Pharmacogenetics Cases: Prescribing Opioids & Antidepressants

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Disclosures

- Melissa Murfin
  - Volunteer member of CPIC
- Jeanine Gargiulo
  - Ethicon
  - Published author in included paper
- Teresa Rogers
  - None

Objectives

1. Explain how genetics plays a role in drug metabolism/response
2. Order appropriate pharmacogenetic testing for a specific patient case
3. Utilize pharmacogenetic prescribing recommendations to optimize choice of opioid medications with clinical correlations to genomic variations
4. Utilize pharmacogenetic prescribing recommendations to optimize choice of antidepressant medications with clinical correlations to genomic variations

PGX Potential

- Minimize drug toxicity
- Maximize drug efficacy
- Predict patients with alternate response to drug intervention
- Help practitioners understand the variability of drug responses
- Assist in drug discovery and development

Pharmacogenetic Prescribing

Decrease potential for adverse drug reactions

Improve likelihood of medication response

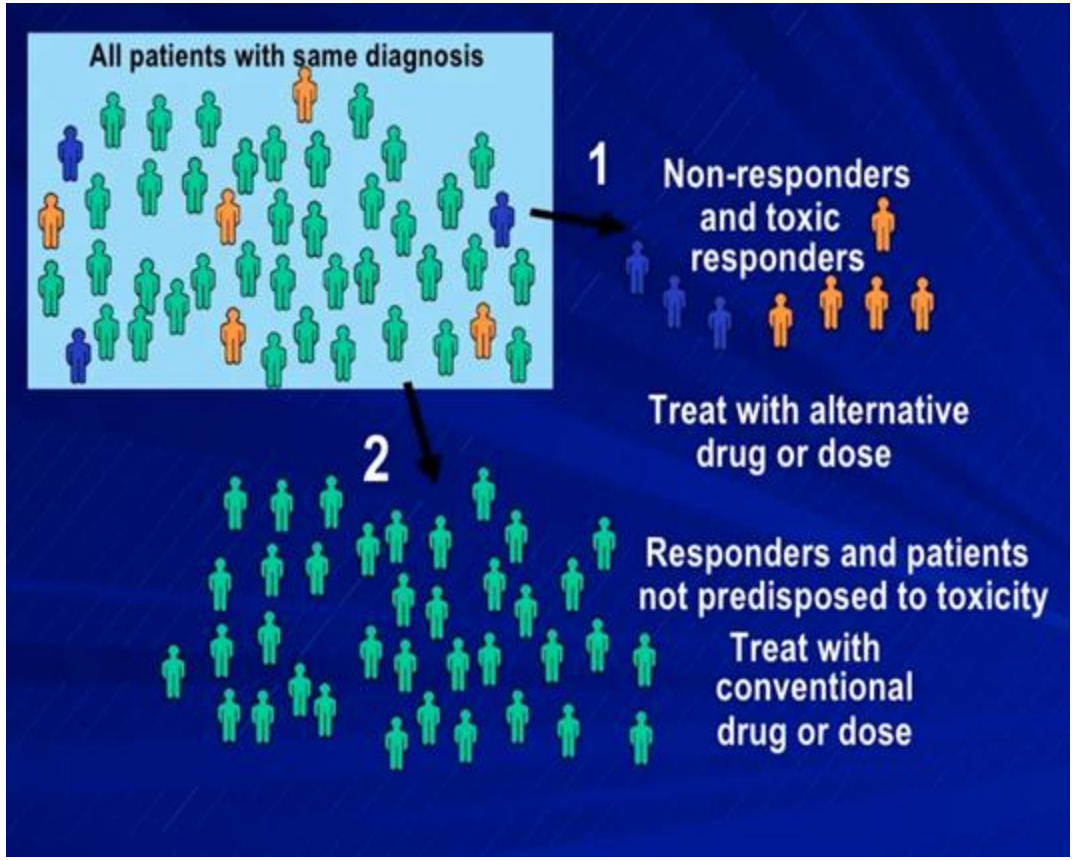
Pharmacogenetic Prescribing

CURRENTLY

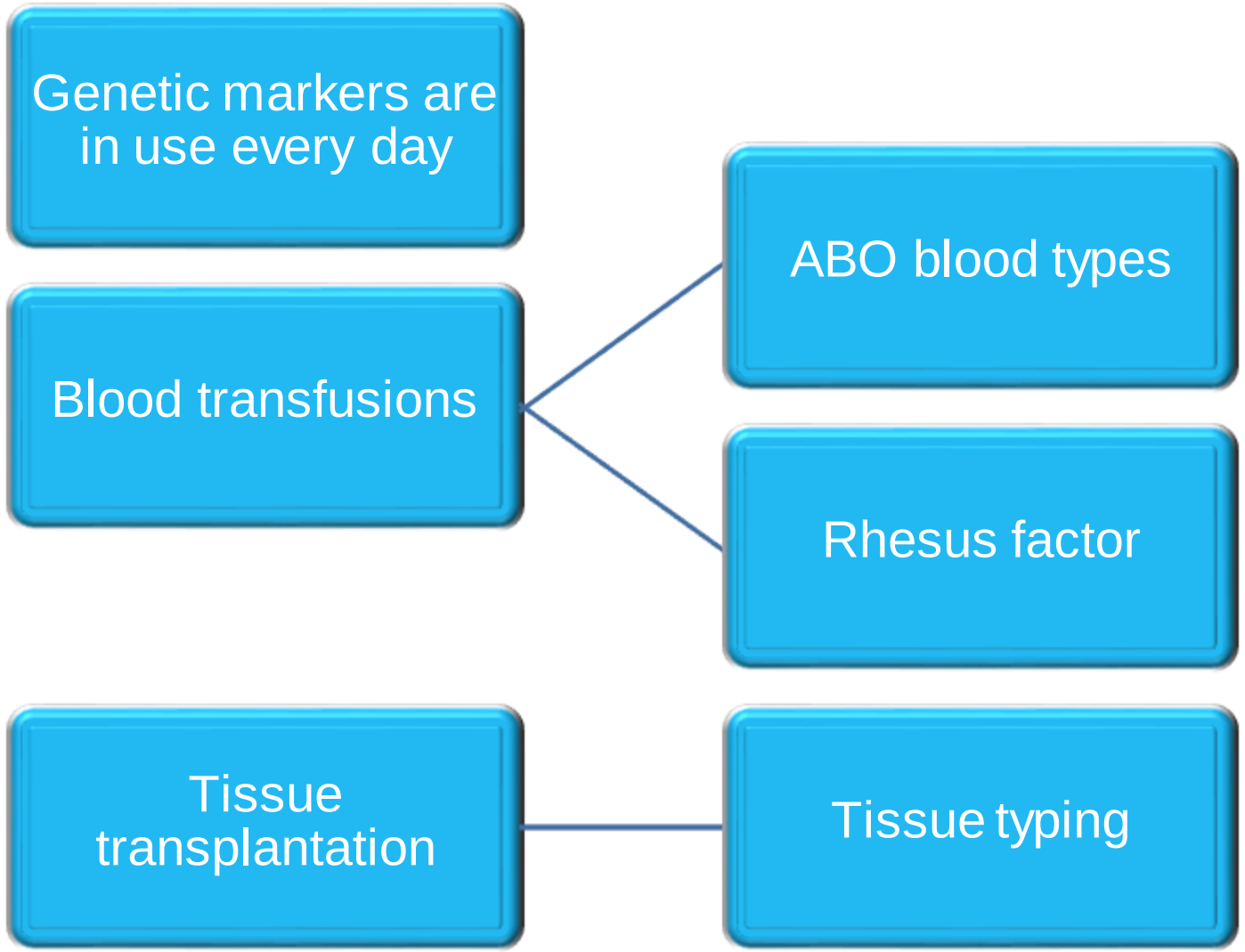
- One size fits all
- Works for up to 40% of patients

CUSTOMIZED

- Drug or dose specifically chosen for the patient
- Ideal for 60% of the of the population
- Decreased risk of ADR



Biomarkers in Practice



Adverse Drug Reactions (ADRs)

- U.S. Emergency Department visits from 2017 – 2019
- National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Report
- 38.6% led to hospitalization
- 6.1 per 1000 due to ADRs

