled on allopurinol. He states he is feeling well but noticing some myalgia since starting simvastatin 3 months ago.

- Genetic testing results:
- SLCO1B1*5*17
- HLA-B*58.01 negative

SIMVASTATIN (ZOCOR)

Table 1: Recommended dosing of simvastatin based on SLCO1B1 phenotype

Adapted from Table 1 and 2 of the 2014 guideline update manuscript.

Phenotype	Examples of diplotypes [a]	Genotype at rs4149056	Implications for simvastatin	Dosing recommendations for simvastatin [b,c]	Classification of recommendations [d]
Normal function, Homozygous wild-type (two normal function alleles)	*1a/*1a, *1a/*1b, *1b/*1b	TT	Normal myopathy risk	Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines.	Strong
Intermediate function, Heterozygous (one normal function allele plus one decreased function allele)	*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17	TC	Intermediate myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); consider routine CK surveillance.	Strong
Low function, Homozygous variant or mutant (two decreased function alleles)	*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17	CC	High myopathy risk	Prescribe a lower dose or consider an alternative statin (e.g. pravastatin or rosuvastatin); consider routine CK surveillance.	Strong

CK, creatine kinase.

https://www.pharmgkb.org/guideline/PA166105005

ALLOPURINOL

	LEVEL	VARIANT	GENE	MOLECULE	TYPE	PHENOTYPE
Read Now	Level 1A	HLA-B*58:01	HLA-B	allopurinol	Toxicity/ADR	Arthritis, Gouty, Drug Hypersensitivity, Epidermal Necrolysis, Toxic, Hyperuricemia, Kidney Failure, Chronic, Stevens-Johnson Syndrome
Read Now	Level 2A	rs2231142	ABCG2	allopurinol	Dosage/Efficacy	Gout
Read Now	Level 2B	HLA-A*33:03	HLA-A	allopurinol	Toxicity/ADR	Drug Hypersensitivity, Stevens-Johnson Syndrome
Read Now	Level 2B	HLA-C*03:02	HLA-C	allopurinol	Toxicity/ADR	Epidermal Necrolysis, Toxic, severe cutaneous adverse reactions, Stevens-Johnson Syndrome
Read Now	Level 3	rs367398	NOTCH4	allopurinol	Toxicity/ADR	severe cutaneous adverse reactions
Read Now	Level 3	rs11678615	AOX1	allopurinol, febuxostat	Dosage	Gout
Read Now	Level 3	HLA-DRB1*15:02:01	HLA-DRB1	allopurinol	Toxicity/ADR	severe cutaneous adverse reactions
Read Now	Level 3	rs2844665		allopurinol	Toxicity/ADR	Epidermal Necrolysis, Toxic, severe cutaneous adverse reactions, Stevens-Johnson Syndrome
Read Now	Level 3	rs3731722	AOX1	allopurinol, febuxostat	Dosage	Gout

CASE #3

- CM is a 46 year old female who reports symptoms of GERD. She has tried OTC omeprazole and lansoprazole with no relief. Her PMH is non-contributory. *H. pylori* test is positive.
- Genetic testing reveals CYP2C19 *1*17.

PROTON PUMP INHIBITORS

Table 1 Assignment of predicted CYP2C19 phenotype based on genotype

Predicted phenotype	Genotype	Examples of *CYP2C19* diplotypes[a]
CYP2C19 ultrarapid metabolizer	An individual carrying two increased function alleles	*17/*17
CYP2C19 rapid metabolizer	An individual carrying one normal function allele and one increased function allele	*1/*17
CYP2C19 normal metabolizer	An individual carrying two normal function alleles	*1/*1
CYP2C19 likely intermediate metabolizer[b]	An individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles	*1/*9, *9/*17, *9/*9
CYP2C19 intermediate metabolizer	An individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele	*1/*2, *1/*3, *2/*17, *3/*17
CYP2C19 likely poor metabolizer[b]	An individual carrying one decreased function allele and one no function allele	*2/*9, *3/*9
CYP2C19 poor metabolizer	An individual carrying two no function alleles	*2/*2, *3/*3, *2/*3
Indeterminate	An individual carrying one or two uncertain function alleles	*1/*12, *2/*12, *12/*14

CYP2C19, cytochrome P450 2C19.
[a]Please refer to the ***CYP2C19* Diplotype-Phenotype Table** online for a complete list.[3,4] [b]There are limited data to characterize the function of decreased function alleles.

