UNIVERSITY OF MONTANA
L.S. SKAGGS INSTITUTE FOR HEALTH INNOVATION

Shodair Medical Genetics
Children's Hospital

Montana's Children's Miracle Network Hospital

Adding Value to Pharmacogenetics

How to implement pharmacogenetics in rural health care?

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No Disclosures

Outline

I. Introduction to Pharmacogenetics

II. Integrated model of pharmacogenetic testing and consultations

I. Introduction to pharmacogenetics

PHARMACOGENETICS BASICS → How does it work?

I. Introduction to pharmacogenetics

EVIDENCE → Does it work?

I. Introduction to pharmacogenetics

CLINICAL UTILITY → Is there a benefit?

I. Introduction to pharmacogenetics

COST EFFECTIVENESS → How much it costs to improve outcome?

I. Introduction to pharmacogenetics

CLINICAL VIGNETTE

Clopidogrel (Plavix)

Prodrug

Poor metabolizer

Genetic polymorphism

CYP2C19

CLINICAL VIGNETTE
ANTIPLATELET MEDICATIONS

65-year-old male with coronary artery disease underwent elective percutaneous coronary angioplasty (PTCA) and stenting using a drug eluting stent (DES).

Dual antiplatelet therapy (DAT) was initiated with **clopidogrel** 300 mg PO x1 with baby aspirin, followed by 75 mg PO daily and daily baby aspirin.

After 2 months, he noticed palpitations during exercise which turned out to be ischemia-induced ventricular ectopy on stress testing.

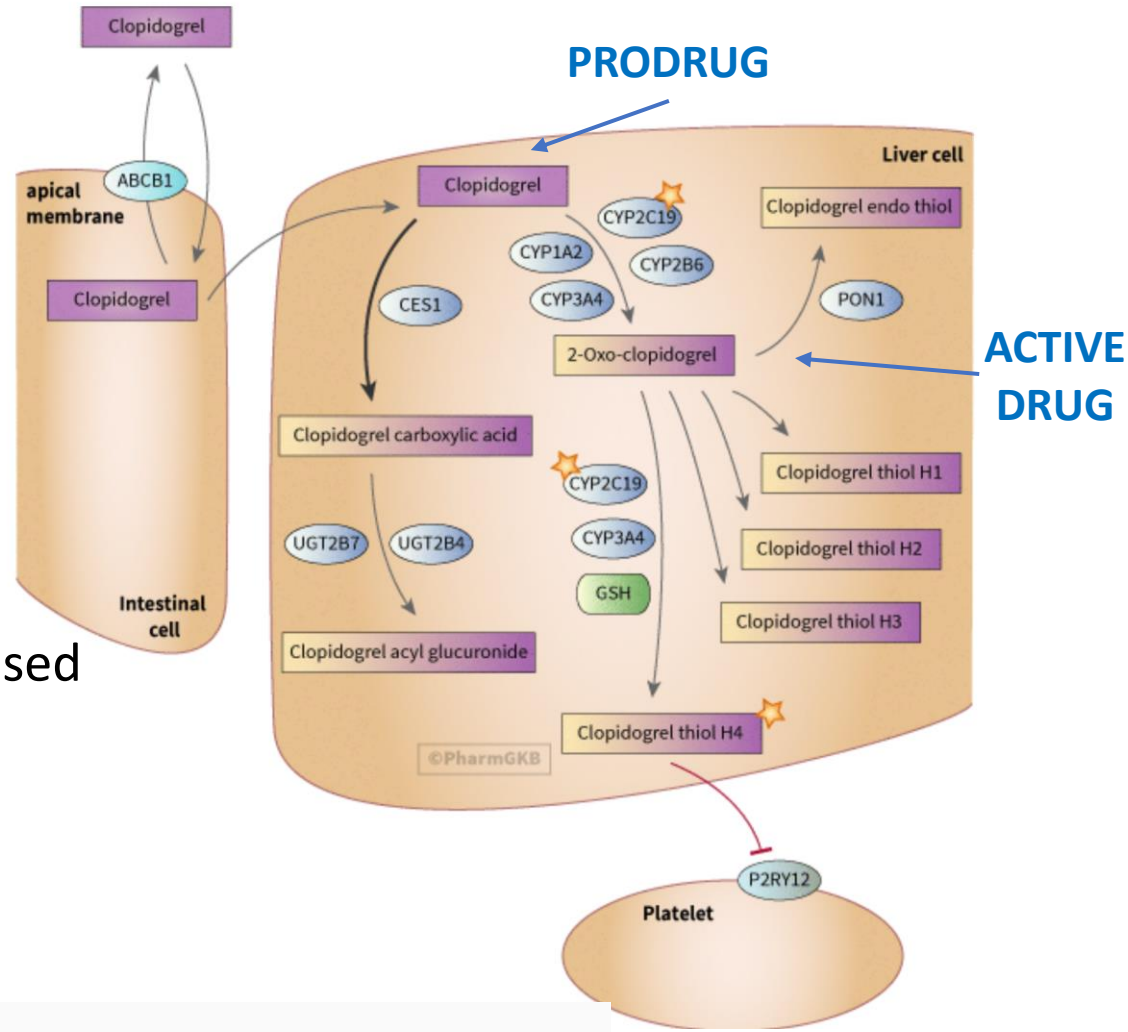
Re-catherization showed in-stent restenosis of 90% and the lesion is re-treated with another DES.

Clopidogrel was discontinued and replaced by another platelet inhibitor, Ticagrelor 180 mg PO x 1 followed by 90 mg PO daily.

He had normal stress testing at 6- and 12-month post intervention.

Clopidogrel

Individuals who are **poor metabolizers (PM)** due to a **genetic polymorphism** have **reduced ability to activate clopidogrel** and are at increased risk for stent thrombosis.



CYP2C19 LOF Alleles → ↓ Clopidogrel Biotransformation → ↓ Platelet Inhibition → ↑ CV Events

PHARMGKB

FDA Black Box Warning

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE *CYP2C19* GENE

- Effectiveness of Plavix depends on conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Tests are available to identify patients who are CYP2C19 poor metabolizers.
- Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

CYP2C19 Alleles & Genotypes

Allele	SNP	CYP2C19 Function
*1	N/A	Normal function
*2	681G>A	No function
*3	636G>A	No function
*17	-808C>T	Increased function

Genotype	Phenotype
*1/*1	Normal Metabolizer (NM)
*1/*2, *1/*3	Intermediate Metabolizer (IM)
*2/*2, *2/*3	Poor Metabolizer (PM)
*1/*17	Rapid Metabolizer (RM)
*17/*17	Ultra-rapid Metabolizer (UM)

Race	PMs	IMs	RM/UM
Whites	2%	25%	40%
Blacks	4%	30%	45%
Asian	14%	50%	<5%

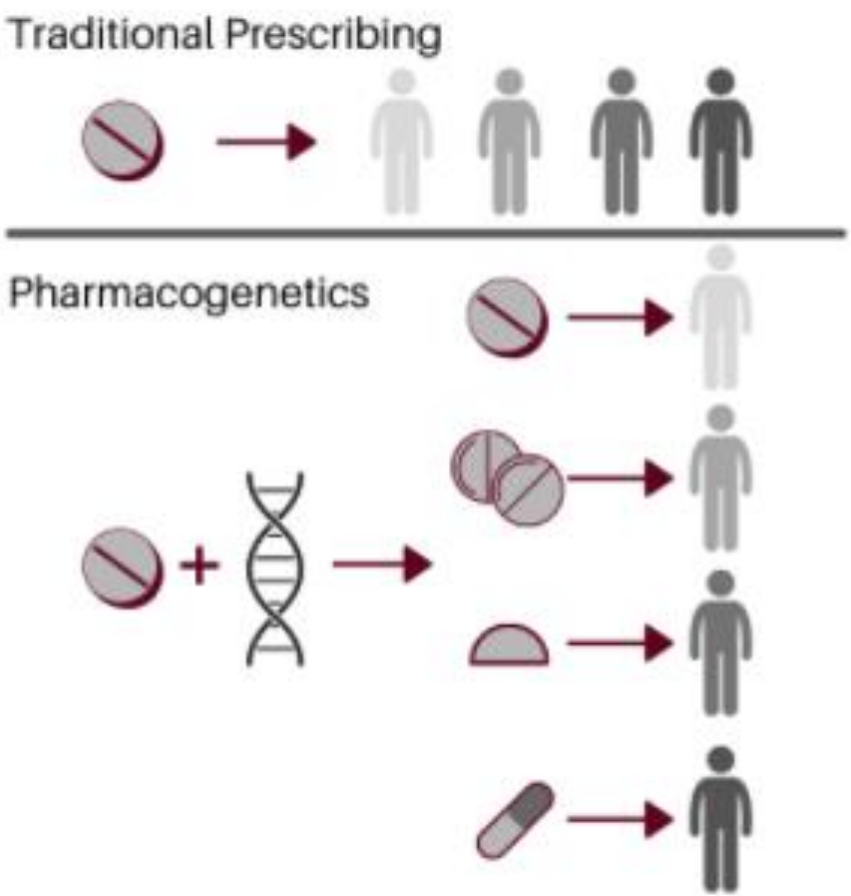
- Genetic polymorphisms account only for 5.2-12% of the variation of platelet aggregation inhibition by clopidogrel in PCI patients, with other factors collectively explaining >80% of the variation.