https://pubmed.ncbi.nlm.nih.gov/34609453/

Drug Response

Prodrugs

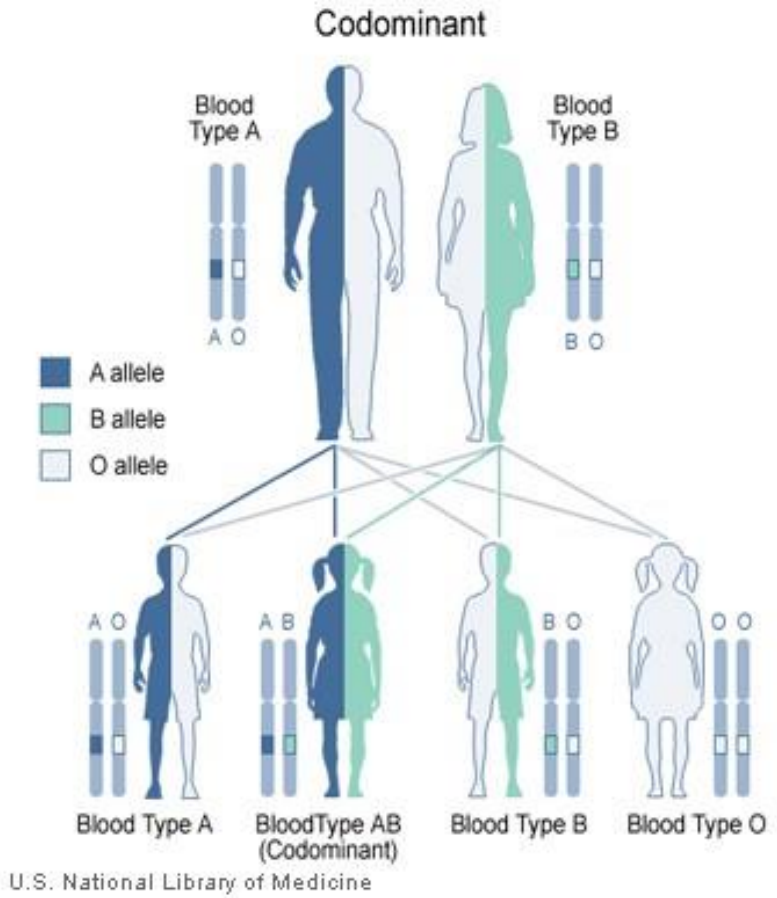
- Clopidogrel (Plavix)
- Codeine

Antidepressants

- 20 – 50 out of 100 patients with symptomatic improvement

https://www.ncbi.nlm.nih.gov/books/NBK361016/#:~:text=Studies%20involving%20adults%20have%20shown,within%20one%20to%20two%20years.

Pharmacogenetics

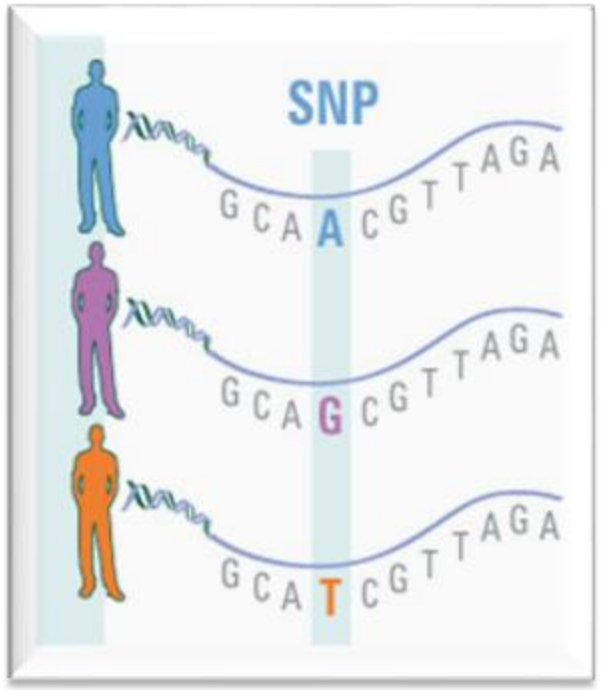


- Polymorphisms
  - Genetic variation among individuals within a specific species or population
  - Promotes genetic diversity
  - Ex: blood types

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

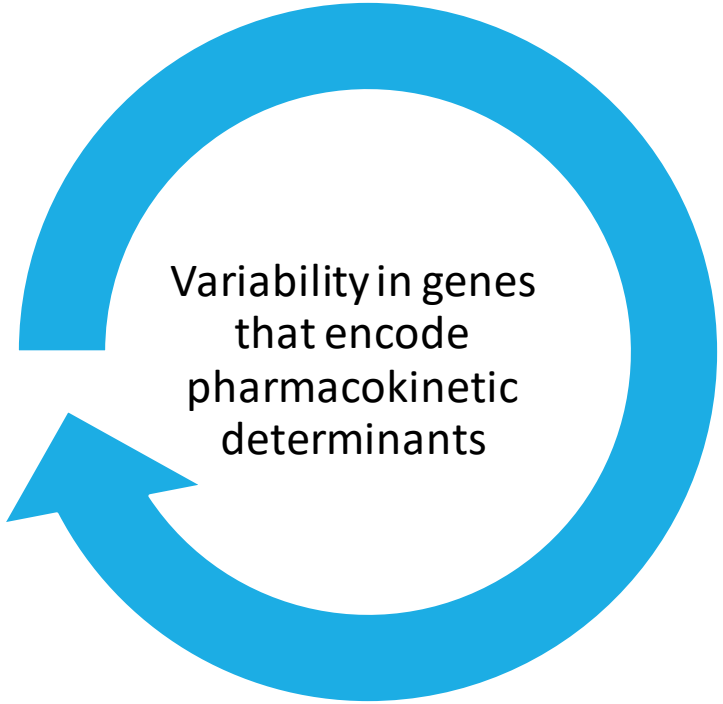
Single Nucleotide Polymorphisms (SNPs)

- 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
- Genotype



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

Pharmacogenetic Phenotypes

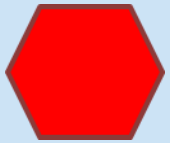
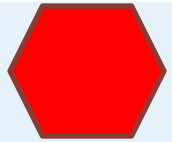


- Metabolizing enzymes
- Determine therapeutic response and ADRs
- Some are monogenic
  - Ex: fast vs slow acetylation
- Some are multigenic
  - Ex: CYP 450 Extensive vs poor metabolizers

Metabolic Phenotypes

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

Clinical Phenotypes

Phenotype	Genotype	Effects	
Extensive metabolizers (EM)	Wild type allele • Homozygous • Heterozygous	• Normal metabolism • No dose modification needed	
Intermediate metabolizers (IM)	Wild type allele • Heterozygous	• May require lower than typical dose	
Poor metabolizers (PM)	Mutation or deletion of both alleles	• Toxicity • Inactivation of prodrug	
Ultrarapid metabolizers (UM)	Gene amplification	• Drug ineffective • Prodrug toxicity	

