PHARMACOGENOMICS 101: MENTAL HEALTH

Dr. Corrie L. Sanders, PharmD., BCACP, CPGx

Founder, Huna Health Pharmacogenomic Consulting

President, Hawai'i Pharmacists Association

TODAY'S ROADMAP

PGx Background and statistics

Nomenclature and Biology

PGX Guidelines & Literature Review

Ordering a PGx Test

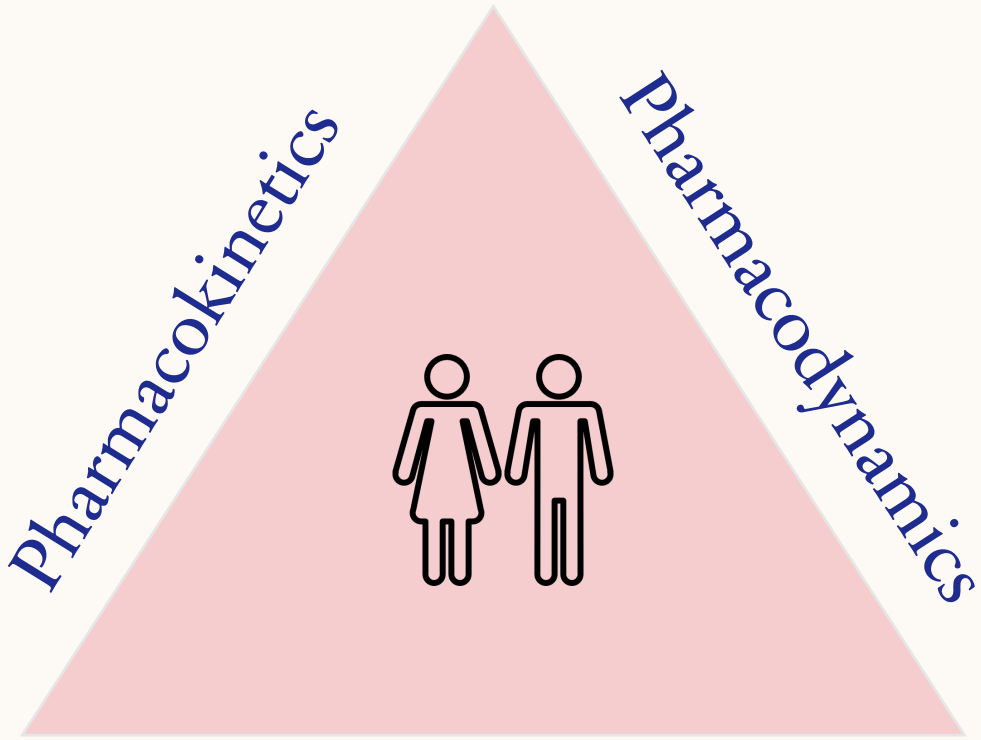
Overlaps in other clinical areas

Phenoconversion

BACKGROUND & STATISTICS

WHERE DOES PGX FIT?

How the body affects the medication



How medication affects the body

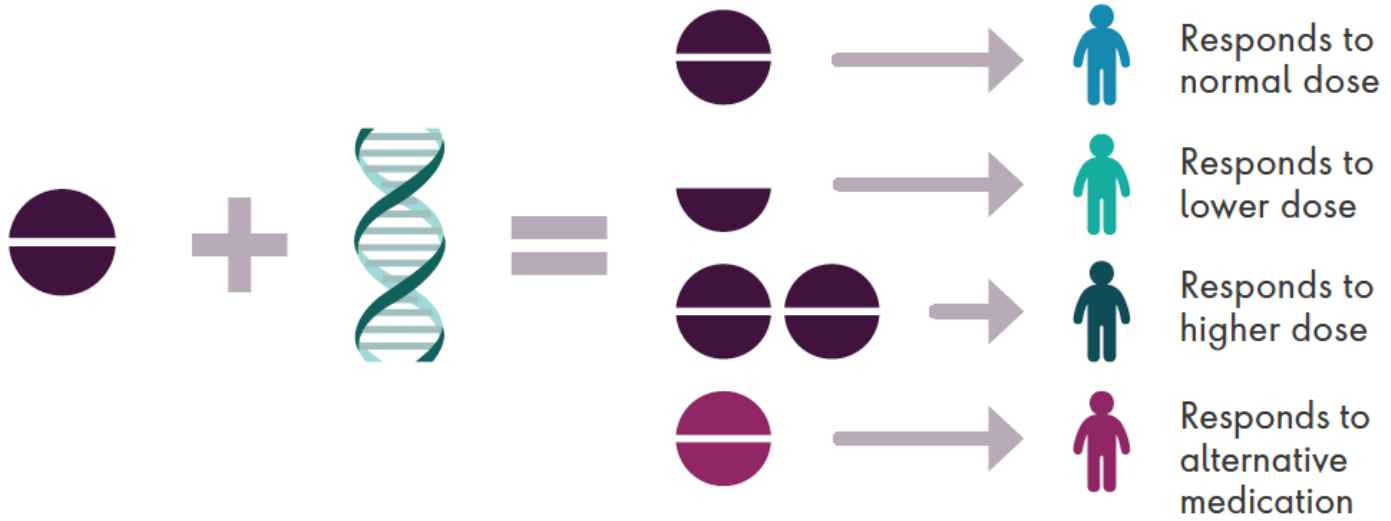
Pharmacogenomics

How genetics impact medication

WHAT IS PHARMACOGENOMICS (PGX)

Blockbuster one-size-fits-all approach to drug development and prescribing

Personalized prescribing enables selection of the right drug and dose



"Find the right drug, at the right dose, the FIRST time"

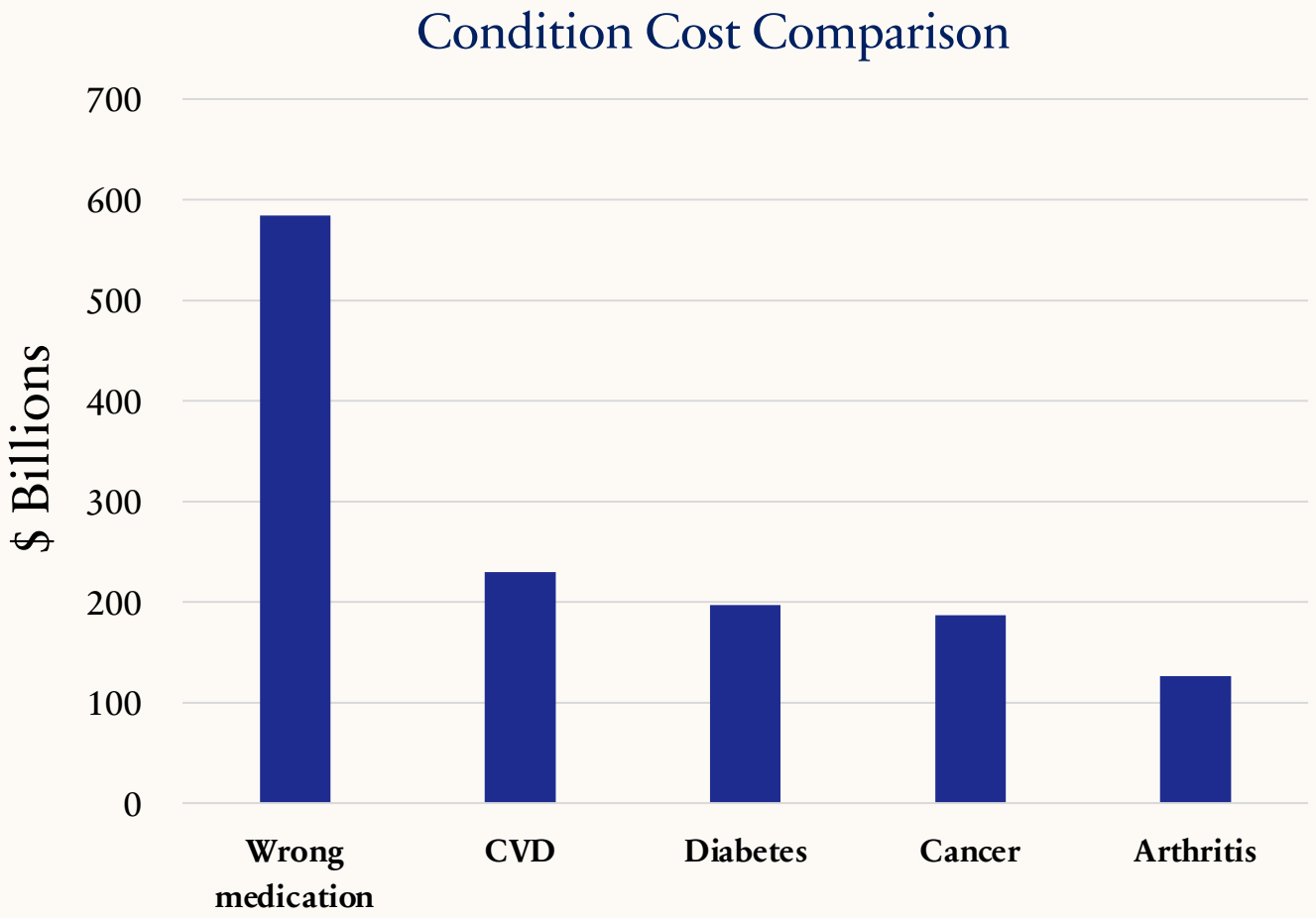
HOW DOES PGX WORK?