Clopidogrel Genetic Testing Recommendations

1. ***Genetic testing might be considered*** to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. (Level of Evidence: C)
2. When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with ***an alternate P2Y12 inhibitor (e.g., prasugrel or ticagrelor) might be considered***. (Level of Evidence: C)
3. The ***routine clinical use of genetic testing*** to screen patients treated with clopidogrel who are undergoing PCI ***is not recommended***. (Level of Evidence: C)

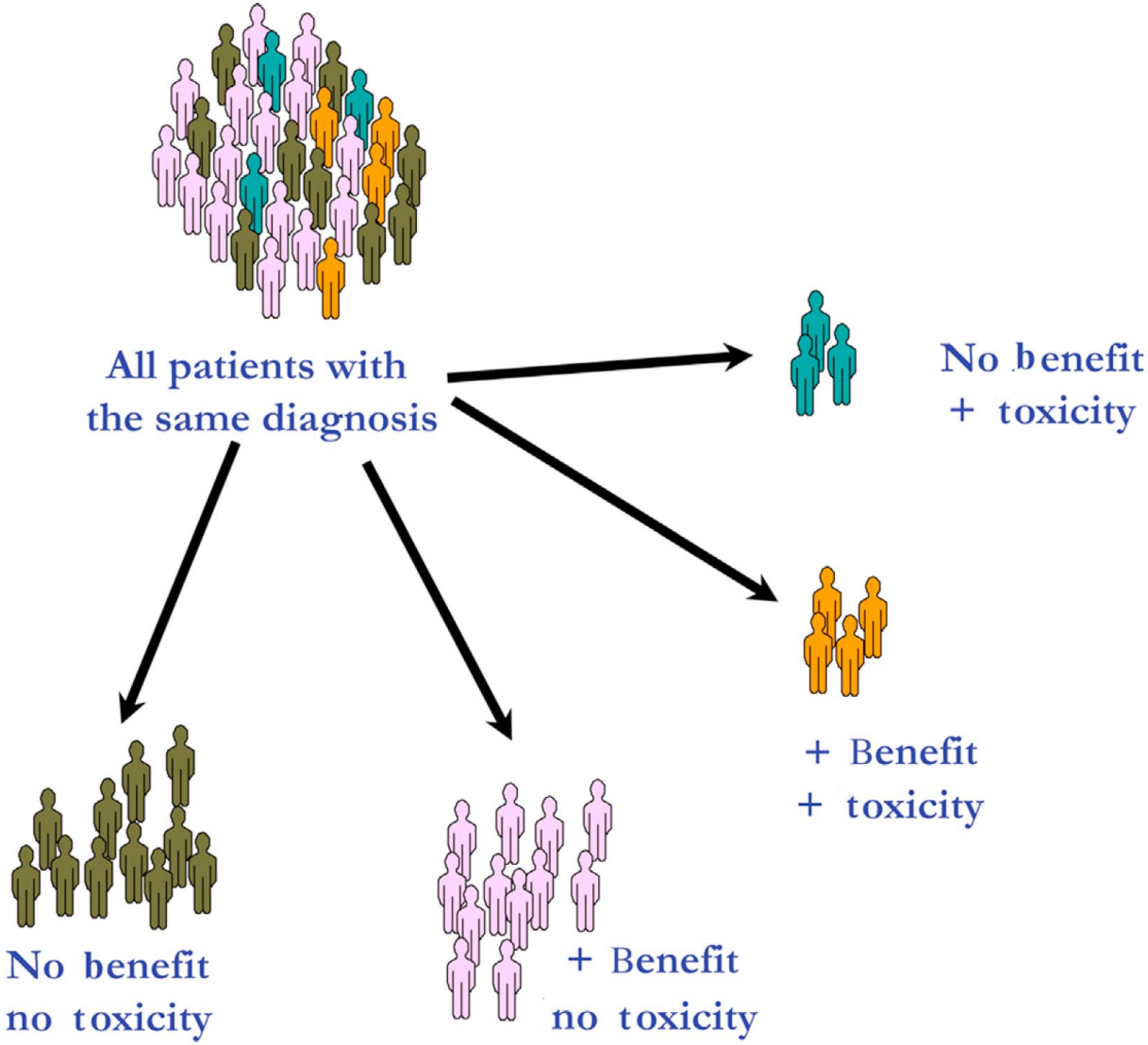
Levine GN, et al. Circulation 2011;124:e574-651.

The promise of Pharmacogenetics

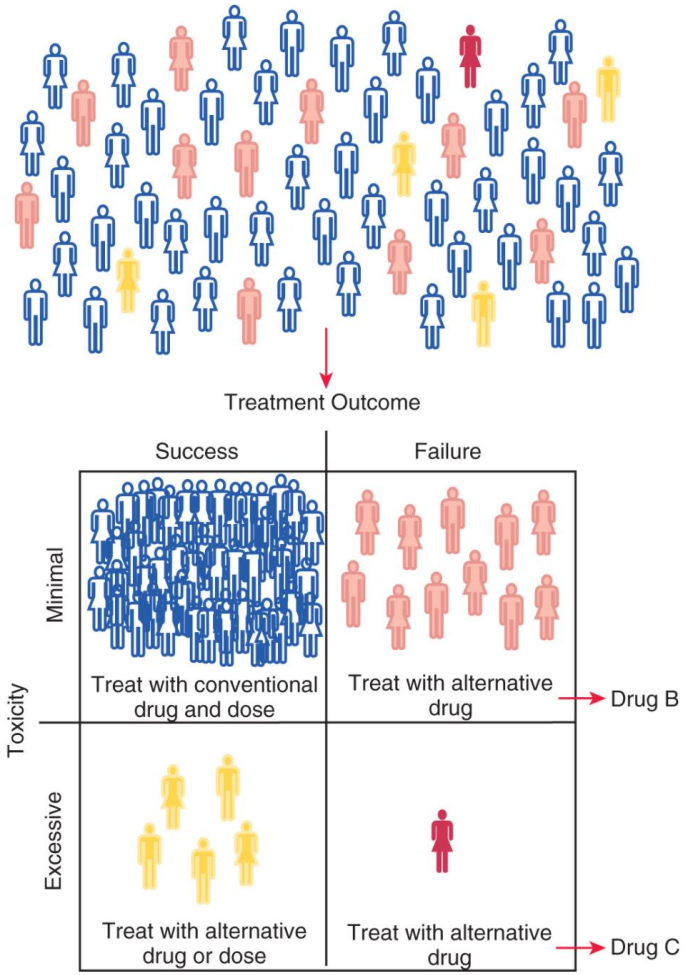


Average patient

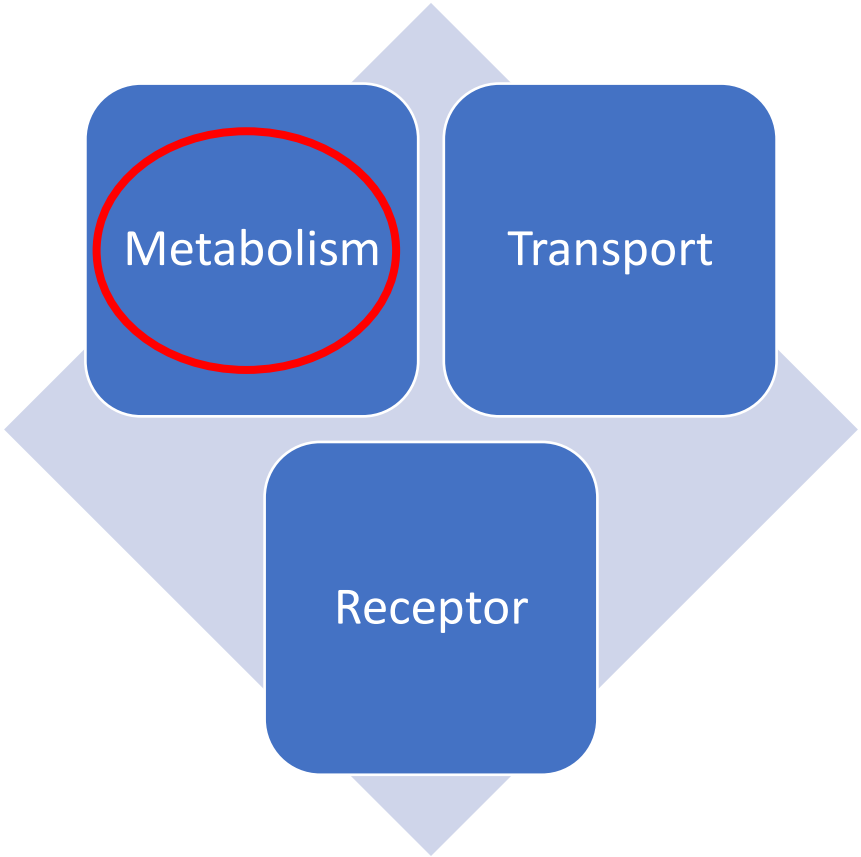
Individual patient



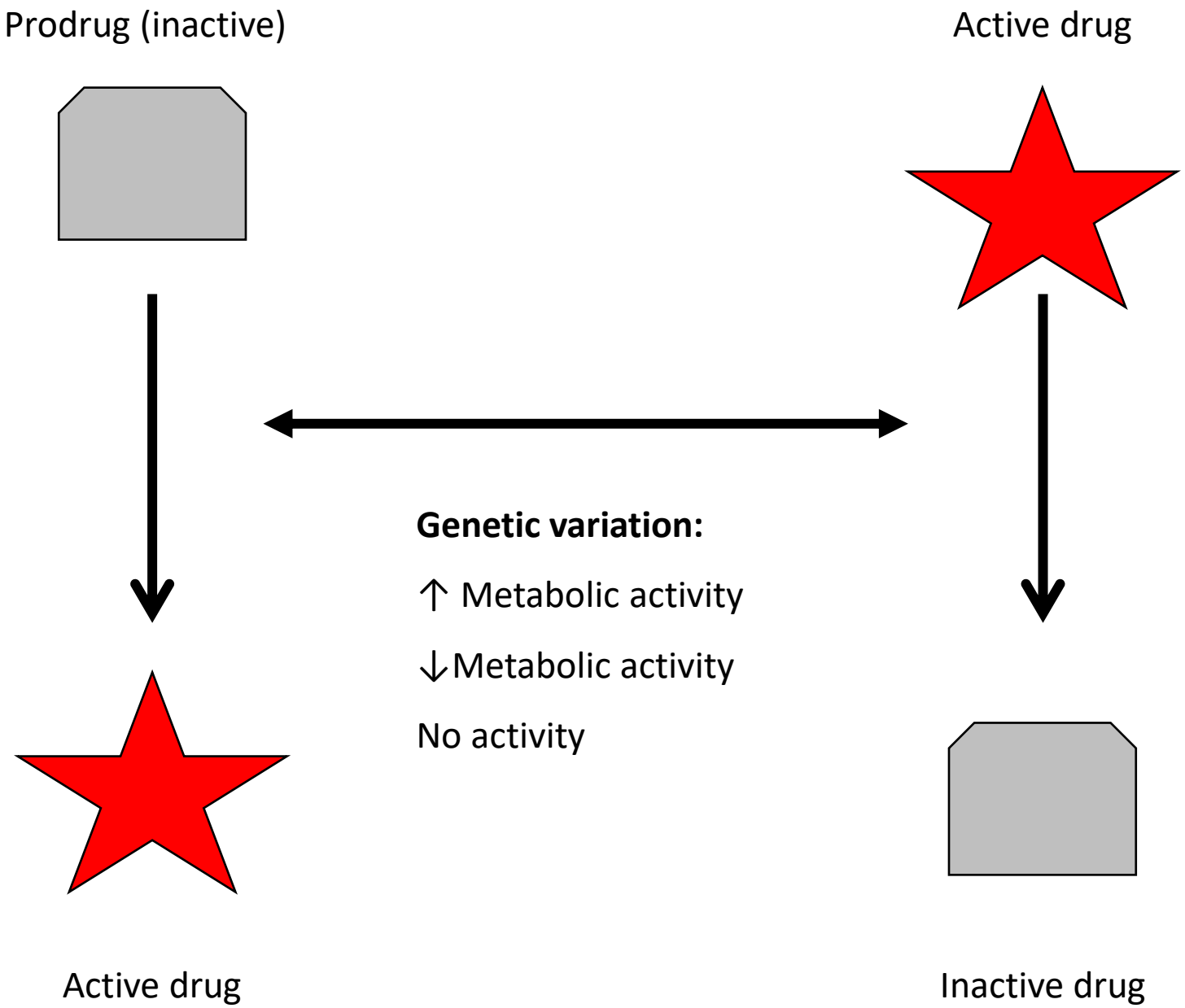
From: Genomic and Precision Medicine, 3rd Edition; eds. Ginsburg, Willard, David. Academic Press