FDA Table of Pharmacogenetic Associations

- Initially published 2020
- Now includes 300+ drugs
- Pharmacogenetic associations that support therapeutic recommendations
- Evidence-based information on safety or response
- Evidence of only pharmacokinetic impact
- Statins, SSRIs SNRI, beta blockers, PPIs, anticoagulants

CPIC Guidelines

https://cpicpgx.org/

Opioids in PGx

- CYPT2D6
- Codeine, tramadol, hydrocodone, oxycodone, methadone
- Ultrarapid and poor metabolizers

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update

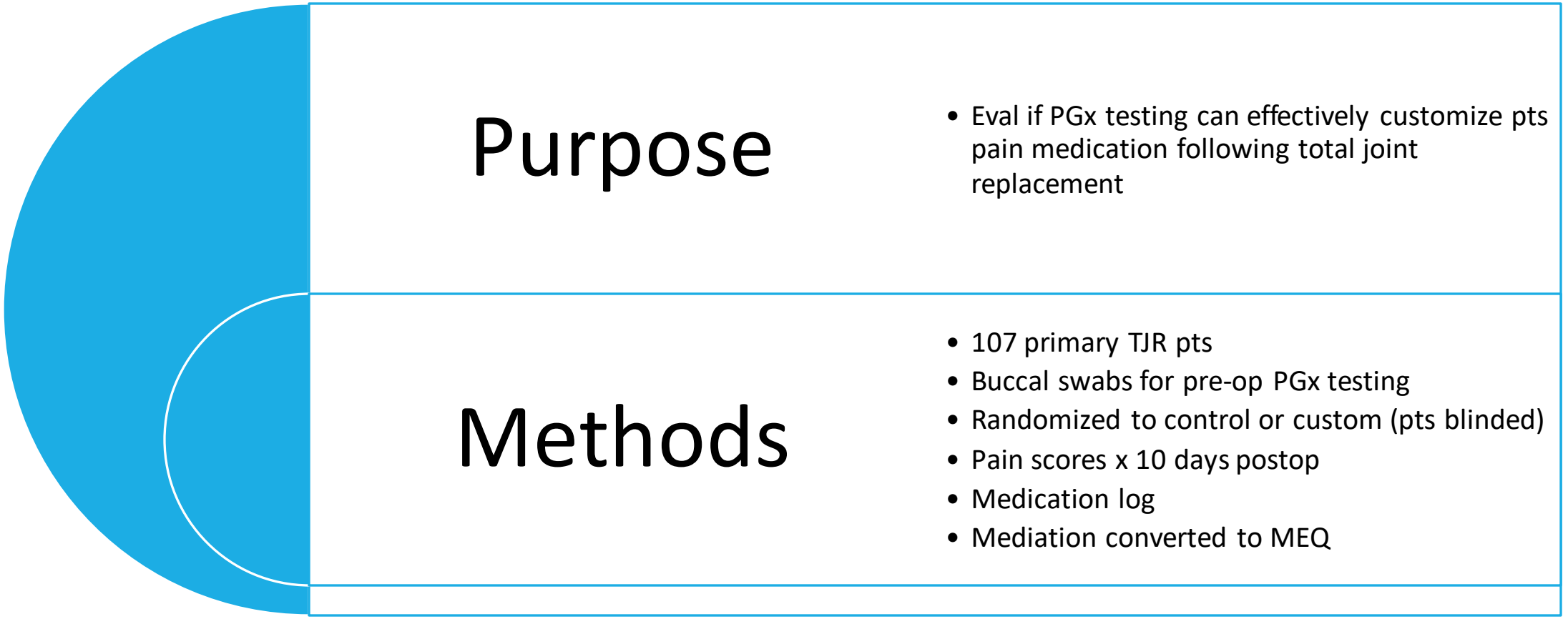
KR Crews[1], A Gaedigk[2,3], HM Dunnenberger[1], JS Leeder[2,3], TE Klein[4], KE Caudle[1], CE Haidar[1], DD Shen[5,6], JT Callaghan[7,8], S Sadhasivam[9,10], CA Prows[11,12], ED Kharasch[13] and TC Skaar[7]

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	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 nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	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 nonopioid 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.[b,c]

Clin Pharmacol Ther. 2014 Apr;95(4):376-82

AORI PGx Study



Opioid Case 1: Control Patient

- Genetic variants in *CYP2D6, CYP2C9*
  - Ultra-rapid metabolizer for tramadol, hydrocodone, oxycodone
  - Intermediate metabolizer for Celebrex

- Standard Rx: tramadol, hydrocodone, Celebrex
  - "Medications never last as long as they say they will"

- Pain levels above 5 all week
- Called POD7 to ask for different meds, changed medication

D1 MEQ	D1 Pain	D2 MEQ	D2 Pain	D3 MEQ	D3 Pain	D4 MEQ	D4 Pain	D5 MEQ	D5 Pain	Thru D10	**Total MEQ**	**Avg pain**
25	6.5	55	7	60	5.5	55	5	60	5	…	520	5.25

