A Pharmacist's Introduction to Clinical Pharmacogenomics

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OBJECTIVES

Pharmacists

- Describe common pharmacodynamic and pharmacokinetic variants that may affect medication efficacy and safety
- Develop individualized drug regimens based on a given pharmacogenomics profile
- Establish a process of retrieving and analyzing pharmacogenetic research and guidelines

Technicians

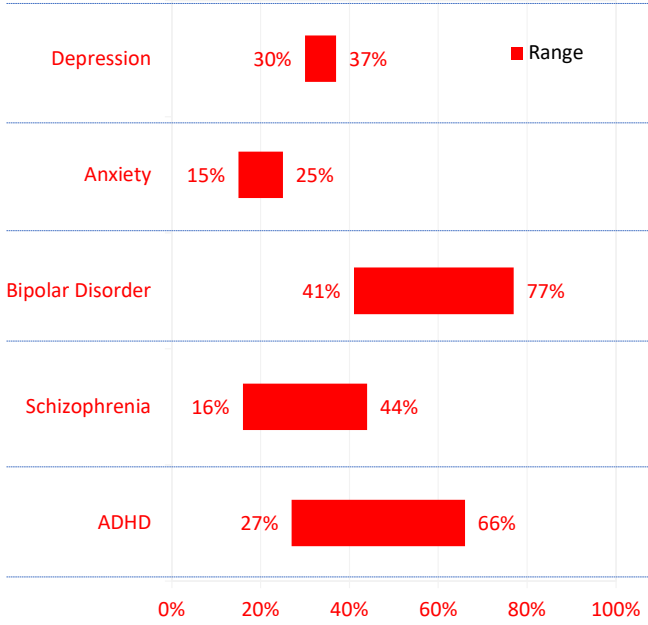
- Identify situations in which obtaining a pharmacogenetic test would be useful
- Understand the utility of pharmacogenetic testing for drug safety and efficacy
- Review some legal, ethical and social issues surrounding pharmacogenetic testing

WHY DO WE TEST?

- How does genetic variation contribute to changes in drug kinetics, dynamics, and toxicity?
- Use this information to guide optimal drug selection and dosing to maximize efficacy and minimize adverse effects

TREATMENT AS USUAL…

Initial Remission Rate



Treatment Resistance / Relapse

50% of patients do not respond to first-line therapies or experience severe adverse reactions
30% treatment resistant following 4 treatments [1]

Recurrence in up to 50% [5,6]

50-70% relapse rates [2,4]

>75% of patients discontinued medication within 18 months [3]

ADHD can persist in about 65% of adults diagnosed as children [7]

STAR-D: NIMH; STEP-BD: NIMH; CATIE:NIMH; Perry et al. (1999); Angst et al. (2009); Yonkers et al. (1996); Faraone et al. (2006)

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PHARMACOGENETIC (PGX) BASICS

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TERMINOLOGY

- Pharmacogenetics- study the relationship between variations in a single gene and variability in drug disposition, response and toxicity
- Pharmacogenomics- study of the relationship between variations in a large collection of genes (up to the whole genome) and variability in drug disposition, response and toxicity

- Genome- organisms complete set of DNA, including all of its genes, regulatory elements, and other nucleotide sequences

  [BOOK]
- Chromosome- single piece of DNA containing many genes regulatory elements and other nucleotide sequences

  [CHAPTER]
- Gene- region of DNA that contains the code for biological component, usually a protein

  [SENTENCE]
- Nucleotide- building blocks of DNA

  [ALPHABET LETTER]