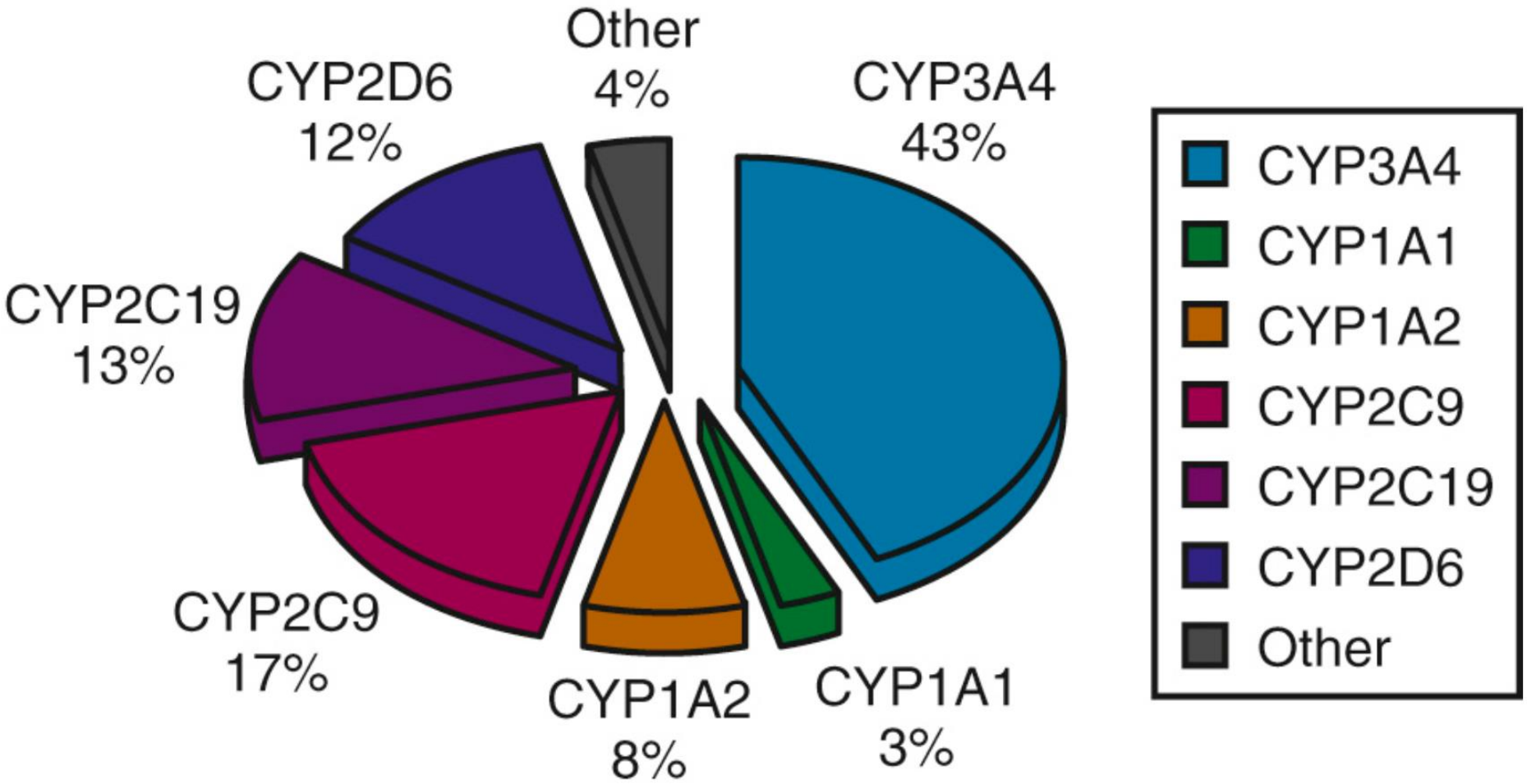
Adapted from Yaffe SJ, Aranda JV: Neonatal and pediatric pharmacology, ed 3, Philadelphia, 2004, Lippincott Williams & Wilkins



Individual drug response profile

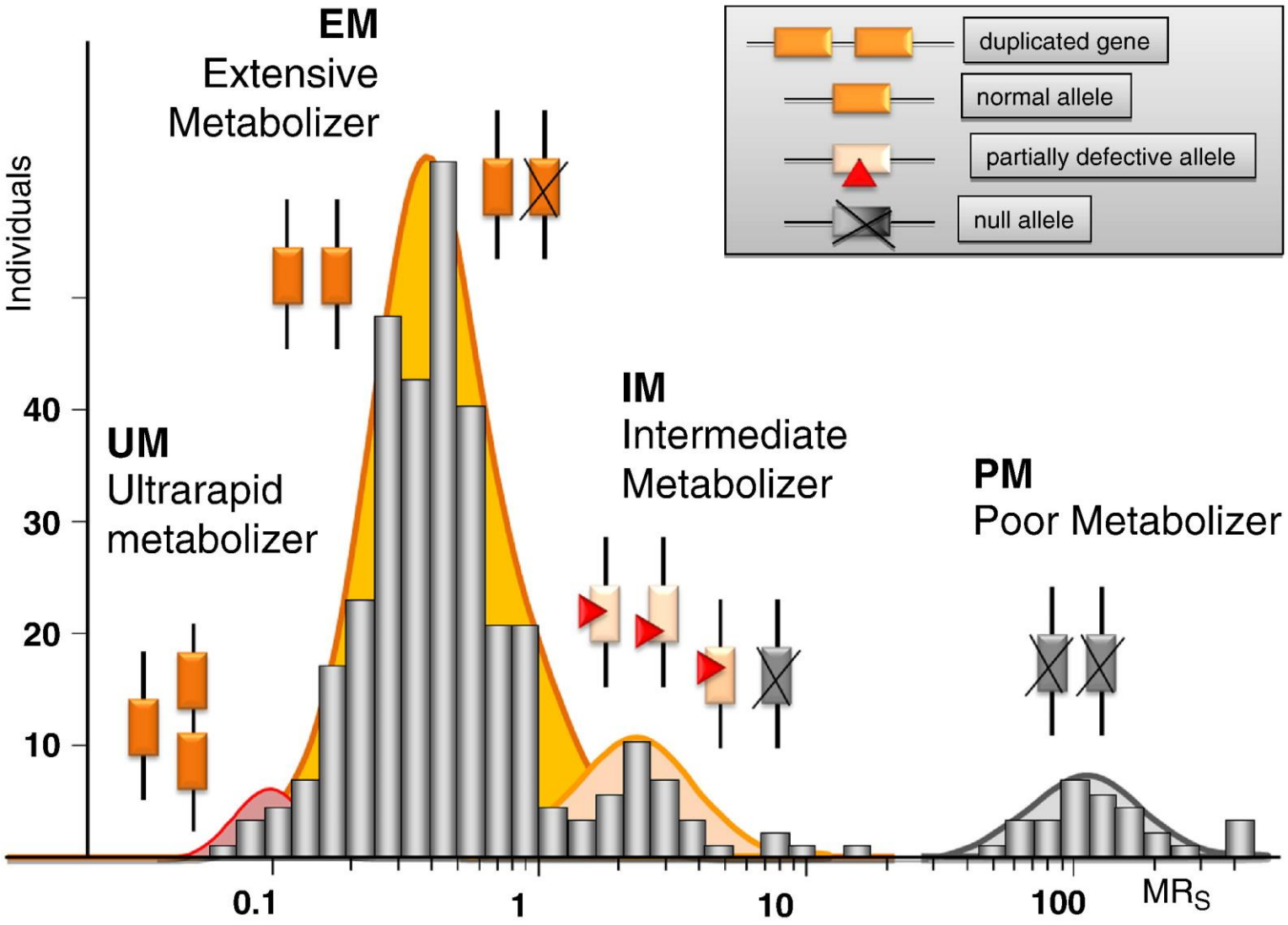

Prodrug (inactive)
Active drug
Genetic variation:
↑ Metabolic activity
↓Metabolic activity
No activity
Active drug
Inactive drug