- Buccal or blood sample taken from patient
- Sample is genotyped for genes and alleles
- Report describes the genotype, phenotype and alleles measured
- Variation in Clinical Decision Support Software (CDSS)

Ideal workflow report would be uploaded into an Electronic Medical Record (EMR) that integrates with both the lab and CDSS

COST BURDEN OF NON-OPTIMIZED MEDICATION USE

- $528 billion estimated impact of improper medication therapy on U.S. annual healthcare spend
- $200 billion annual cost of treating each of the following diseases that drive pharmacy trend
  - Cardiovascular disease (CVD)
  - Diabetes
  - Cancer



Watanabe JH, et al. Annals of Pharmacotherapy. 2018;52(9):829-837.

IMPORTANCE OF PGX

- 99% of individuals harbor a genetic variant that may impact medication response[1]
- Every two minutes in the United States a life is lost from non-optimized medication[1]
- Adverse Drug Reactions are the 4th leading cause of death in the US, ahead of pulmonary disease, diabetes, and automobile accidents[2]
- 50% of patients are on a prescription drug that is ineffective or toxic for them[3]

1. Nature. 2015; 526(7571): 68–74
2. JAMA 1998;279:1200–120
3. Epilepsia. 2001; 42 Suppl 5:31-4

Hawaii's mental health crisis growing as demand surges

By Kristen Consillio Mar 15, 2022 Updated Apr 5, 2022 0

Hawaii's Mental Health Care Crisis

The lack of psychiatrists is a particular problem for people who rely on the state's public health insurance for low-income residents.

HAWAII NEWS

Kaiser's mental health shortage puts patient safety at risk, national agency finds

The Current Access to Psychiatric Care Problem in Hawaii

The mental health needs of individuals across our state continue to outweigh the capacity of our mental health system. According to a Report on Findings from the Hawai'i Physician Workforce

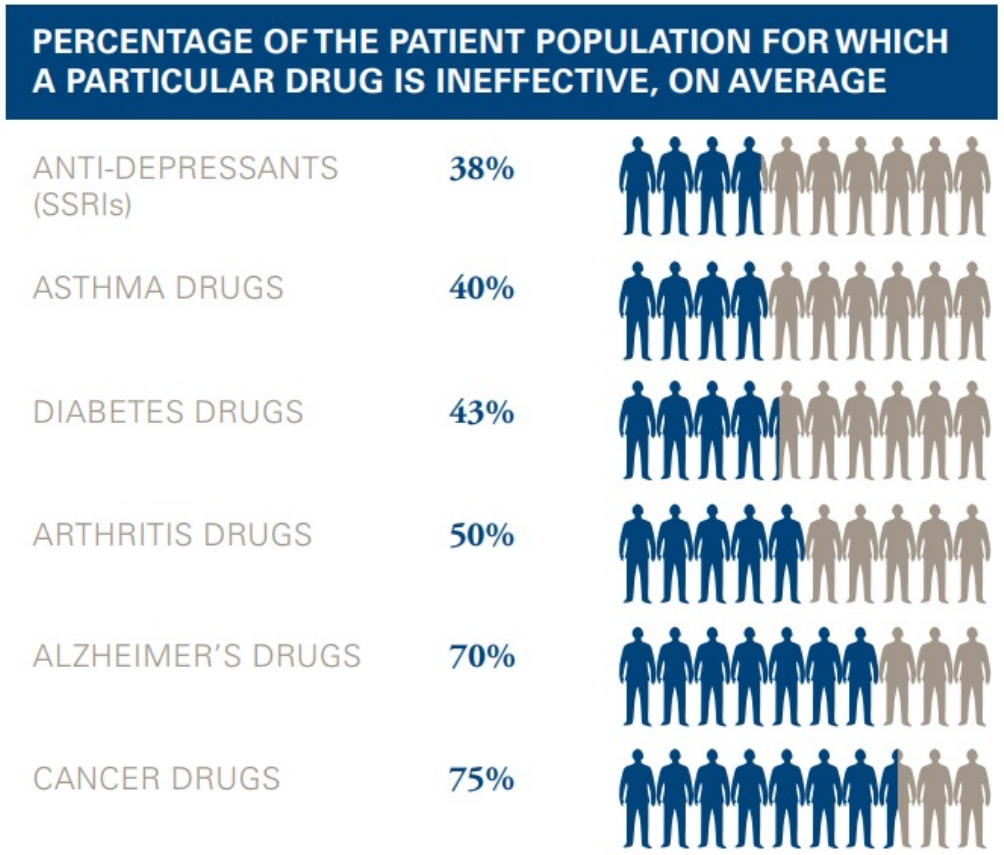
Psychiatrist shortage hot topic again at legislature

Does Hawai'i Have Enough Psychiatrists? Assessing Mental Health Workforce Versus Demand in the Aloha State

Psychiatry and mental health counseling are, far and away, the two professional areas needed most, according to providers. Though medical service needs abound due to widespread shortages in a number of medical specialties.

Source of Data: Community First Access to Care Report. 2022

FIGURE 2. One Size Does Not Fit All



Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffery Huff, "Clinical Trends in Molecular Medicine," Volume 7, Issue 5, 1 May 2001, Pages 201-204.

PGX IN MENTAL HEALTH

- The standard of care in many aspects of mental health prescribing is a trial-and-error process that requires months per trial

- Insurance companies often require the patient has multiple documented medication failures.