CYP2C19 phenotype[a]	Implications for phenotypic measures	Therapeutic recommendation	Classification of recommendation[b] – omeprazole, lansoprazole, and pantoprazole	Classification of recommendation[b] – dexlansoprazole
CYP2C19 ultrarapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Increase starting daily dose by 100%. Daily dose may be given in divided doses. Monitor for efficacy	Optional	Optional
CYP2C19 rapid metabolizer	Decreased plasma concentrations of PPIs compared with CYP2C19 NMs; increased risk of therapeutic failure	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *Helicobacter pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy.	Moderate	Optional
CYP2C19 normal metabolizer	Normal PPI metabolism; may be at increased risk of therapeutic failure compared with CYP2C19 IMs and PMs	Initiate standard starting daily dose. Consider increasing dose by 50–100% for the treatment of *H. pylori* infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy	Moderate	Optional
CYP2C19 likely intermediate metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional[c]	Optional[c]
CYP2C19 intermediate metabolizer	Increased plasma concentration of PPI compared with CYP2C19 NMs; increased chance of efficacy and potentially toxicity	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Optional	Optional
CYP2C19 likely poor metabolizer	Likely increased plasma concentration of PPI compared with CYP2C19 NMs; likely increased	Initiate standard starting daily dose. For chronic therapy (> 12 weeks) and efficacy achieved, consider 50% reduction in daily dose and monitor for continued efficacy	Moderate[c]	Optional[c]

PGX IMPLICATIONS

Modified drug labels

Identification of new therapeutic targets

Identification of patients likely to benefit or not from treatments

- Clopidogrel
- Antidepressants
- ? opioids

Identification of patients likely to be harmed by treatment

- Codeine
- Simvastatin

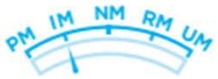
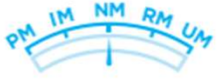
PGX TESTING

- OneOme RightMed Testing
- $449 27 genes
- PGxOne Plus 60 genes
  - Cash $1200
  - Hardship $300
- Genelex 25 genes
  $379
- Genomind
  - Cash $2000
  - Insurance $399
  - Medicare $0

CPT codes

- 2C19 81225
- 2D6 81226
- 2C9 81227
- 3A4/5 81401
- VKORC1 81355

Gene and phenotype summary

Gene	Genotype		Phenotype summary / Metabolic status
CYP1A2	*1F/*1V		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/*6		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.
CYP2C9	*1/*1		Normal Normal level of activity. Drugs metabolized at a normal rate.
CYP2C19	*1/*1		Normal Normal level of activity. Drugs metabolized at a normal rate.
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/*4		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.
CYP3A4	*1/*1		Normal Normal level of activity. Drugs metabolized at a normal rate.

CHOOSING A LAB

- Which genes is the lab testing?
- Which gene variants?
- How are the results reported?
- How is the phenotype interpreted?

- Always check yourself

REFERENCES

- Cpic® guideline for nsaids based on cyp2c9 genotype. Accessed February 14, 2021. https://cpicpgx.org/guidelines/cpic-guideline-for-nsaids-based-on-cyp2c9-genotype/
- Cpic® guideline for selective serotonin reuptake inhibitors and cyp2d6 and cyp2c19. Accessed February 14, 2021. https://cpicpgx.org/guidelines/guideline-for-selective-serotonin-reuptake-inhibitors-and-cyp2d6-and-cyp2c19/
- Cpic® guideline for proton pump inhibitors and cyp2c19. Accessed February 14, 2021. https://cpicpgx.org/guidelines/cpic-guideline-for-proton-pump-inhibitors-and-cyp2c19/

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