Cytochrome P-450 (CYP) drug metabolizing enzymes

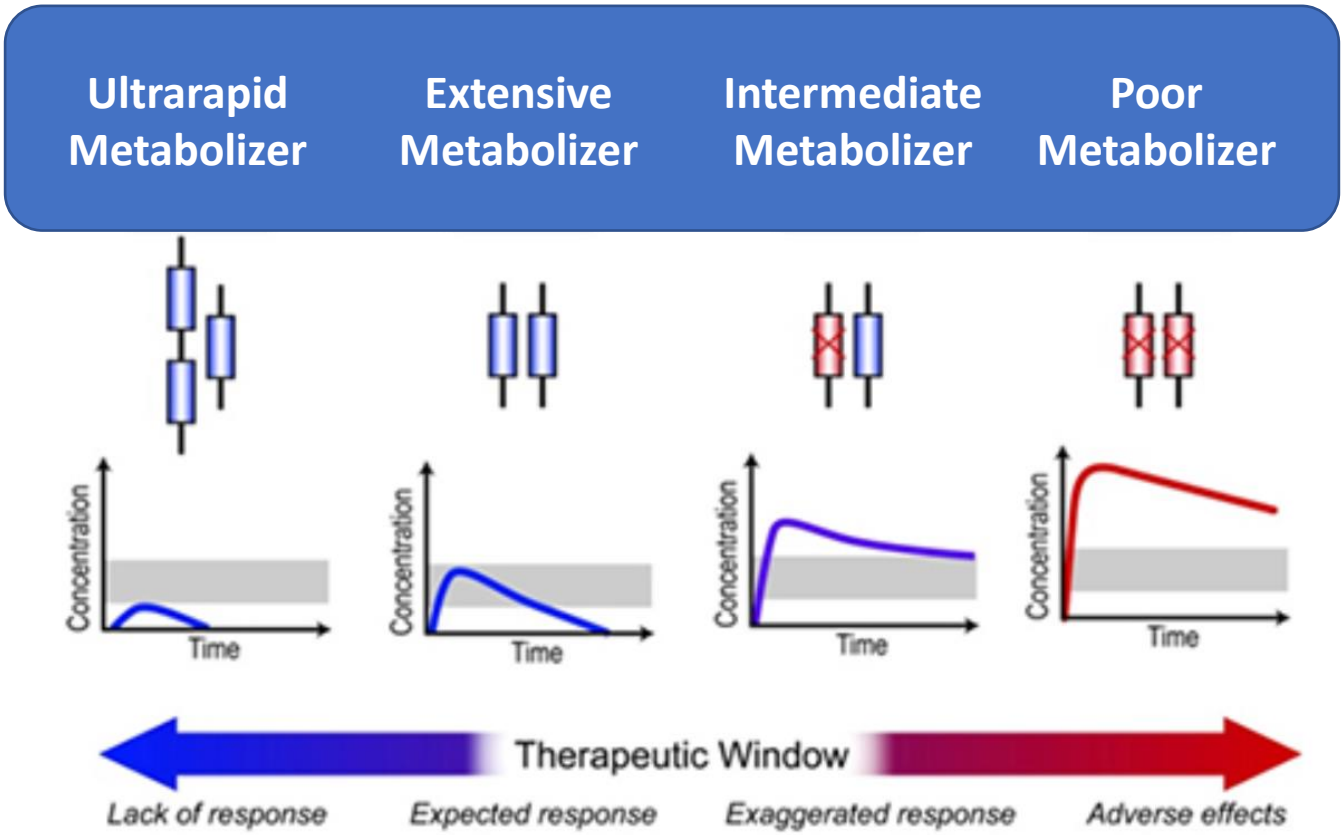


From: Thompson & Thompson Genetics in Medicine, 8th edition; eds. Willard, McInnes, Nussbaum. Elsevier Health Sciences

Alleles (genotype) and effect on metabolizing enzyme activity (phenotype)



Zanger UM, Schwab M. Pharmacol Ther. 2013 Apr;138(1):103-41. PMID: 23333322.


Ultrarapid Metabolizer
Extensive Metabolizer
Intermediate Metabolizer
Poor Metabolizer
Concentration
Time
Concentration
Time
Concentration
Time
Concentration
Time
Therapeutic Window
Lack of response
Expected response
Exaggerated response
Adverse effects

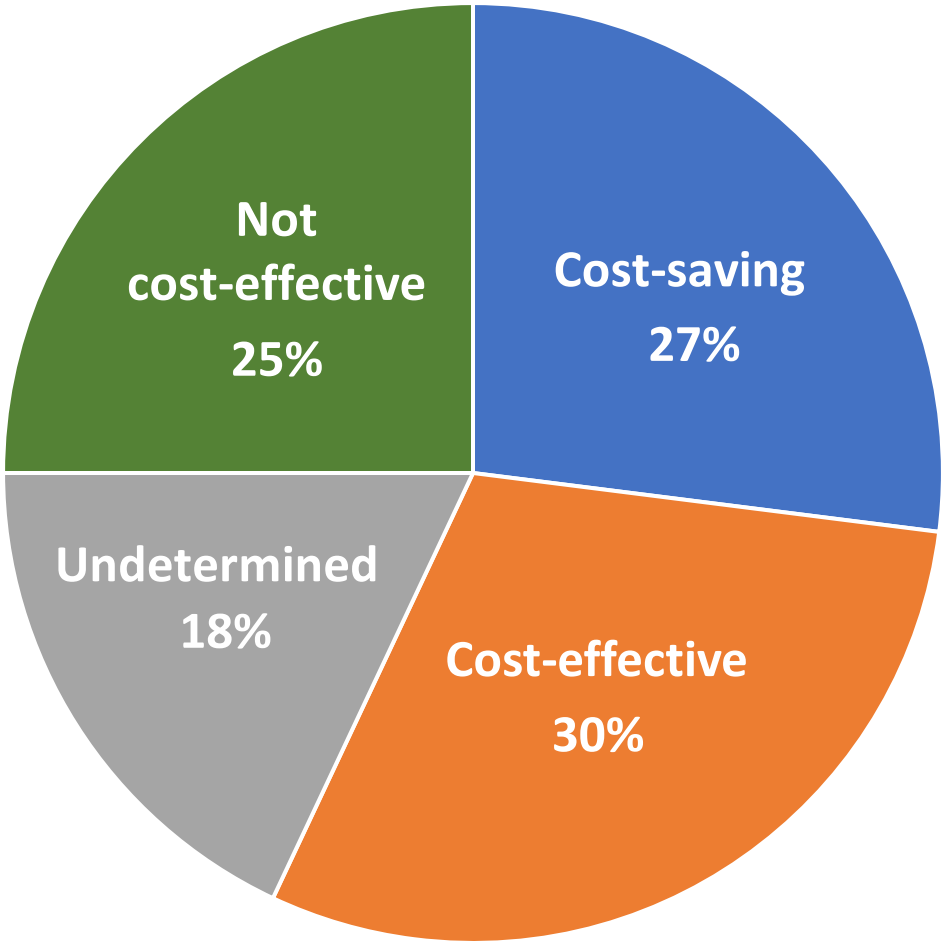
Evidence for pharmacogenetics-guided therapy in psychiatry

Prospective RCTs comparing PG guided vs non-guided pharmacotherapy, treatment as uual (TAU).

Genotyping method	Study design	Outcome
CYP1A2, CYP2D6, CYP2C19 (Genesight I)	Open label, prospective cohort: n = 25 genotyping guided vs n = 26 TAU (Hall-Flavin et al. (2012))	Genotyping leads to more reduction in depression scores
CYP1A2, CYP2D6 CYP2C19 (Genesight II)	Open label, prospective cohort: n = 114 genotyping guided vs n = 113 TAU (Hall-Flavin et al. (2013))	Genotyping leads to more reduction in depression symptoms
CYP1A2, 2C9, 2C19, 2D6, SCL6A4, 5HTR2A	RCT, double-blind: n = 26 guided vs n = 25 TAU (Singh (2015))	Genotyping results in higher response and remission rates
CYP2D6, CYP2C19, ABCB1, not otherwise specified	RCT, double-blind: n = 74 genotyping guided vs n = 74 TAU (Winner et al. (2013))	Genotyping 2.52 times more likely to remit
CYP2D6 and others, not specified (Neuro Pharmagen)	KT, double-blind: N = 155 guided vs n = 161 TAU (Perez et al. (2017))	Genotyping results in higher response rate and better tolerability
CYP1A2, 2C9, 2C19, 2D6, 3A4, 3A5, SCL6A4, COMT, HTR2A, MHFR (NeurolDgenetix)	RCT: n = 352 genotyping guided vs n = 333 TAU(Bradley et al. (2018))	Genotyping leads to higher response rates and remission rates in patients with depression or anxiety.
CYP1A2, 2C9, 2C19, 2B6, 2D6, HTR2A, SCL6A4	Prospective double-blind RCT: n = 1167 in total (Greden et al. (2019))	Genotyping leads to higher response and remission rates in depressed patients

van Westrhenen et al. Front Pharmacol. 2021 Apr 12;12:640032. PMID: 33995044;

Cost-effectiveness of PGx-guided therapy



Modified from: Verbelen et al., Pharmacogenomics J. 2017 Oct;17(5):395-402. PMID: 28607506

- Develops and publishes guidelines for multiple drug-gene pairs focusing on the question of what might be an appropriate drug dose adjustment given the availability of genetic data.
- Does not address the question of when or how such genetic testing should be done.

Independent Record

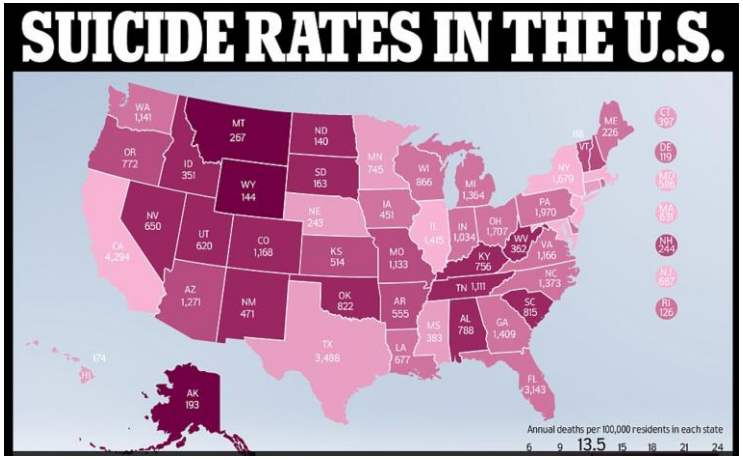
Sunday, October 31, 2021 | Print Edition

406 POLITICS

MT students report highest-ever depression rates, sustainable solutions elusive

Seaborn Larson

A recent survey found 41% of Montana high school students — the highest rate ever documented — self-reported symptoms of depression over the last year.



Many of Montana's communities have limited health care and scarce public transportation.

Fewer social services or other needed services exist for people with disabilities.