- The trial-and-error process can negatively affect multiple aspects of patient care
  - Compliance
  - Treatment resistant depression
  - Adverse drug reactions (ADRs)
  - Patient-provider relationship

NOMENCLATURE & BIOLOGY

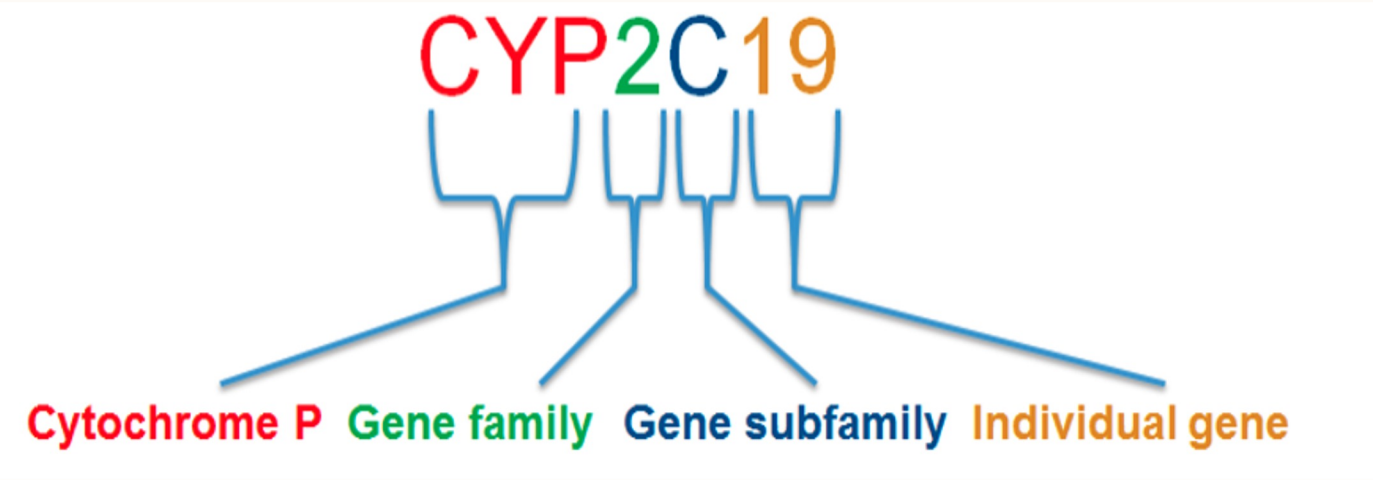
NOMENCLATURE – CYP450 ENZYMES

Gene designated with the abbreviation CYP

Number indicating the gene family

Capital letter indicating the subfamily

Numeral for the individual gene



NOMENCLATURE CONT'D

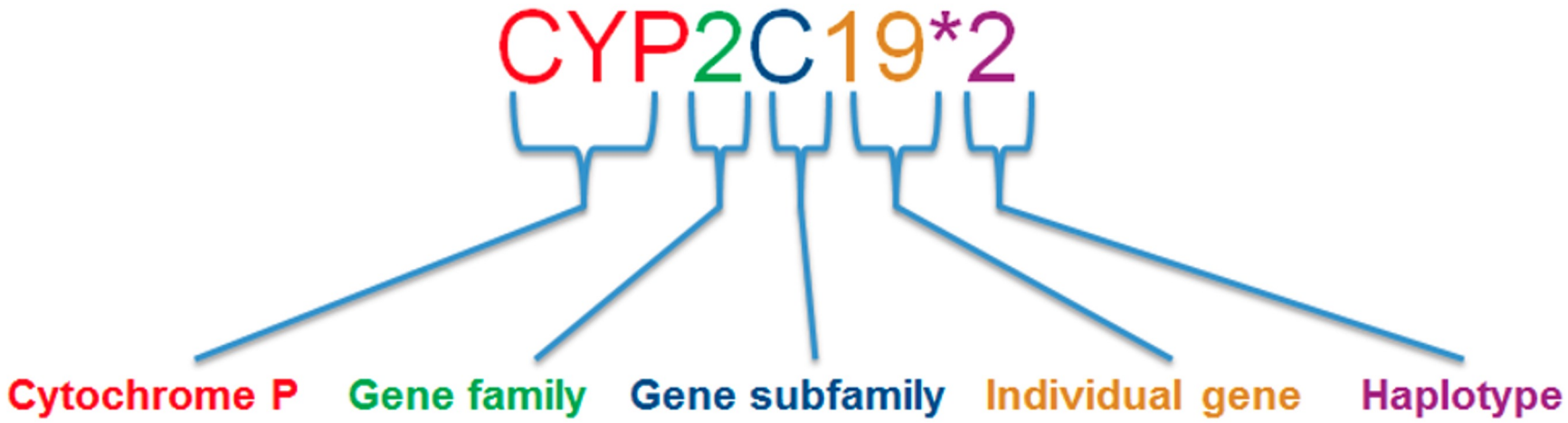
* (star) alleles – pharmacogenomic haplotype

Normal function/enzyme activity (wild type) denoted by *1

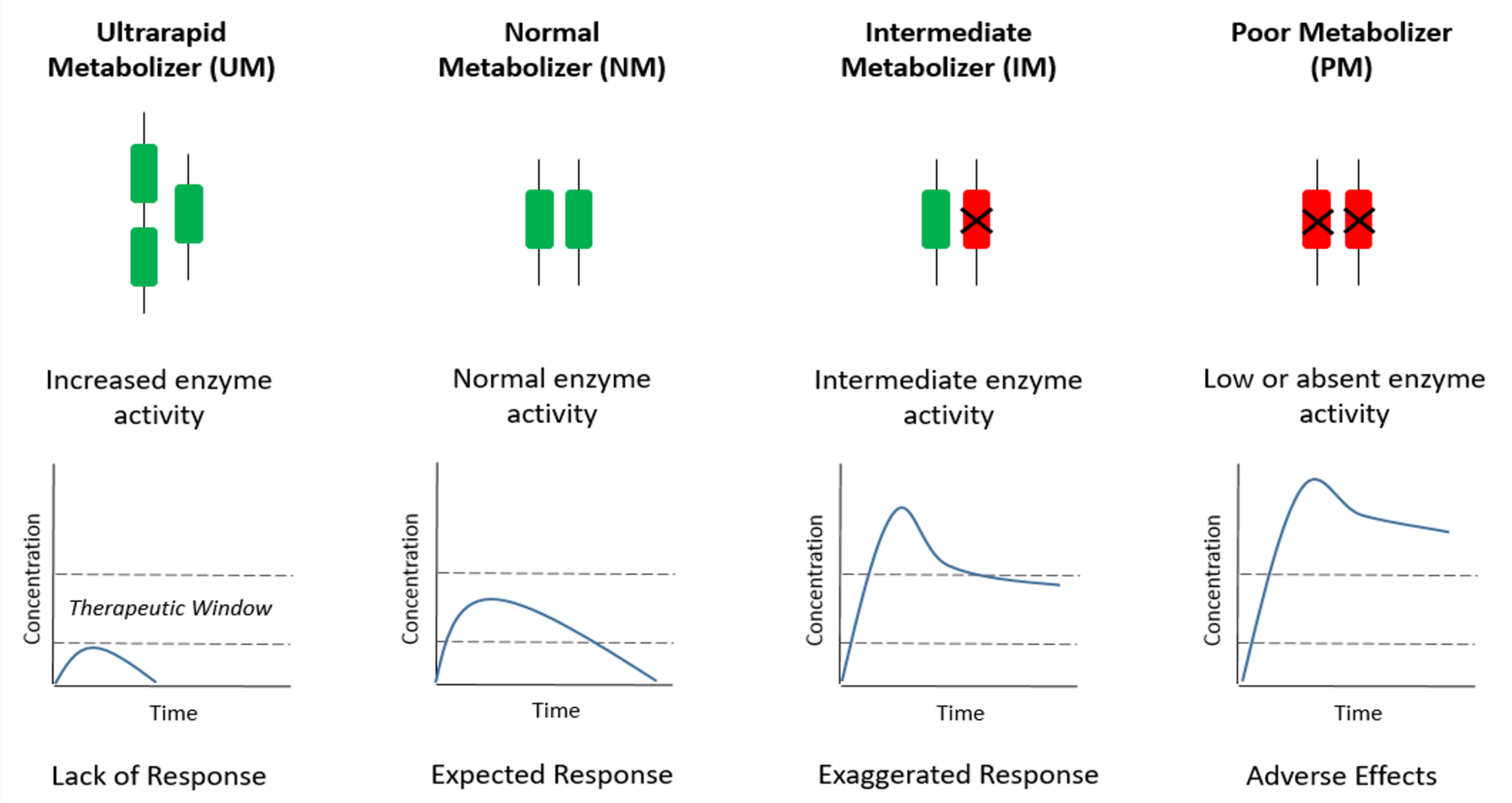
Altered function variant: *2, *3, *4, etc.