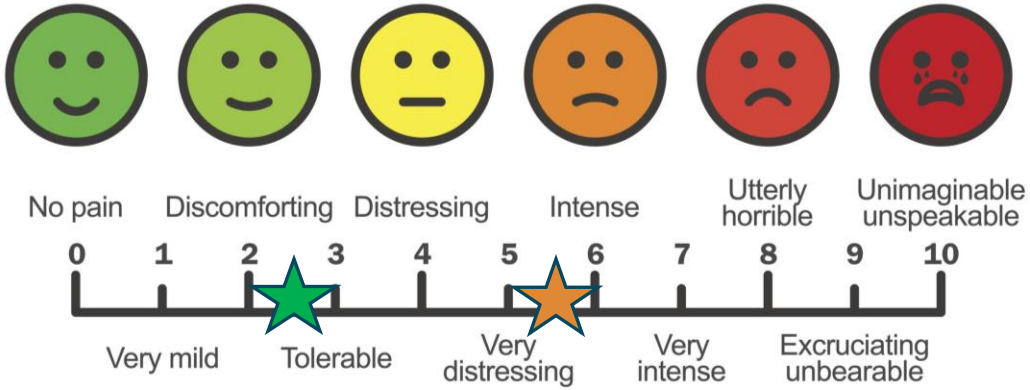
Opioid Case 2: Custom Patient

- Genetic variants in *CYP2D6*
  - Poor metabolizer for tramadol, hydrocodone, oxycodone

- Custom Rx: hydromorphone, Celebrex

D1 MEQ	D1 Pain	D2 MEQ	D2 Pain	D3 MEQ	D3 Pain	D4 MEQ	D4 Pain	D5 MEQ	D5 Pain	Thru D10	**Total MEQ**	**Avg pain**
0	2	24	4	8	3	0	2	0	2	…	32	2.4

Opioid Cases



- Control
  - 10-day total MEQ of 520, **more than twice** the average

D1 MEQ	D1 Pain	D2 MEQ	D2 Pain	D3 MEQ	D3 Pain	D4 MEQ	D4 Pain	D5 MEQ	D5 Pain	**Total MEQ**	**Avg pain**
25	6.5	55	7	60	5.5	55	5	60	5	**520**	**5.25**

- Custom
  - 10-day total MEQ of 32, **less than most daily** MEQ for control patient

D1 MEQ	D1 Pain	D2 MEQ	D2 Pain	D3 MEQ	D3 Pain	D4 MEQ	D4 Pain	D5 MEQ	D5 Pain	**Total MEQ**	**Avg pain**
0	2	24	4	8	3	0	2	0	2	**32**	**2.4**

AORI PGx Study

Control

- 4.2 avg pain score
- 162.6 MEQ

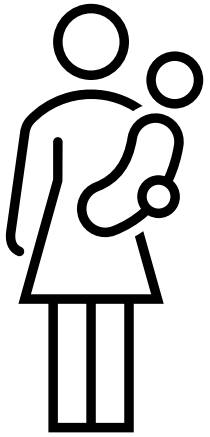
Custom

- 3.1 avg pain score
- 86.7 MEQ

- 24/107 (22.4%) had genetic variations
- Custom postop pain prescribing based on PGx testing **can** achieve lower pain levels while *reducing* consumption of pain medication