Long travel distances, long winters, and unmet needs for rural health-care providers are compounding factors.

Clinical utility of pharmacogenetics in psychiatry

- Pharmacotherapy in psychiatry is hampered by side-effects and lack of effectivity.
- Only 30% of patients who suffer from psychiatric disorders remain compliant with their medication and reach full and stable remission.
- 30–50% of patients with major depressive disorder do not respond to their first antidepressant.
- Remission rates for SSRI's are as low as 37%.
- About 25,000 patients in US present to the emergency department each year due to antidepressant-induced adverse events.
- A major factor for side effects and lack of efficacy is the relation between dosage and systemic exposure to the drug.

II. Integrated model of pharmacogenetic testing and consultations

CLINICAL VIGNETTE
ANTIANXIETY MEDICATIONS

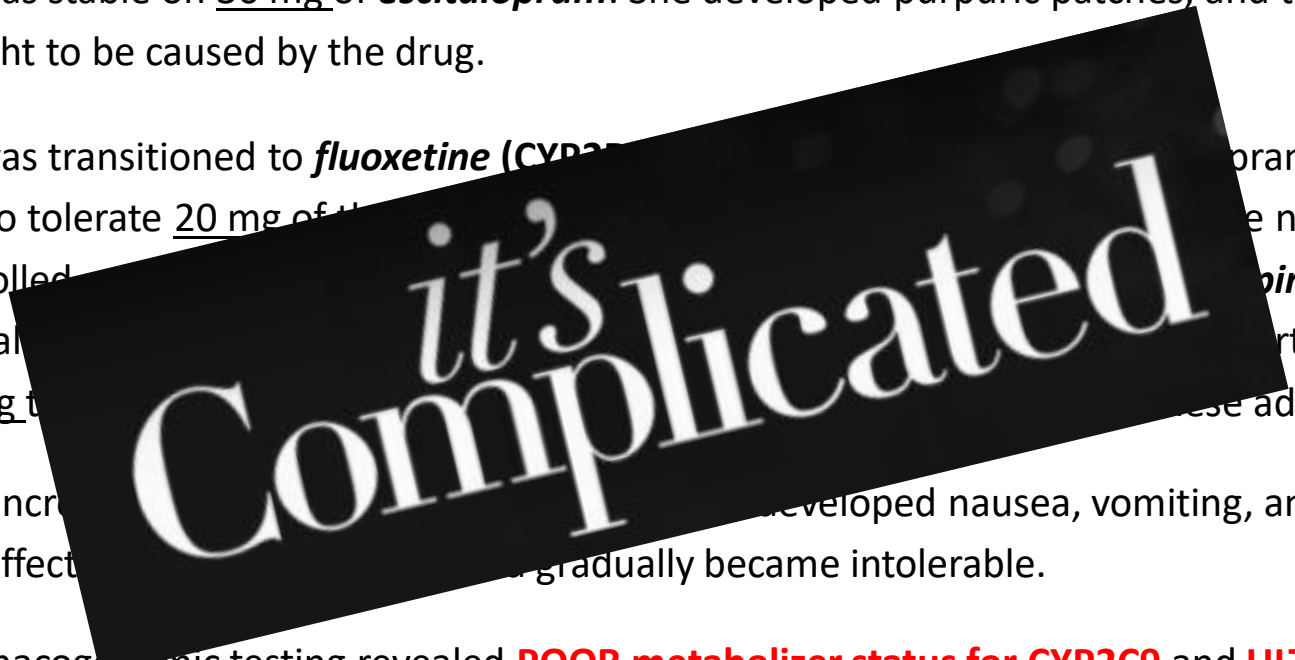
- A 19-year-old female presented with generalized anxiety disorder (GAD) and panic disorder. She was stable on 30 mg of ***escitalopram***. She developed purpuric patches, and these were thought to be caused by the drug.

- She was transitioned to ***fluoxetine*** (**CYP2**[illegible]**pram**. She was able to tolerate 20 mg of [illegible] **e** not optimally controlled [illegible] ***pirone*** **(CYP3A4)** at total [illegible] **rtial** substrate) 0.5 mg t[illegible] **ese additions.**

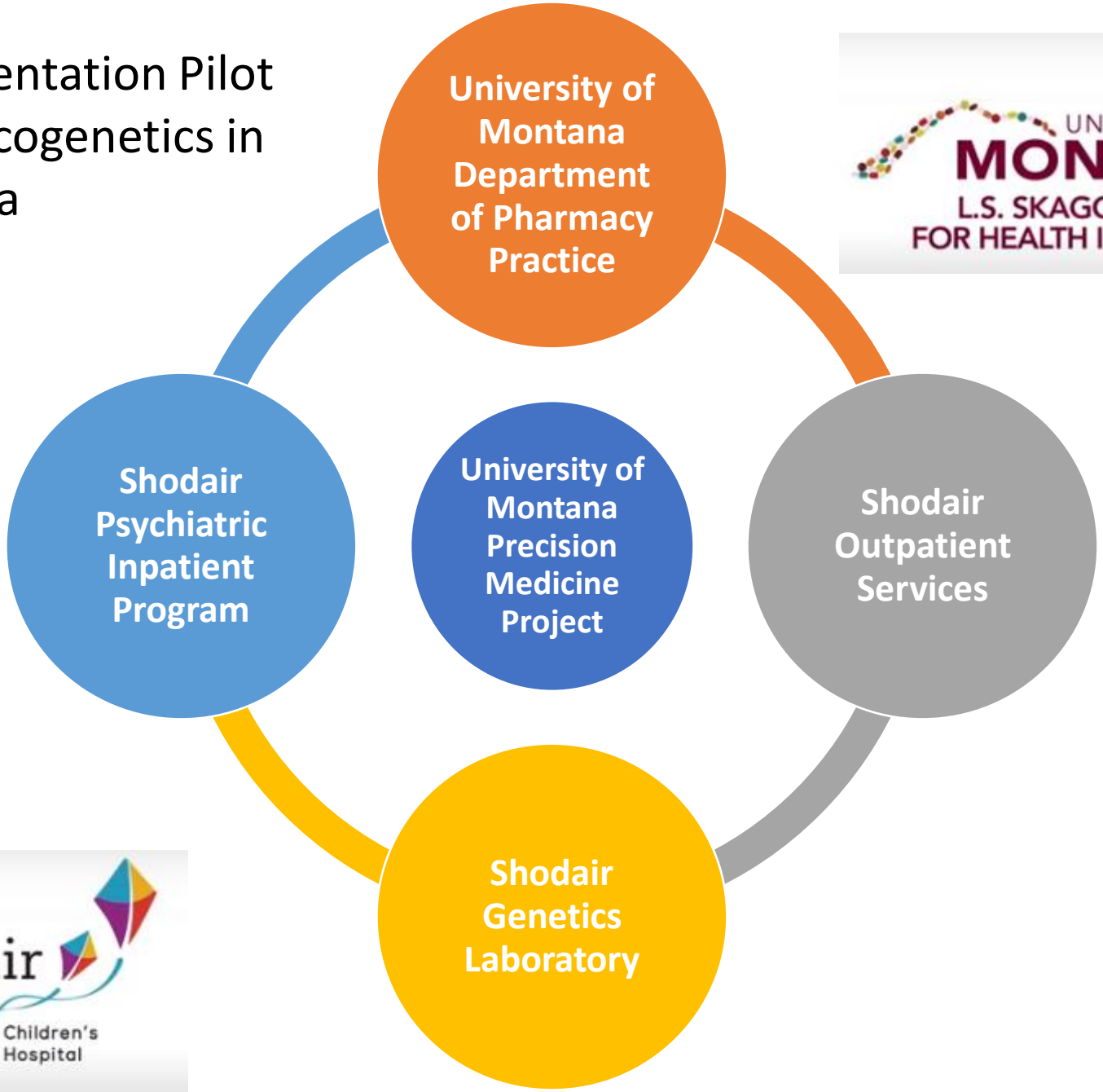
- With incr[illegible] **developed** nausea, vomiting, and fatigue. Side effect[illegible] **gradually** became intolerable.

- Pharmacogenomic testing revealed **POOR metabolizer status for CYP2C9** and **ULTRARAPID metabolizer status for CYP2D6.**

- She is started ***venlafaxine extended release*** (**2D6**, 2C19, 3A4). Venlafaxine works well for her. She was stabilized on 150 mg with concomitant ***clonazepam*** (3A4 partial substrate) and continues to do well with optimal control of both anxiety and panic symptoms.