Single genes (CYP2C19) have many star alleles (e.g., CYP2C19*2, CYP2C19*3)

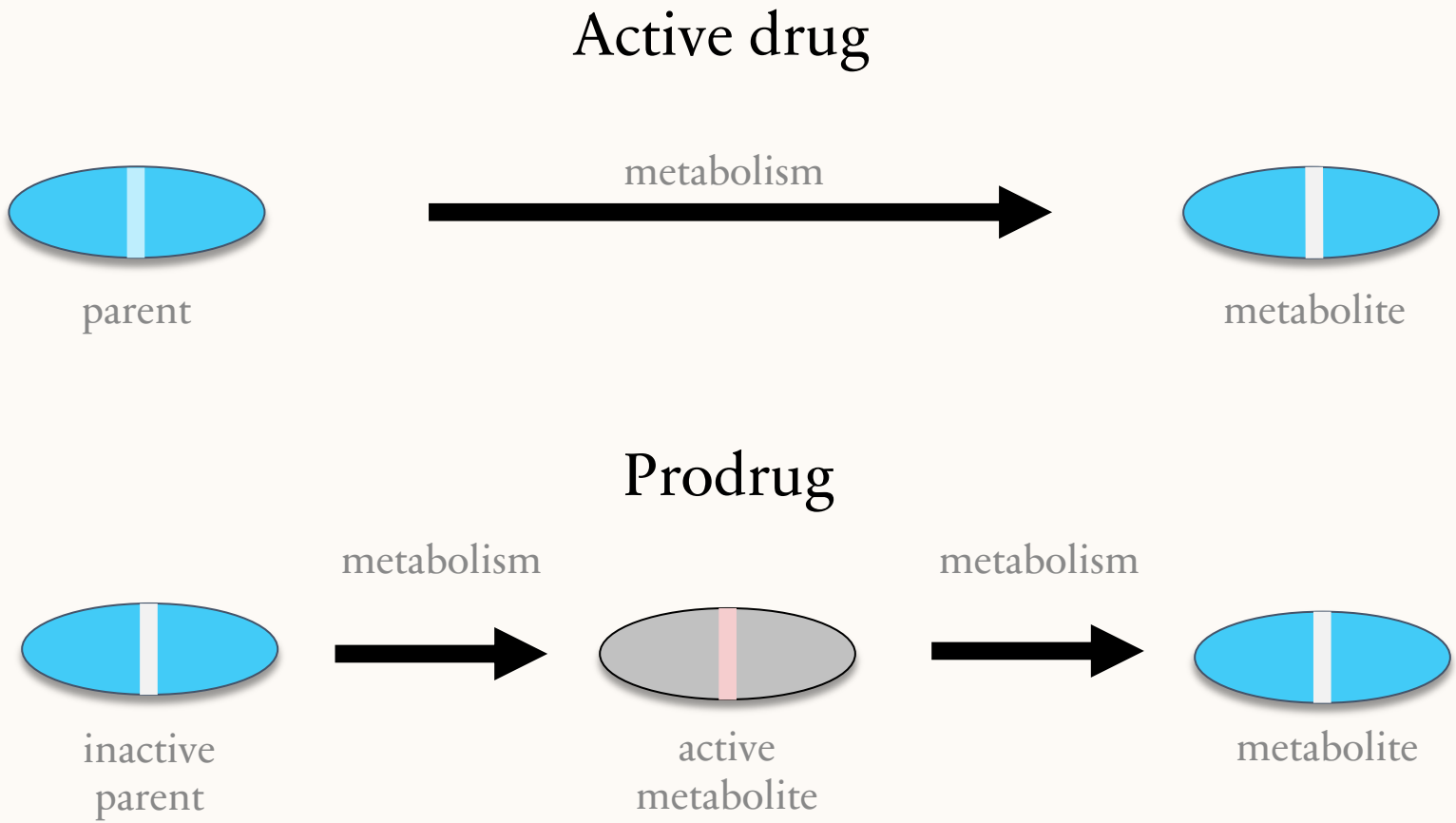
Results reported as diplotypes: CYP2C19*1/*17



ENZYME BIOLOGY



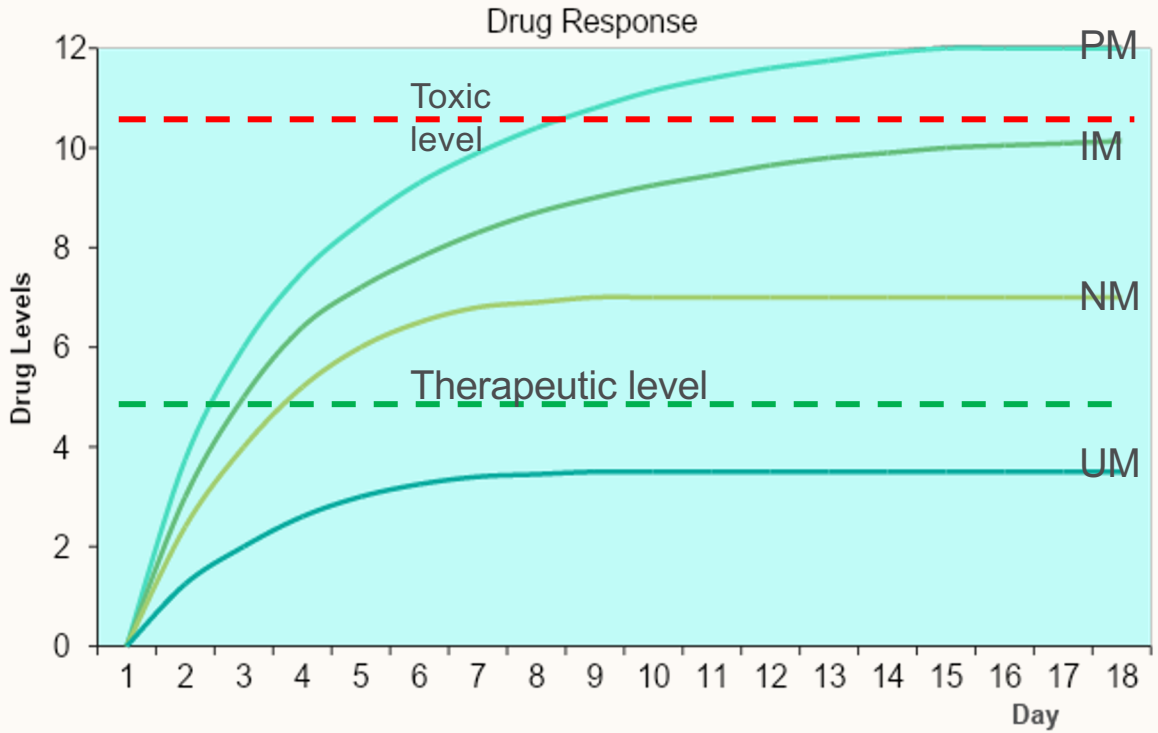
ACTIVE DRUGS VS. PRODRUGS



DRUG RESPONSE: ACTIVE DRUG

At steady state, we expect:

- **PM** – low-absent enzymatic activity; more likely to experience adverse effects due to high levels of unmetabolized drugs
- **IM** – possibly more adverse effects compared to NM due to decreased enzymatic activity
- **NM** – typical response at standard doses
- **UM** – less likely to experience therapeutic effect at standard doses due to increased enzymatic activity