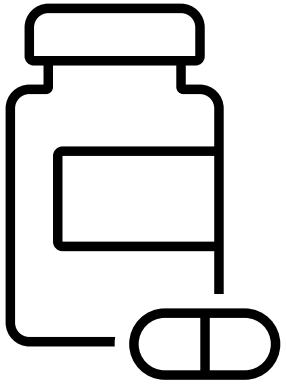
Antidepressant Case

History



Family history:
Mother w/
history of MDD
Treated with Prozac

Psychiatric History:
Various psychiatrists
Treated for MDD
No psychotherapy



Medications:
Trials of Fluoxetine,
Escitalopram, and
Venlafaxine

Social History

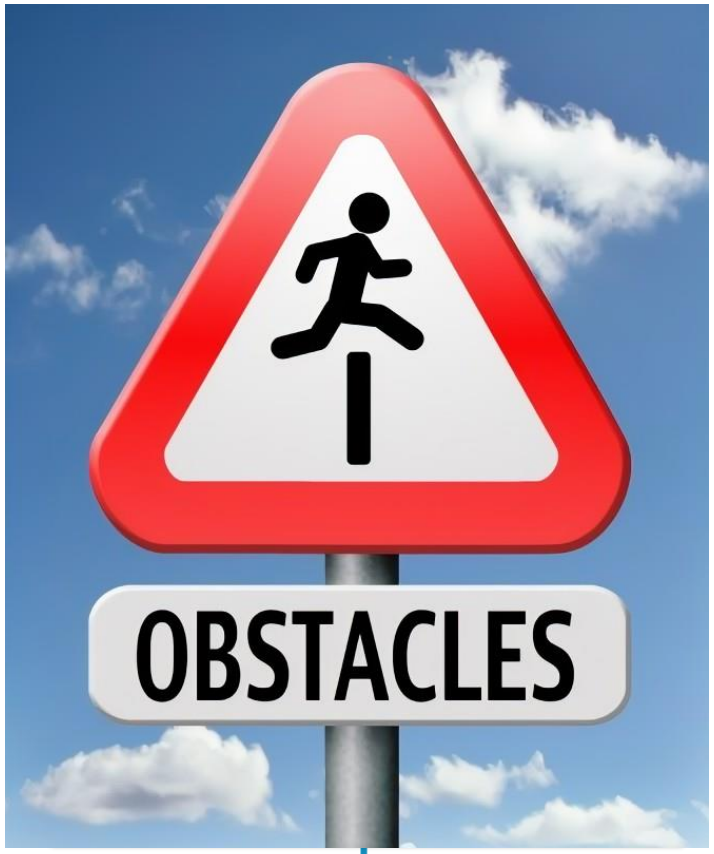
Further Evaluation

Physical examination unremarkable

Mental status exam

Labs

- Thyroid function tests - wnl
- CBC - wnl
- CMP- wnl
- Urinalysis - negative
- Urine toxicology screen – negative
- Vitamin D - low



- Low understanding of anti-depressants
- Lack of confidence in efficacy in any medication
- Past trials of multiple different medications
- Poor follow up

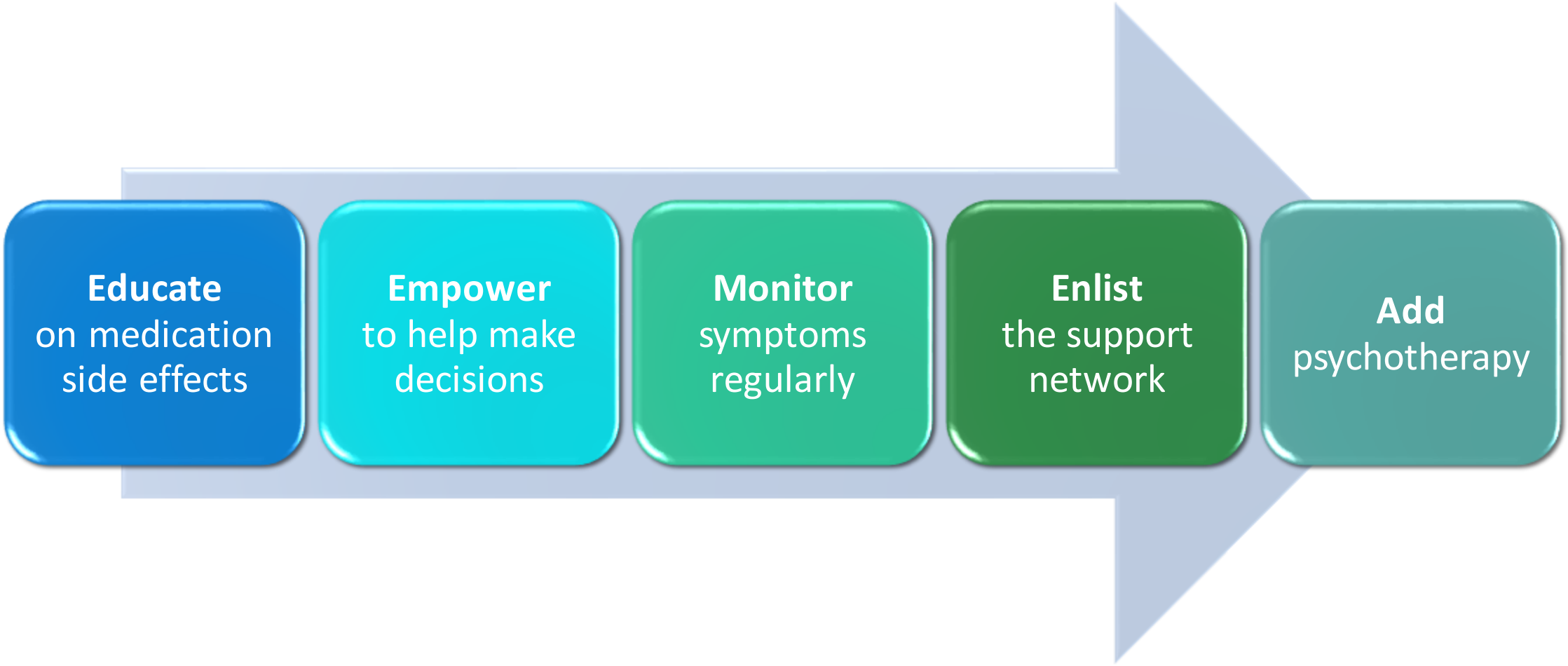
ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
desvenlafaxine (Pristiq®)	**bupropion** (Wellbutrin®)	1	**fluoxetine** (Prozac®)	1,6
levomilnacipran (Fetzima®)	**desipramine** (Norpramin®)	1	**paroxetine** (Paxil®)	1,4,6
selegiline (Emsam®)	**doxepin** (Sinequan®)	1		
vilazodone (Viibryd®)	**nortriptyline** (Pamelor®)	1		
	venlafaxine (Effexor®)	1		
	vortioxetine (Trintellix®)	1		
	citalopram (Celexa®)	4		
	escitalopram (Lexapro®)	4		
	sertraline (Zoloft®)	4		
	duloxetine (Cymbalta®)	2,7		
	fluvoxamine (Luvox®)	2,7		
	amitriptyline (Elavil®)	3,7		
	clomipramine (Anafranil®)	3,7		
	imipramine (Tofranil®)	3,7		
	mirtazapine (Remeron®)	3,7		
	trazodone (Desyrel®)	3,7		

Past medication trials:

- Sertraline 150mg PO daily
- Fluoxetine 60mg PO daily
- Venlafaxine – unknown dose and duration

Where Do We Go From Here?