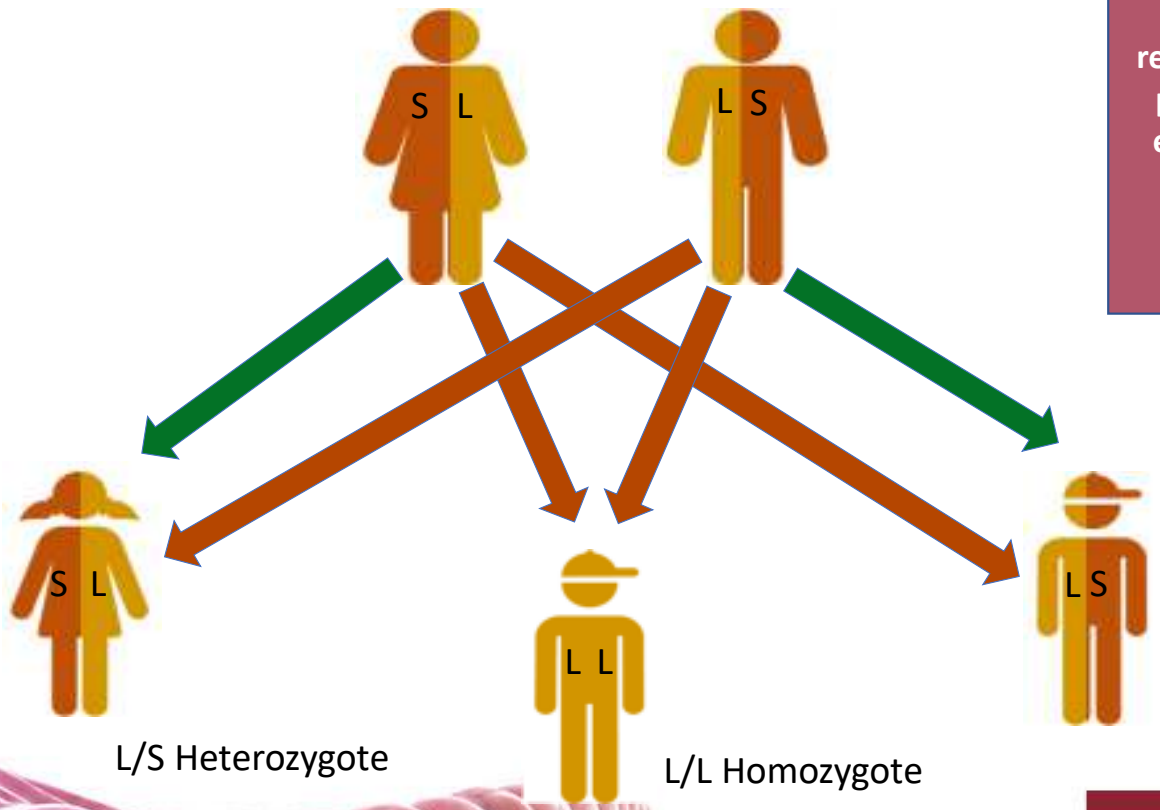
MORE TERMINOLOGY

- Estimated around 3 billion DNA base pairs with varying estimates of 20,000-30,000 genes

- Genetic variant- difference in the DNA sequence compared with a reference sequence
- Polymorphism- genetic variant that is common, often defined as 1% or more of the population
- Mutation- genetic variant that is rare, often define as less than 1% of the population

ALLELE INHERITANCE

Alleles are different variants of a gene. Humans are diploid organisms and receive one allele from each parent. We do not inherit entire intact chromosome from each parent due to recombination



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POTENTIAL CLINICAL OUTCOMES

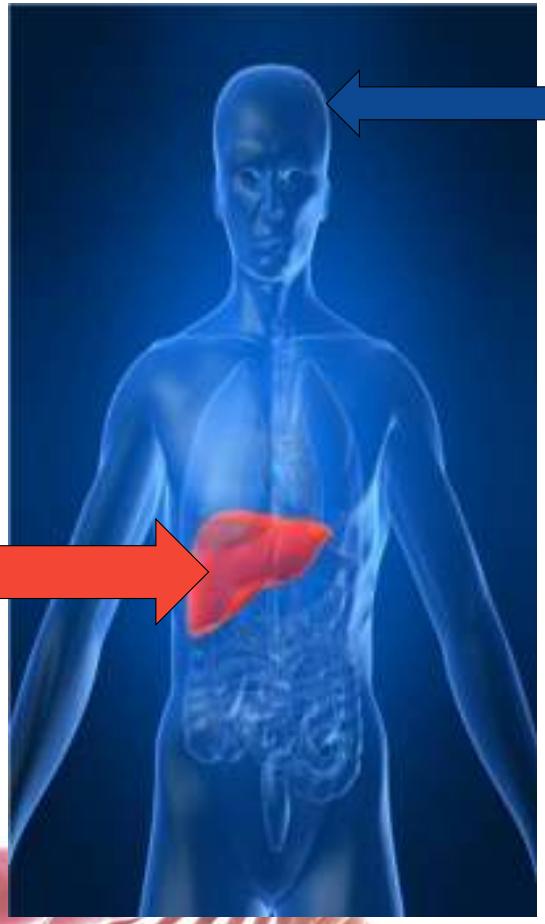
Phenotype	Active Parent Drug	Prodrugs
(PM) DDDD → M	➢ Increased efficacy, toxicity ➢ Consider lower doses	➢ Decreased efficacy, toxicity (?) ➢ Consider higher doses
(IM) DDDD → MMm	➢ Possible increased efficacy , toxicity ➢ +/- lower doses	➢ Possible decreased efficacy, toxicity ➢ +/- lower doses
(EM) DDDD → MMM	Average efficacy & toxicity (if known)	Average efficacy & toxicity (if known)
(UM) DDDD → MMMMmmm	➢ Decreased efficacy, toxicity ➢ Consider higher doses	➢ Increased efficacy, toxicity ➢ Consider lower doses