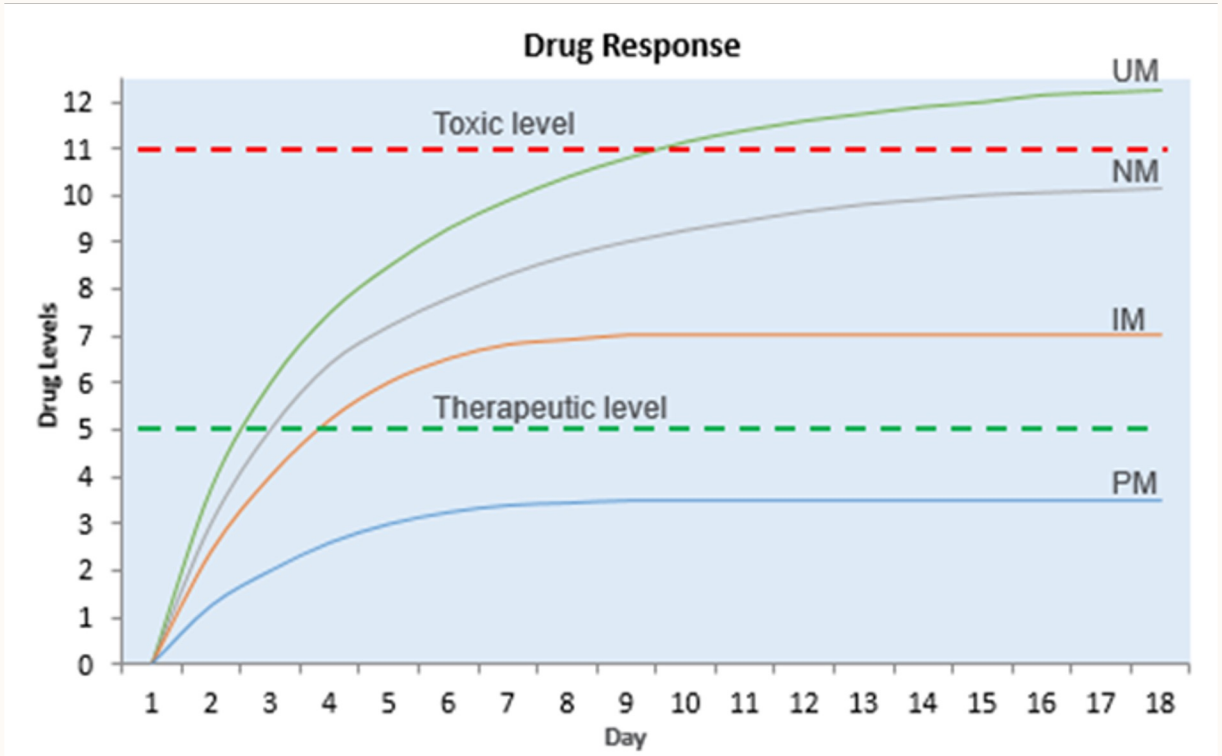


DRUG RESPONSE: PRODRUG

A prodrug is a biologically inactive precursor drug that must undergo chemical conversion before becoming an active pharmacological agent (active metabolite).

At steady state, we expect:

- **UM** – more likely to experience adverse effects due increased/rapid formation of active metabolites
- **NM** – typical response at standard doses, possibly more adverse effects
- **IM** – typical response at standard doses; possibly less therapeutic effects
- **PM** – less likely to experience therapeutic effect since the inactive parent compound is not been converted to the active form

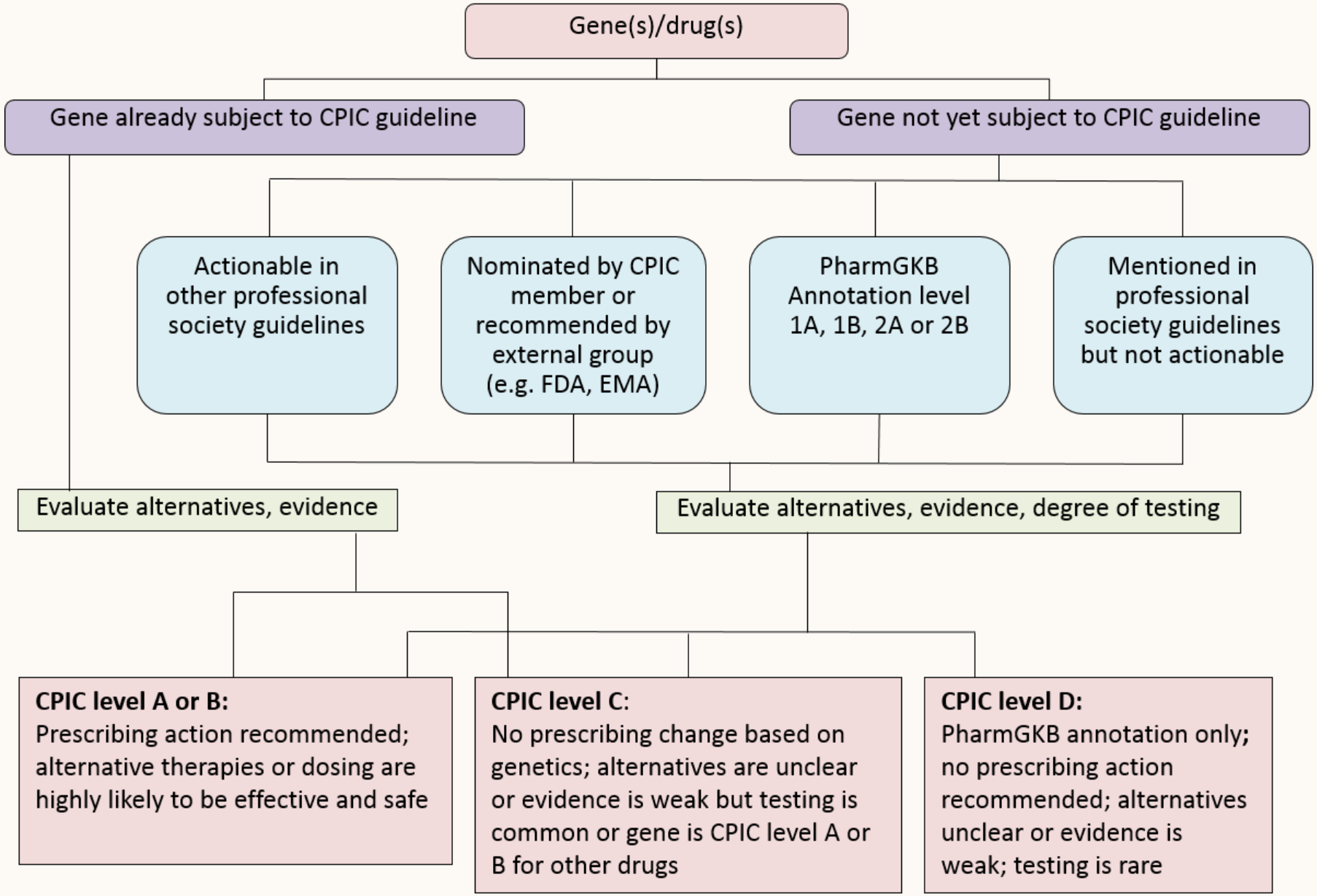


GUIDELINE & LITERATURE REVIEW

PGX INFORMATION RESOURCES

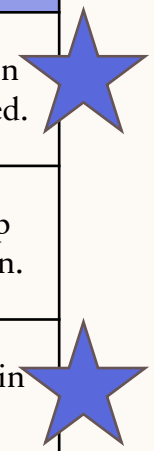
CPIC	PharmGKb	FDA
Clinical Pharmacogenetics Implementation Consortium Guideline actionable drug-gene pairs. Endorsed by mutiple medical societies Indexed as guidelines in PubMed	Data aggregate resource that identifies consistent genetic variant-drug response interactions.	The FDA publishes information on pharmacogenomic associations in three categories: 1. Sufficient scientific evidence for therapeutic management 2. Potential impact on safety 3. Potential impact on pharmacokinetic properties only