Symptom Monitoring

- Depressed mood
- Anhedonia (loss of interest)
- Low energy
- Sleeping difficulties
- Feelings of hopelessness
- Decreased appetite
- Excessive guilt feelings

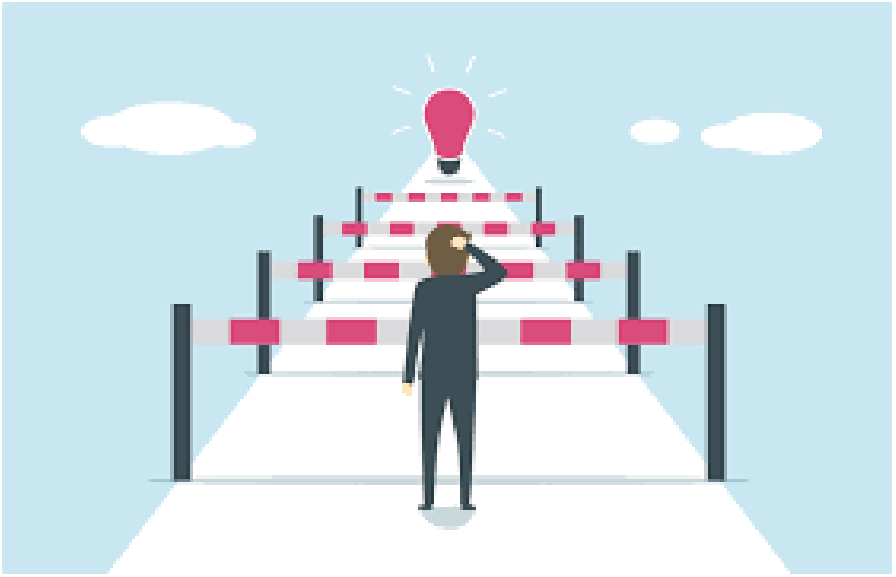
Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the qu

1.
   0 I do not feel sad.
   1 I feel sad
   2 I am sad all the time and I can't snap out of it.
   3 I am so sad and unhappy that I can't stand it.
2.
   0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel the future is hopeless and that things cannot improve.
3.
   0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failures.
   3 I feel I am a complete failure as a person.
4.
   0 I get as much satisfaction out of things as I used to.
   1 I don't enjoy things the way I used to.
   2 I don't get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.
5.
   0 I don't feel particularly guilty
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.
6.
   0 I don't feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.
7.
   0 I don't feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.
8.
   0 I don't feel I am any worse than anybody else.
   1 I am critical of myself for my weaknesses or mistakes.
   2 I blame myself all the time for my faults.
   3 I blame myself for everything bad that happens.
9.
   0 I don't have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.
10.
   0 I don't cry any more than usual.
   1 I cry more now than I used to.
   2 I cry all the time now.
   3 I used to be able to cry, but now I can't cry even though I want to.