REMEMBER some drugs have multiple metabolites and phases!

CANDIDATE GENES: KINETIC VS. DYNAMIC

Pharmacokinetic Genes:

CYP3A4/5
CYP2D6
CYP2C19
CYP1A2
CYP2B6
CYP2C9
UGT
ABCB1



Pharmacodynamic Genes:

SLC6A4
COMT
ADRA2A
DRD2
MC4R
5HT2A
5HT2C
OPRM1
GRIK1
MTHFR
BDNF
HLA-A/B

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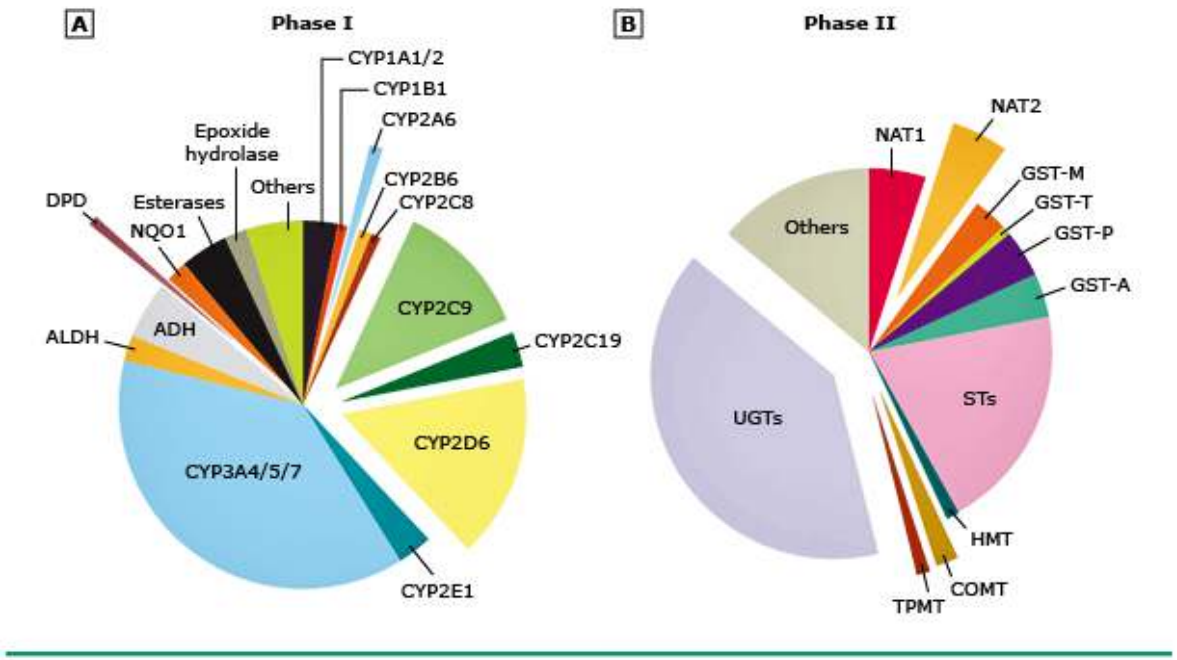
Häggström, M. (2014). Medical gallery of Mikael Häggström 2014. *WikiJournal of Medicine* 1 (2). DOI 10.15347/wjm/2014.008. ISSN 20018762.