CPIC LEVELS OF EVIDENCE



https://cpicpgx.org/prioritization/

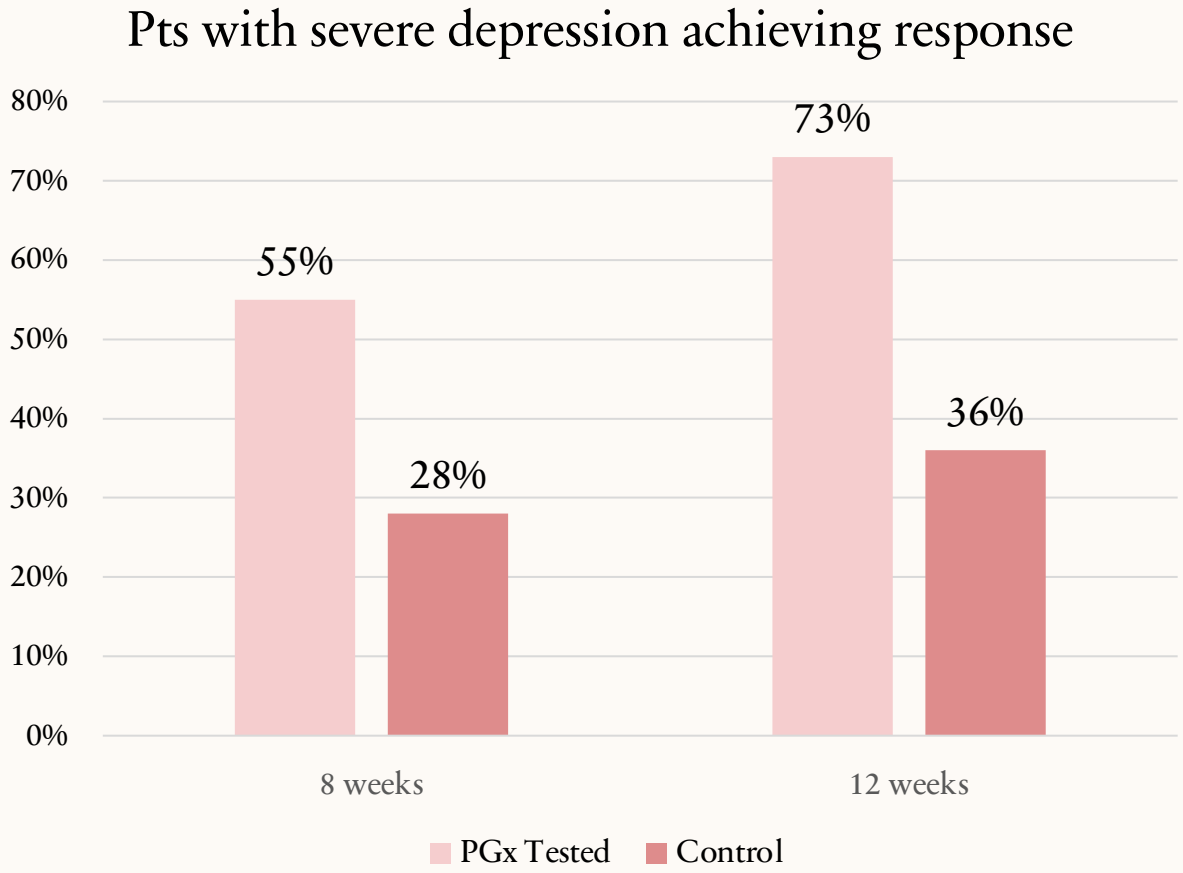
CPIC level	Clinical context	Level of evidence	Strength of recommendation
A	Genetic information should be used to change prescribing of affected drug.	Preponderance of evidence is high or moderate in favor of changing prescribing.	At least one moderate or strong action (change in prescribing) recommended.
A/B	Preliminary review indicates it is likely that the definitive CPIC level will be either A or B.	Full evidence review needed to assess level of evidence, but prescribing actionability is likely.	Full review by expert guideline group to assign strength of recommendation.
B	Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing.	Preponderance of evidence is weak with little conflicting data.	At least one optional action (change in prescribing) is recommended.
B/C	Preliminary review indicates it is likely that the definitive CPIC level will be either B or C.	Prescribing actionability based on genetics is not clear without further evidence review.	Full review by expert guideline group to assess strength of recommendation.
C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical, or (c) few published studies or mostly weak evidence and clinical actions are unclear.	Evidence levels can vary.	No prescribing actions are recommended.
C/D	Preliminary review indicates it is likely that the definitive CPIC level will be either C or D.	Evidence levels can vary.	No prescribing actions are recommended.
D	There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.	Evidence levels can vary.	No prescribing actions are recommended.



https://cpicpgx.org/prioritization/

PGX IN DEPRESSION & ANXIETY [23]

- PGx testing showed an increase in the number of patients with Major Depressive Disorder (MDD) who responded to antidepressant therapy
- Remission rates also improved
  - 35% PGx vs. 13% standard of care
- NNT = 3
  - Patients with severe depression to respond to treatment after 12



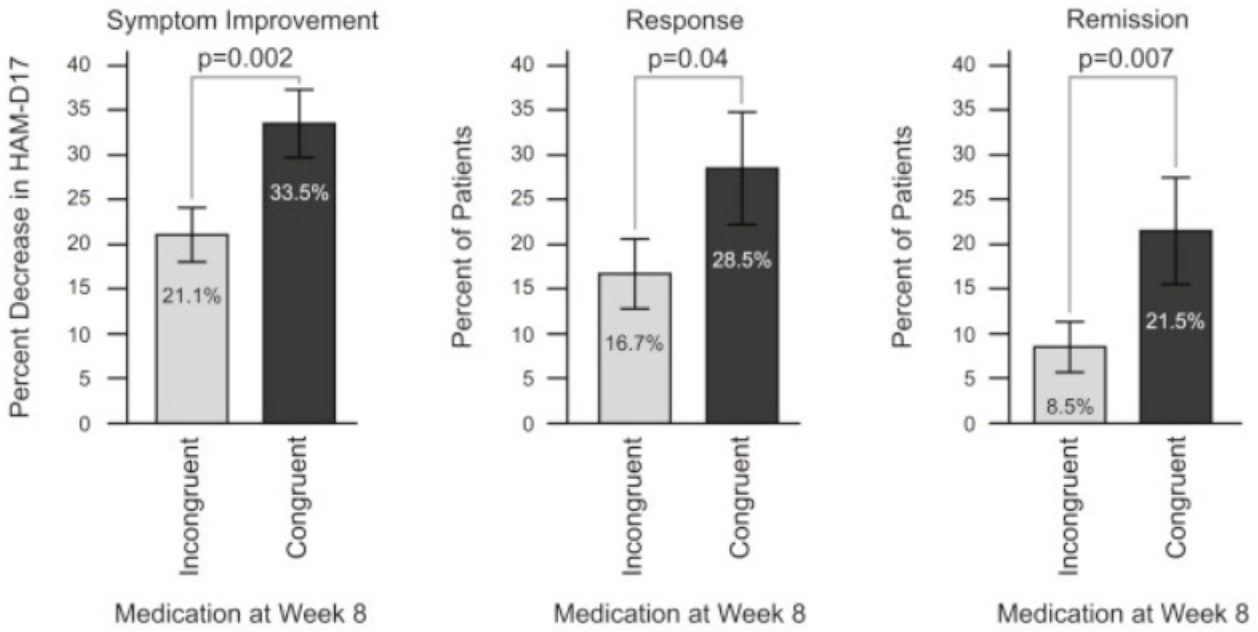
J Psychiatr Res. 2018 Jan;96:100-107/

PGX IN MDD: GUIDED TRIAL

- Large (n=1167) blinded, placebo-controlled study in outpatients with treatment resistant depression