Implementation Pilot Pharmacogenetics in Montana



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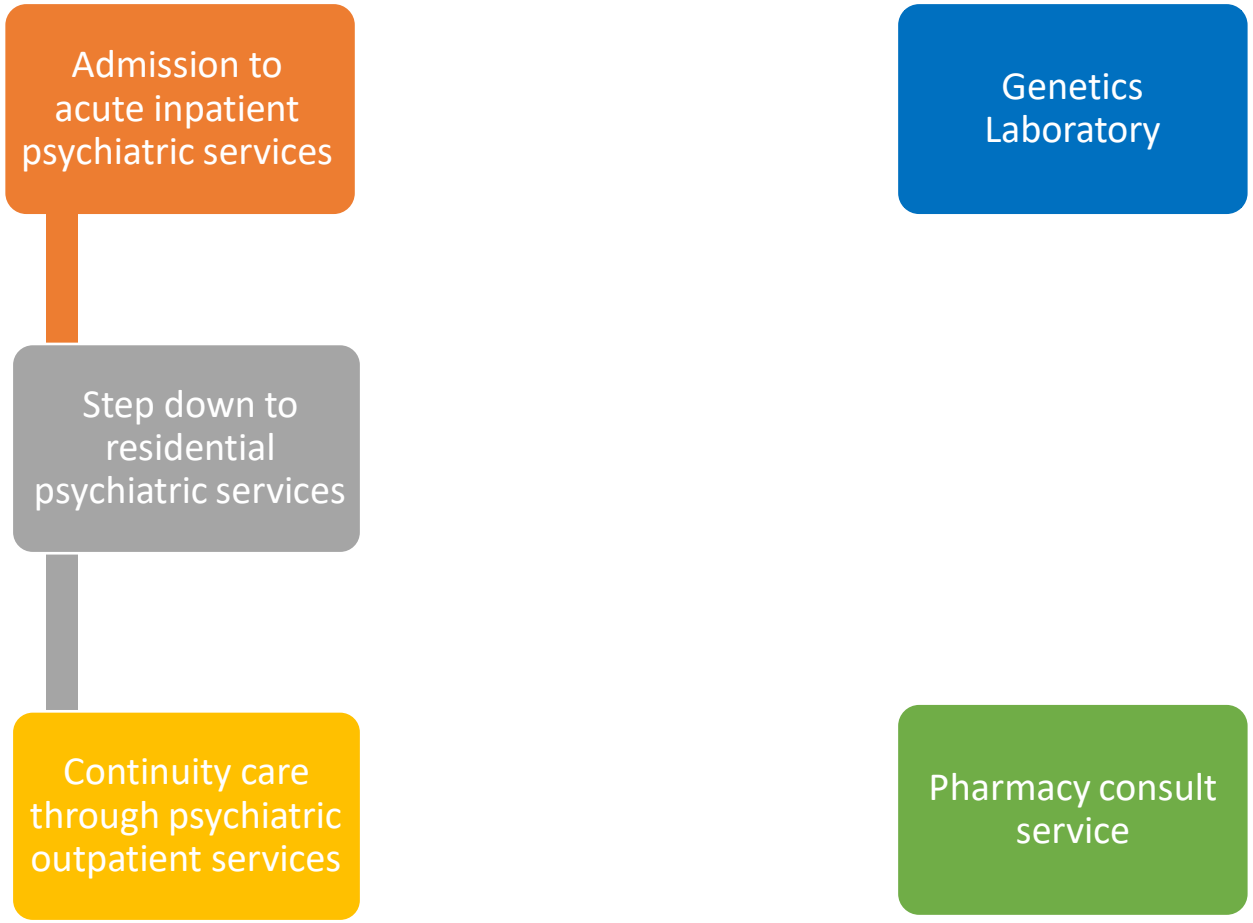
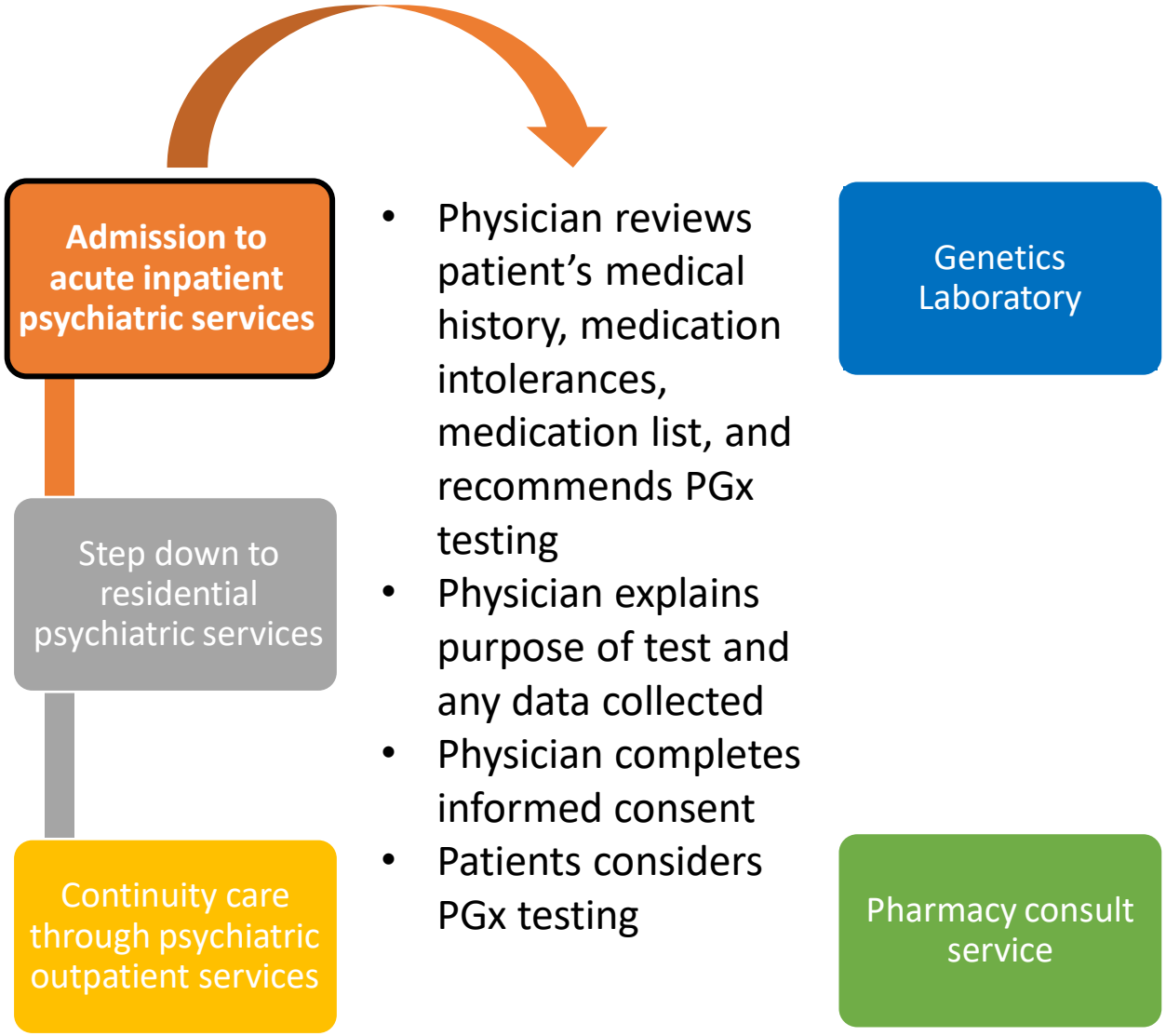
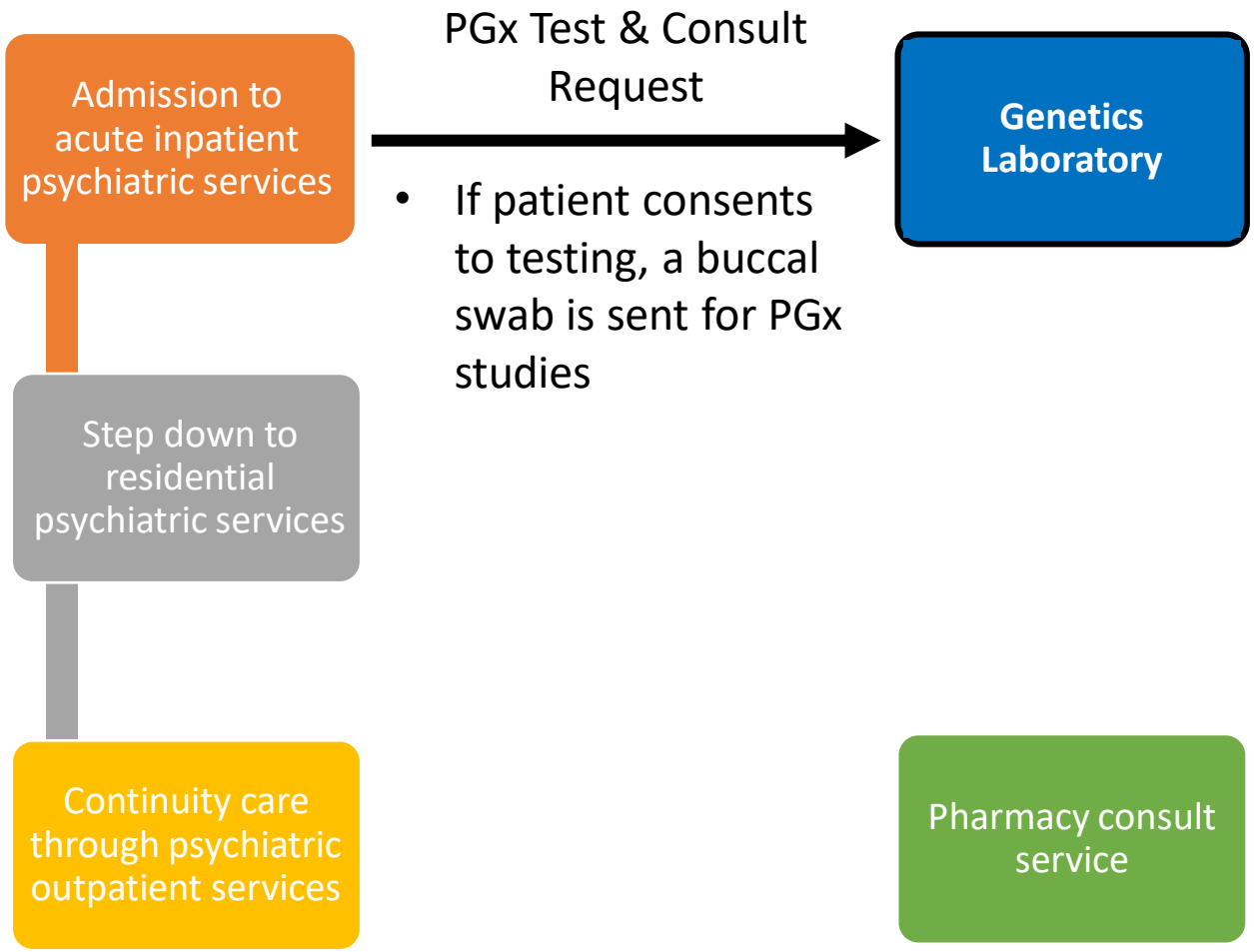
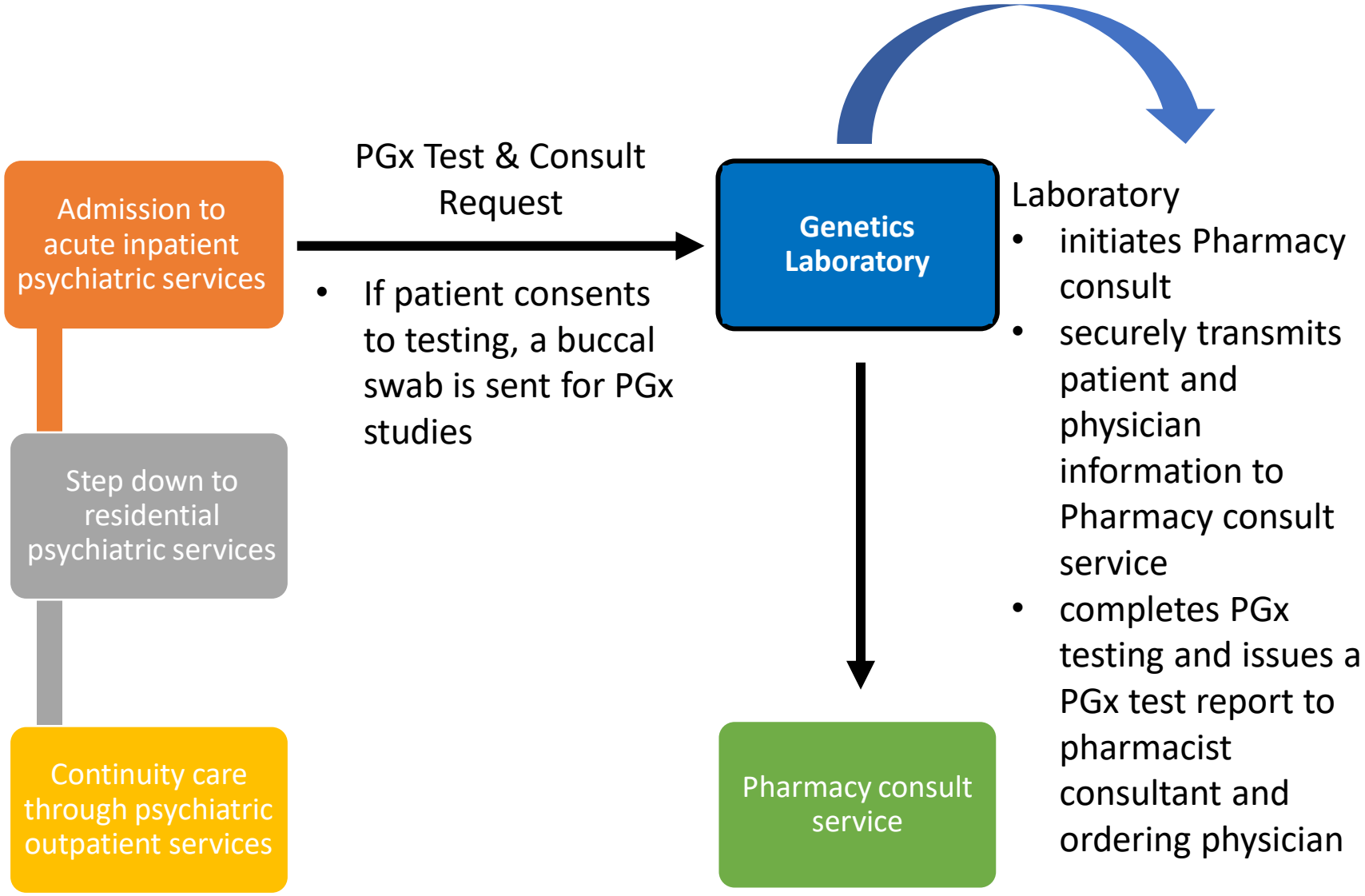
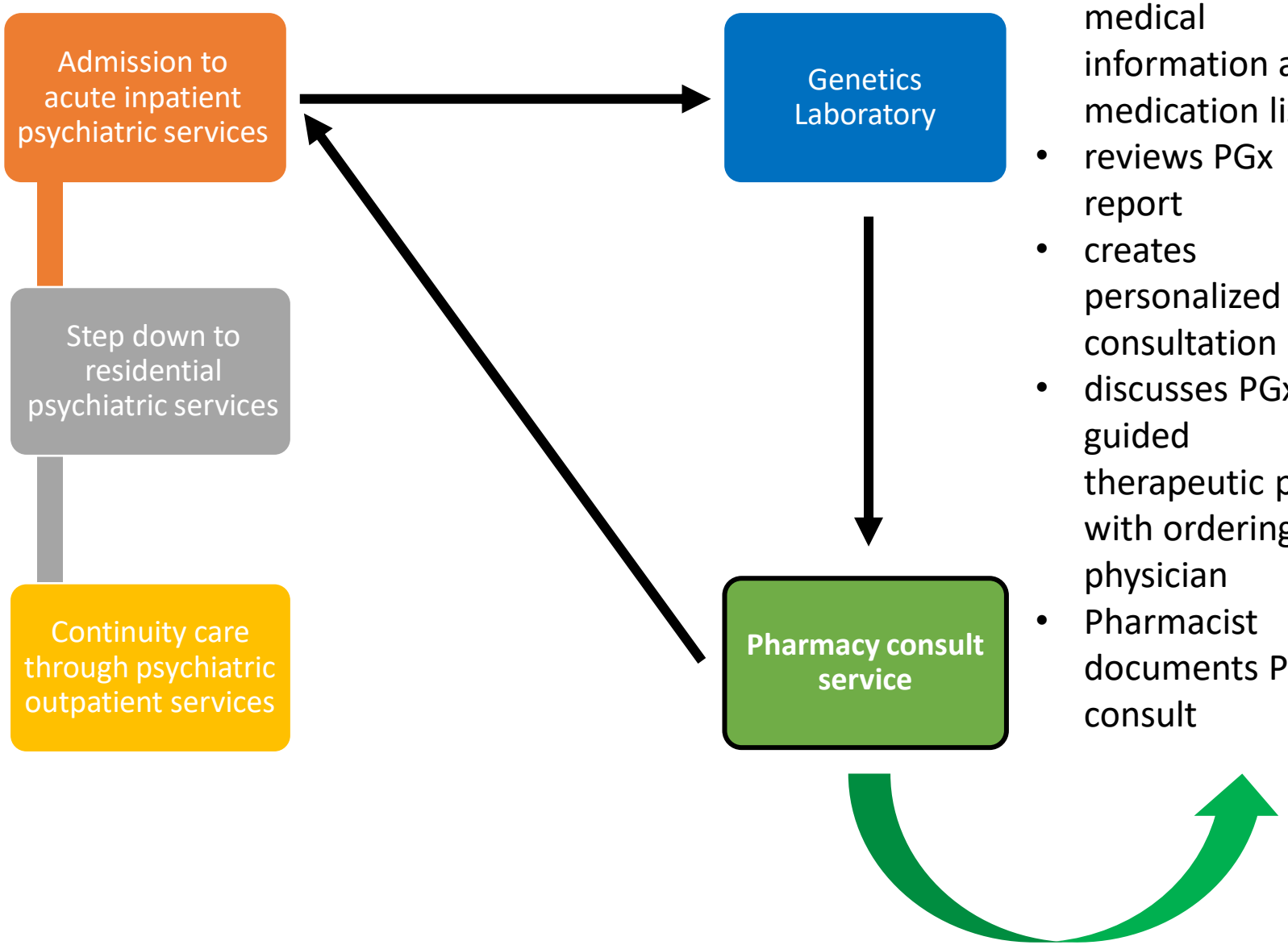
Components of pharmacogenetics implementation