Barriers

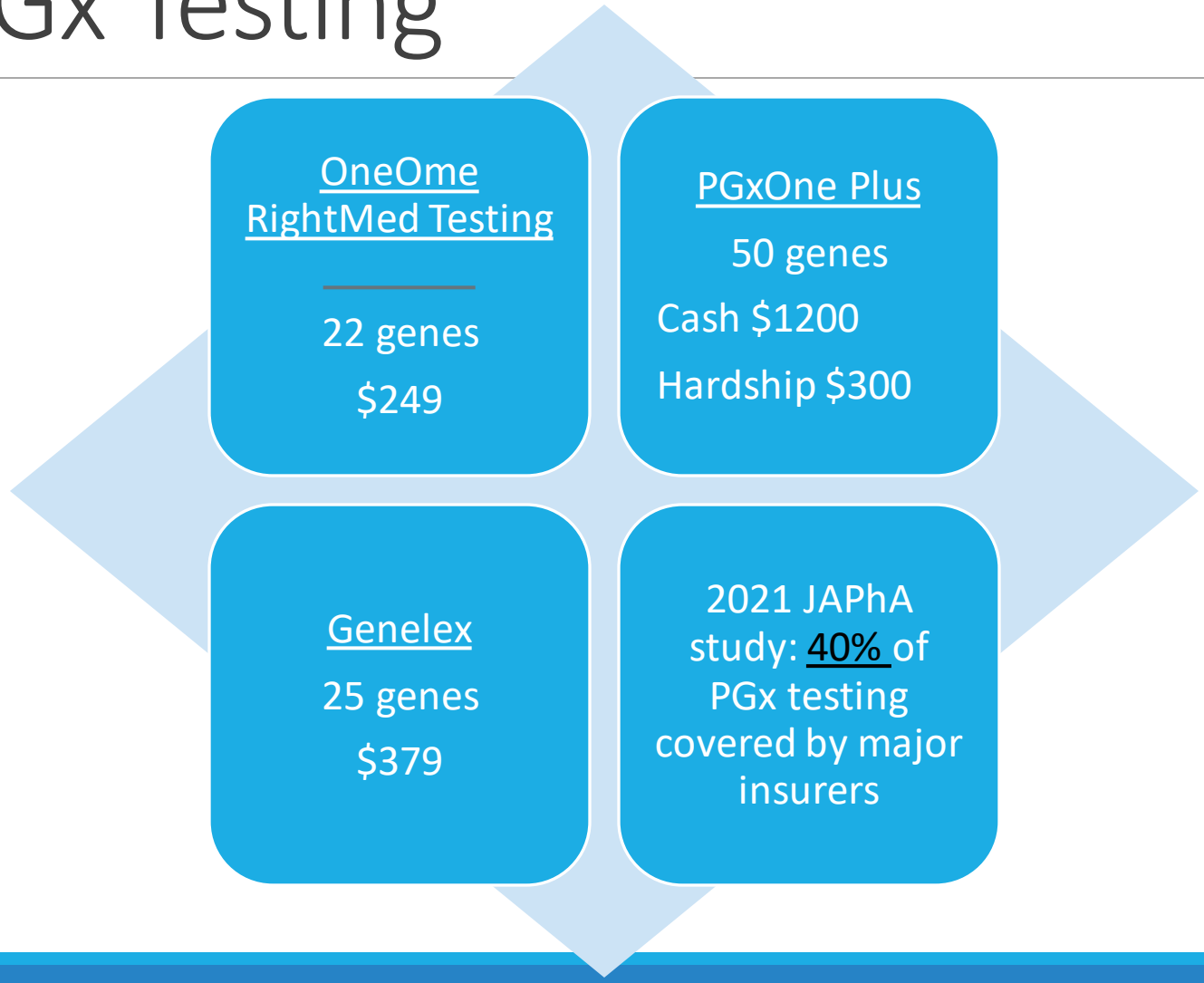
- Who will pay?
- Proactive vs reactive testing
- Validity of testing
  - Direct to consumer options
- Funding and resource allocation



PGx Lab Testing Options

- Single Gene
- LabCorp
- Quest
- Point of care
- Spartan Rx
- Luminex
- Multigene
- OneOme
- Invitae
- GeneSight

PGx Testing

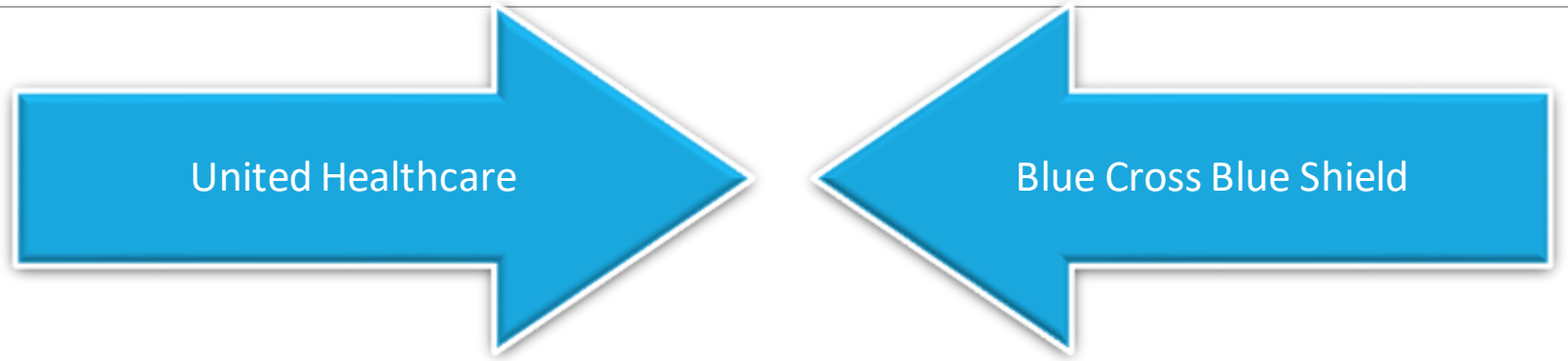


CPT Codes

2C19 81225	2D6 81226
2C9 81227	3A4/5 81401
SLCO1B1 81479	

https://www.sciencedirect.com/science/article/abs/pii/S1544319119304522

Insurance Coverage



- Psychiatric medication pharmacogenetic testing:
  - Pt with MDD or GAD diagnosis
  - Pt has failed at least one antidepressant
  - Specific multigene panels

- CYP2D6, CYP2C9, and CYP2C19 for specific medications
- PGx testing for warfarin
- Once per lifetime

Questions?