- PGx vs. treatment as usual
  - No difference in symptom improvement on the HAM-D scale (27.2% vs. 24.4%, p=.107)
  - Differences in response rates (26.0% vs. 19.9%, p=0.013) and remission rates (15.3% vs 10.1%, p=0.008) were significant in favor of PGx guided treatment

- Patients switched off medications with significant gene-drug interactions showed greater improvements and fewer adverse effects than those that remained on them



J Psychiatr Res. 2019, Apr;111:59-67

PGX IN DEPRESSION: COMMUNITY PHARMACY

- Patients with depression or anxiety (n=213) presenting to a community pharmacy who were dissatisfied with their depression treatment. Blinded treatment groups of PGx vs. treatment as usual

- Patients in PGx group showed significantly greater improvements on PHQ-9 and GAD-7 than those in TAU after 6 months

- Prescribers were more likely to accept recommendations from pharmacist when PGx as used vs. not used
  - 75.2% vs. 52.85, p=0.001
  - Prescribers were primarily PCPs
  - Payor mix influenced recommendation acceptance

Clin Transl Sci. 2021 Jul;14(4):1359-1368

PGX IN DEPRESSION: META ANALYSIS

- 150 screened articles, 13 met inclusion criteria.
  - 10 randomized controlled trials
  - 3 open label trials
- Prospective, controlled trial assessing PGx efficacy in depression
- Relative risk of remission = 1.41
- Risk ratio increased in favor of genome guided treatment as
  - Number of trials of antidepressants increased
  - Depression severity increased

Bradley P, et al. J Psychiatr Res. 2018 Jan;96:100-107/

PGX IN DEPRESSION: VETERANS

- Randomized trial comparing PGx guided therapy to TAU (n=1944) over the course of 24 weeks
- Outcomes:
  - Number of drug-gene interactions
  - Remission based on PHQ-9
- Increased minority representation

Results

- PGx guided care did help avoid negative gene-drug interactions. Response and reduction in symptoms favored PGx.
- Remission rates were affected by race, PTSD, treatment resistant depression.
- No assessment of treatment emergent adverse effects
- PGx arm achieved greater rate of remission over 24 weeks but did NOT significantly differ after 24 weeks
- Negative PGx trial in

JAMA. 2022;328(2):151–161.

CURRENT PGX APPLICATIONS: PSYCHIATRY

Drug Name	Brand Name(s)	Gene(s)
amitriptyline	Elavil	CYP2C19, CYP2D6
amoxapine	Asendin	CYP2D6
aripiprazole	Abilify	CYP2D6
aripiprazole lauroxil	Aristada	CYP2D6
atomoxetine	Strattera	CYP2D6
brexpiprazole	Rexulti	CYP2D6
citalopram	Celexa	CYP2C19
clomipramine	Anafranil	CYP2C19, CYP2D6
clozapine	Clozaril, Versacloz	CYP2D6
desipramine	Norpramin	CYP2D6
diazepam	Valium	CYP2C19
doxepin	Silenor	CYP2C19, CYP2D6
duloxetine	Cymbalta, Drizalma Sprinkle	CYP2D6
escitalopram	Lexapro	CYP2C19

CURRENT PGX APPLICATIONS: PSYCHIATRY

Drug Name	Brand Name(s)	Gene(s)
fluvoxamine	Luvox	CYP2D6
iloperidone	Fanapt	CYP2D6
imipramine	Tofranil	CYP2C19, CYP2D6
lofexidine	Lucemyra	CYP2D6
nortriptyline	Pamelor	CYP2D6
paroxetine	Brisdelle, Paxil	CYP2D6
perphenazine	Trilafon	CYP2D6
protriptyline	Vivactil	CYP2D6
risperidone	Perseris, Risperdal	CYP2D6
sertraline	Zoloft	CYP2C19
thioridazine	Mellaril	CYP2D6
trimipramine	Surmontil	CYP2C19, CYP2D6
venlafaxine	Effexor	CYP2D6
vortioxetine	Trintellix	CYP2D6

TESTING CONSIDERATIONS

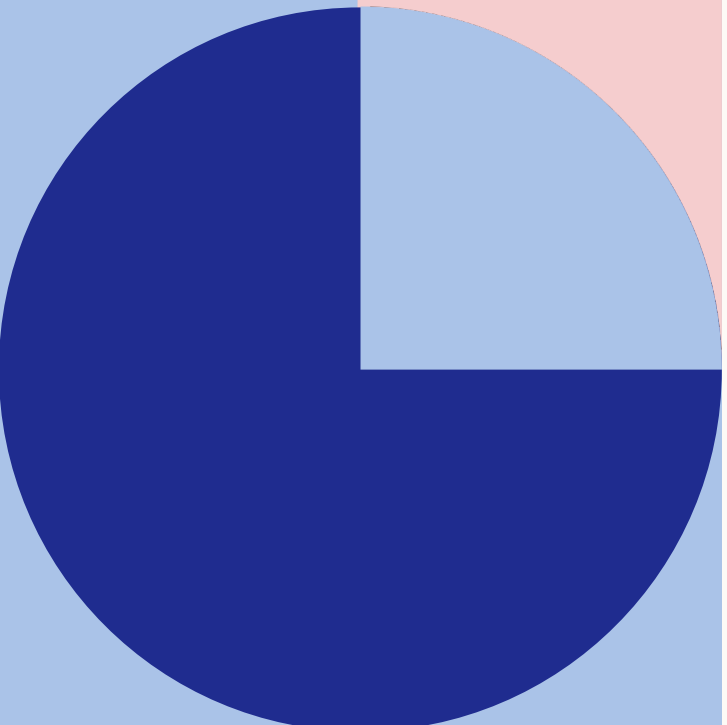
TESTING CONSIDERATIONS

Timing	Scope	Reporting
Reactive “just in time”	Single gene “targeted panel”	Presentation of Clinical Decision Support Tools and information “lights vs. letters”
Proactive “just in case”	Multi gene “broad panel”	Is the evidence for each recommendation available?
Turn around time and implication	Breadth of evidence in decision making process	Is the lab within a billable network?
	FDA approval (23&me)	

OVERLAPS IN OTHER AREAS OF PRACTICE

IMPLICATIONS IN HAWAI'I

- A large majority of pharmacogenomic research is done on those of European ancestry (Caucasian)
- In 2019, 25% of Hawaii's population was multiracial. Only 2.8% of the US population was multiracial. Whereas the United States was three-fourths Caucasian Alone, there was no majority race in Hawaii
- Asian American and Pacific Islanders (AAPI) have significantly different medication processing pathways than Caucasians and are more at risk for medication related complications



Annual Report on Findings from the Hawai'i Physician Workforce Assessment Project Act 18, December 2022
Hawaii Population Characteristics, Census Hawaii 2019