Admission to acute inpatient psychiatric services
Step down to residential psychiatric services
Continuity care through psychiatric outpatient services
• Physician reviews patient's medical history, medication intolerances, medication list, and recommends PGx testing
• Physician explains purpose of test and any data collected
• Physician completes informed consent
• Patients considers PGx testing
Genetics Laboratory
Pharmacy consult service

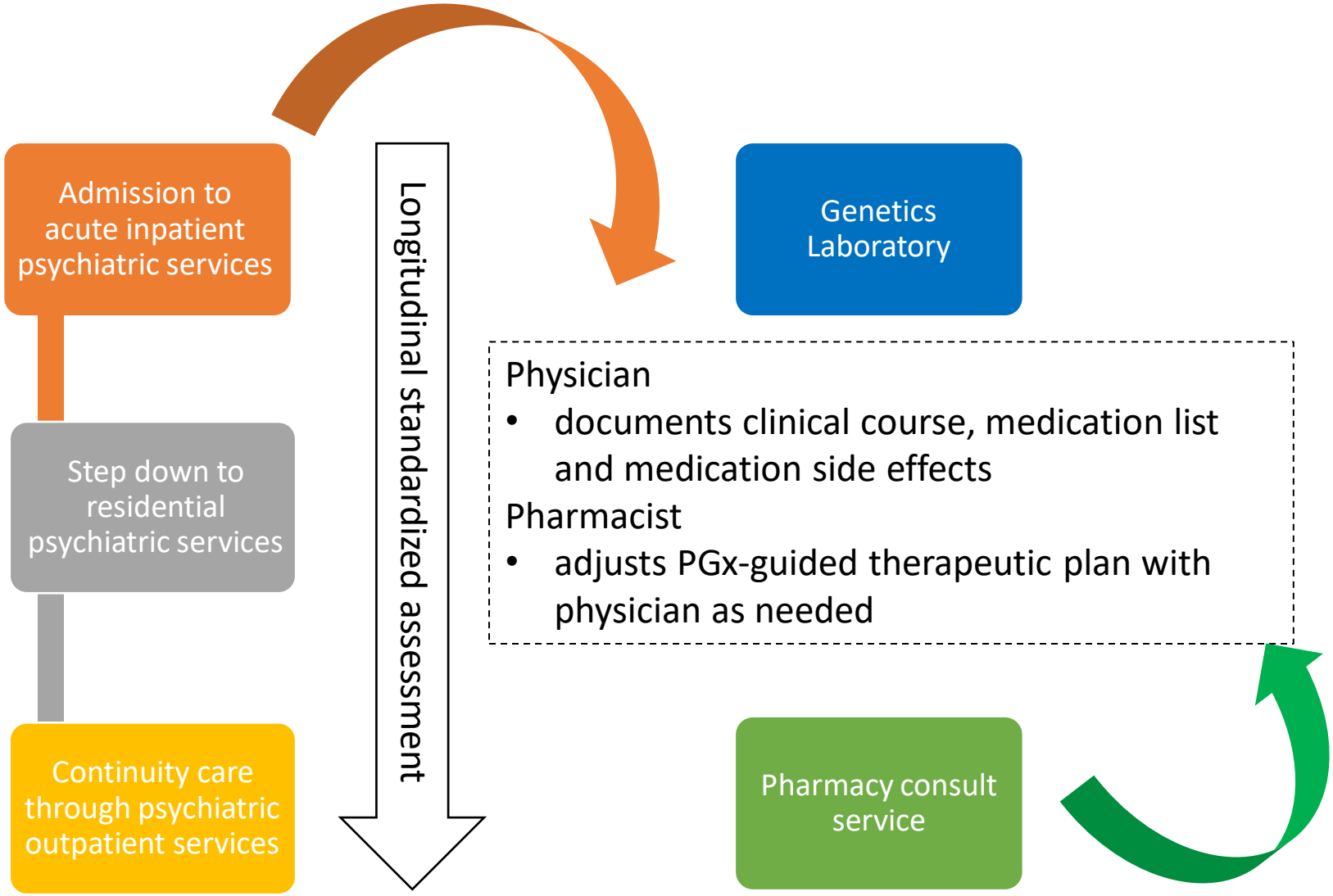

Admission to acute inpatient psychiatric services
PGx Test & Consult Request
Genetics Laboratory
• If patient consents to testing, a buccal swab is sent for PGx studies
Step down to residential psychiatric services
Continuity care through psychiatric outpatient services
Pharmacy consult service