Drug	Select gene and phenotype	Frequency in Asian subgroups	Increase in Asians having risk phenotype[b,c]	Side effect/toxicity	CPIC recommended action if found to have an at-risk genotype
Clopidogrel	CYP2C19 poor and intermediate metabolizer	0.62 (East Asians)	2.1×	Decreased antiplatelet activity (lack of efficacy)	Consider prescribing an alternative agent such as prasugrel or ticagrelor
Warfarin	VKORC rs9923231 SNP carrier	0.88 (East Asians)	2.1×	Excessive anticoagulation (supratherapeutic)	Lower dose to maintain target concentration
Tamoxifen	CYP2D6 intermediate or poor metabolizer	0.87 (East Asians)	1.2× for intermediate metabolizer	Lower drug concentrations; increased risk of cancer recurrence	Consider alternative hormonal therapy, such as aromatase inhibitor
Allopurinol	HLA-B*5801 carrier	0.05 (East and Central Asians)	6.7×	Significantly increased risk of SCARs, such as SJS and TENS	Do not use allopurinol; may consider an alternative agent, such as febuxostat
Carbamazepine	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use carbamazepine; may consider an alternative agent
Oxcarbazepine	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use oxcarbamazepine; may consider an alternative agent
Phenytoin	HLA-B*15:02 carrier	0.069 (East and Central Asians)	172×	Increased risk of SJS and TENS	Do not use phenytoin; may consider an alternative agent
Selective Serotonin Reuptake inhibitors[d]	CYP2C19 poor metabolizer	0.62 (East Asians)	5.8×	Potential for arrhythmia at supratherapeutic doses (QT prolongation for citalopram)	Consider 50% dose reduction and monitor response; consider alternative agent
Tricyclic antidepressants	CYP2C19 poor metabolizer	0.62 (East Asians)	5.8x	Potential for suboptimal response	Consider alternative drug not metabolized by CYP2C19, such as secondary amines nortriptyline and desipramine, or 50% dose reduction
Thiopurines	NUDT15 intermediate or poor metabolizer	0.009	620× increase in East Asian for poor metabolizer	Increased risk of myelosuppression	Consider alternative drug class in nonmalignant conditions; use reduced dose of thiopurines in malignant conditions
Voriconazole	CYP2C19 poor metabolizer	0.15	5.8× increase in East Asians	Potential for hepatotoxicity, visual disturbances, and neurologic dysfunction	Consider alternative agent such as liposomal amphotericin B or posaconazole

Clin Transl Sci (2020) 12, 861-870.

DEPARTMENT OF THE ATTORNEY GENERAL

DAVID Y. IGE
GOVERNOR

CLARE E. CONNORS
ATTORNEY GENERAL

For Immediate Release
February 15, 2021

News Release 2021-13

$834 Million Order Entered in Hawai'i State Court Against Bristol-Myers Squibb and Sanofi For Failing to Investigate and Disclose Ineffectiveness of Plavix®

HONOLULU – Hawai'i Attorney General Clare E. Connors announced today the entry of an $834 million state court order against Bristol-Myers Squibb Company and three U.S.-based subsidiaries of French pharmaceutical company Sanofi for violating the State of Hawai'i's unfair and deceptive practices laws. The substantial amount reflects the fact the Defendants earned enormous profits while engaged in deceptive conduct that spanned more than a decade.

The order arises out of the Defendants' acts in developing, marketing and promoting Plavix, a prescription drug designed to reduce the risk of serious cardiovascular events such as heart attacks, strokes and blood clots. According to evidence presented in court, the Defendants began marketing the drug to Hawai'i physicians and consumers in 1998, knowing that it was not effective for many patients, including Asian and Pacific Island patients. Defendants only began warning Hawai'i physicians and consumers about this issue in March 2010, when the U.S. Food and Drug Administration (FDA) required them to place a "black box" warning on the label accompanying the drug.

- CYP2C19 *2 or *3 carriers have reduced hepatic *2C19* activity, lowering conversion of clopidogrel to its active metabolite
- The population of Hawaii is **42% East Asian**, 24% White, **10% Pacific Islander**
- ***2 variant frequency is 23–45% in East Asians** and **40–77% in Pacific Islanders**
- Nearly double cardiovascular death rate as a percentage of patients suffering an AMI

PHENOCONVERSION: THE ACHILLES HEEL OF PGX

DRUG-DRUG-GENE INTERACTIONS

- Phenoconverstion: the mismatch between the clinically observed phenotype and the genetically determined phenotype. We want to look at both drug-drug and drug-gene interaction.
- Drug-drug-gene interactions (DDGIs) impact 1 in 4 patients on medications with high evidence of PGx interactions.
- 1 in 4 patients on a PGx medication are prescribed an inhibitor or inducer of the respective enzyme.
- Strongly supports the need to account for DDGI in CDSS

Health Informatics Meets eHealth
D. Hayn and G. Schreier (Eds.)

doi:10.3233/978-1-61499-759-7-121

Table 4. Ten most common EADDGIs (i.e., phenoconversion) with cumulative impact on AUC.

Affected Drug	Gene	Drug 2	AUC Change: Affected Drug + – Gene	AUC Change: Affected Drug + – Drug 2	Estimated AUC Change: Affected Drug + Gene + Drug 2
clopidogrel (metabolite)	CYP2C19 Intermediate Metabolizer	tramadol	−31–50%	−31–50%	−51–80%
citalopram	CYP2C19 Rapid Metabolizer	esomeprazole	−31–50%	26–75%	−0–30%
clopidogrel (metabolite)	CYP2C19 Intermediate Metabolizer	oxycodone	−31–50%	−31–50%	−51–80%
amitriptyline	CYP2D6 Intermediate Metabolizer	bupropion	26–75%	26–75%	76–200%
clopidogrel (metabolite)	CYP2C19 Intermediate Metabolizer	morphine	−31–50%	−31–50%	−51–80%
metoprolol	CYP2D6 Intermediate Metabolizer	dronedarone	76–200%	26–75%	>200%
clopidogrel (metabolite)	CYP2C19 Intermediate Metabolizer	hydrocodone	−31–50%	−31–50%	−51–80%
clopidogrel (metabolite)	CYP2C19 Poor Metabolizer	tramadol	−51–80%	−31–50%	−81–100%
amitriptyline	CYP2D6 Poor Metabolizer	bupropion	76–200%	26–75%	>200%
citalopram	CYP2C19 Rapid Metabolizer	fluvoxamine	−31–50%	26–75%	−0–30%

Abbreviation: area under the curve, AUC.

BARRIERS TO STANDARDIZATION

- **Lack of Reimbursement**
  - Between 15% and 20% of both privately and publicly insured individuals experience coverage disruptions or change plans each year*
- **Already overburdened healthcare system**
- **Technology has outpaced education**
- **Lack of electronic medical record infrastructure**
- **No pharmacogenomics labs on island**

**JAMA Netw Open.* 2022;5(2):e220320

HOT TAKES

- PGx in mental health has one of the larges benefits of any specialty area that could not only change, but truly save lives
- There is a possibility that the standard of care looks drastically different in Hawai'i than anywhere else in the United States
- Need to stop referring to personalized medicine as 'the future'
- Consumers are more educated than ever before
- Pharmacists are playing a key role in PGx management and implementation across the country – team-based care is the answer

“IF IT’S NOT SAFE, IT’S NOT CARE”

Dr. Tedros Adhanom Ghebreyesus
World Health Organization Director-General
2023 Global Ministerial Summit on Patient Safety

QUESTIONS?

THANK YOU!

Dr. Corrie L. Sanders, PharmD., BCACP, CPGx

Founder, Huna Health Pharmacogenomic Consulting

corrie@huna-health.com; huna-health.com

MEDICARE LCDS EXPANDED PGX COVERAGE

"PGx tests are indicated when medications are being considered for use (or already being administered) that are medically necessary, appropriate, and approved for use in the patient's condition and are known to have a gene(s)-drug interaction that has been demonstrated to be clinically actionable as defined by the **FDA** (PGx information required for safe drug administration) or **Clinical Pharmacogenetic Implementation Consortium** (**CPIC**) **guidelines** (**category A and B**)."

Multigene panels can be performed when (as defined in the policy):

- More than one gene is reasonable and necessary for the safe use of the drug being considered or in use
- More than one drug is in consideration or use that is associated with a gene-drug interaction (includes multi-gene coverage for TCAs and SSRIs)

https://cpicpgx.org/genes-drugs/

https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38337