Admission to acute inpatient psychiatric services
Step down to residential psychiatric services
Continuity care through psychiatric outpatient services
PGx Test & Consult Request
If patient consents to testing, a buccal swab is sent for PGx studies
Genetics Laboratory
Laboratory
initiates Pharmacy consult
securely transmits patient and physician information to Pharmacy consult service
completes PGx testing and issues a PGx test report to pharmacist consultant and ordering physician
Pharmacy consult service



Pharmacist

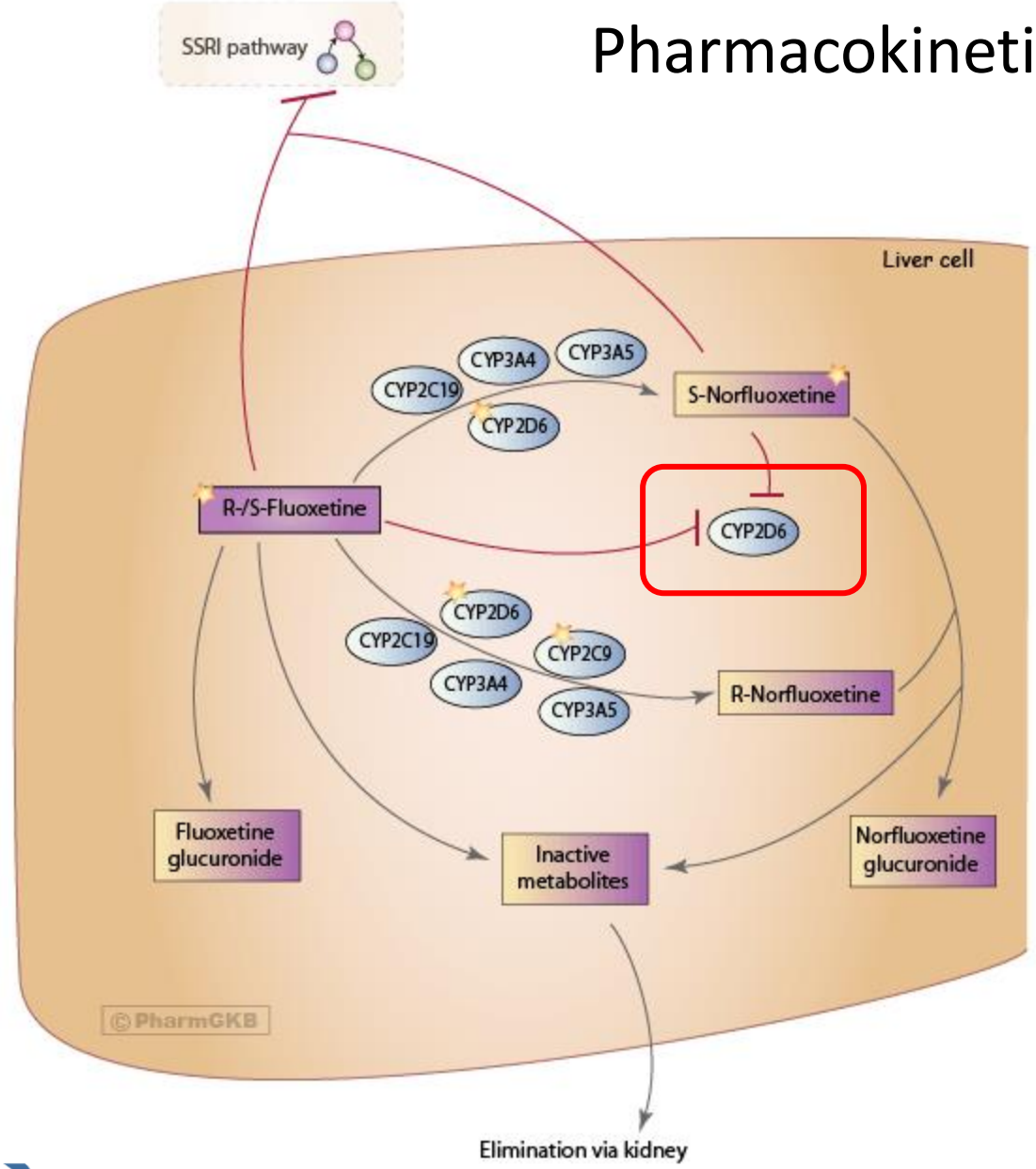
- updates patient's medical information and medication list
- reviews PGx report
- creates personalized PGx consultation
- discusses PGx-guided therapeutic plan with ordering physician
- Pharmacist documents PGx consult


Admission to acute inpatient psychiatric services
Step down to residential psychiatric services
Continuity care through psychiatric outpatient services
Longitudinal standardized assessment
Genetics Laboratory
Physician
• documents clinical course, medication list and medication side effects
Pharmacist
• adjusts PGx-guided therapeutic plan with physician as needed
Pharmacy consult service

CLINICAL VIGNETTE
ANTIANXIETY MEDICATIONS

- A 19-year-old female presented with generalized anxiety disorder (GAD) and panic disorder. She was stable on 30 mg of ***escitalopram***. She developed purpuric patches, and these were thought to be the cause for the purpura.
- She was transitioned to ***fluoxetine*** **(CYP2D6**, CYP2C19**)** after tapering escitalopram. She was able to tolerate 20 mg of the medication; however, her anxiety symptoms were not optimally controlled on this dose of fluoxetine. After an initial concomitant trial with ***buspirone*** **(CYP3A4)** at total daily doses of 30 to 60 mg, she was transitioned to ***clonazepam*** (3A4 partial substrate) 0.5 mg to be used twice daily. The anxiety symptoms did not respond to these additions.
- With increase in dose of ***fluoxetine*** to 40 mg, she developed nausea, vomiting, and fatigue. Side effects continued to persist and gradually became intolerable.
- Pharmacogenomic testing revealed **POOR metabolizer status for CYP2C9** and **ULTRARAPID metabolizer status for CYP2D6.**
- She is started ***venlafaxine extended release*** (**2D6**, 2C19, 3A4). Venlafaxine works well for her. She was stabilized on 150 mg with concomitant ***clonazepam*** (3A4 partial substrate) and continues to do well with optimal control of both anxiety and panic symptoms.

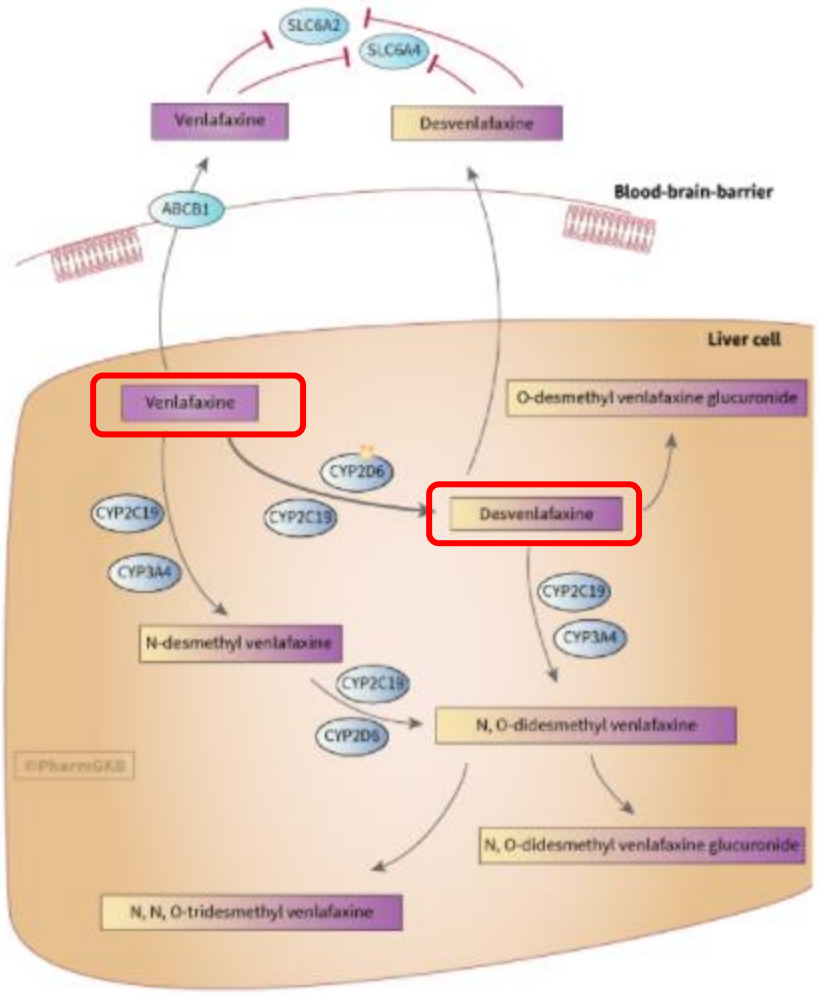
Pharmacokinetics of Fluoxetine



PHARMGKB

https://www.pharmgkb.org/pathway/PA161749012

Pharmacokinetics of Venlafaxine



PHARMGKB

https://www.pharmgkb.org/pathway/PA166014758

Thank you!

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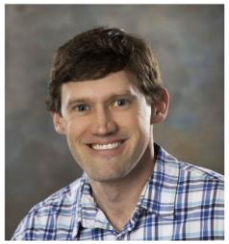
Medical & Laboratory Director



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