VARIABILITY

Drug-metabolizing enzymes exhibiting clinically relevant genetic polymorphisms



- General population has 40-60% phenotype variability
- CYP450 enzymes most frequently involved
- Genetic differences impact 25% of all drugs

Cavallari LH, Limdi NA. *Curr Opin Mol Ther*. 2009 Jun;11(3):243-51.
Lynch T, Price A. *Am Fam Physician*. 2007; 76(3):391-6.
Ma JD, Lee KC, Kuo GM. *J Pharm Pract*. 2012 Aug;25(4):417–27.
Evans WE, Relling MV. Science 1999; 286:487.

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DISCLAIMER SLIDE!

- It is estimated that 42% of antidepressant response is due to genetic variation
- That means 58% is due to environment:
  - Adherence
  - Placebo effect
  - Access to medications and quality providers

- <u>Do not overestimate the influence genetic variants have on treatment outcomes</u>
- <u>Make reasonable recommendations based on best available evidence</u>

PHARMACOGENETIC LITERATURE SEARCH
(interested and want MORE…?)

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BIG PLAYERS?

- CPIC- Clinical Pharmacogenetics Implementation Consortium
  - CPIC creates dosing guidelines for many drugs (SSRIs, TCAs, Anticoagulants, etc.)
  - https://cpicpgx.org/
- PharmGKB- Pharmacogenomics Knowledge Base
  - Aggregates PGx literature
  - Levels of evidence
  - https://www.pharmgkb.org/
- FDA guidance
  - FDA maintains a list of actionable genetic biomarkers (over 200 drugs)
  - https://www.fda.gov/downloads/Drugs/ScienceResearch/UCM578588.pdf

OTHERS TO CONSIDER

- DPWG (Dutch Pharmacogenetic Working Group)
- Professional societies with their own recommendations for relevant gene-drug pairs
  - American College of Rheumatology and allopurinol
- Clinical Genome Resource (GlinGen)
- Swiss Agency of Therapeutic Products (Swissmedic)
- European Medicine Agency (EMA)

CPIC

https://cpicpgx.org/

*CPIC assumes clinicians will HAVE patients' genotypes available

- Consensus guidelines indexed by PubMed
- Endorsed and referenced by numerous clinical organizations (ex: APHA)
- Standardized guideline format
- Grading of evidence recommendations Peer reviewed
- Free to access
- Guideline updates with new evidence published
- Guidelines help with HOW a test result should be used to optimize drug and NOT if a patient qualifies for a test

CPIC™ Clinical Pharmacogenetics Implementation Consortium

Published 25 guidelines and 12 updates, covering 20 genes and > 61 drugs

2011

- *TPMT* – thiopurines
- *CYP2C19*– clopidogrel
- *CYP2C9, VKORC*1 – warfarin

2012

- *CYP2D6* – codeine
- *HLA-B* – abacavir
- *SLCO1B1* – simvastatin

2013

- *HLA-B* – allopurinol
- *CYP2D6, CYP2C19* – TCAs
- *HLA-B* – carbamazepine
- *DPYD* -- 5FU / capecitabine
- *TPMT* – thiopurines—UPDATE
- *CYP2C19* – clopidogrel--UPDATE

https://cpicpgx.org/guidelines/

2014

- *IL28B* -- PEG interferon α
- *CFTR* -- Ivacaftor
- *G6PD* -- Rasburicase
- *CYP2C9, HLA-B* -- Phenytoin
- *CYP2D6* – codeine--UPDATE
- *HLA-B* – abacavir--UPDATE
- *SLCO1B1* – simvastatin—UPDATE

2015

- *CYP3A5* – tacrolimus
- *CYP2D6*, *CYP2C19*– SSRIs
- *UGT1A1* – atazanavir
- *HLA-B* – allopurinol—UPDATE

2016

- *CYP2C19* – voriconazole
- *CYP2D6* – ondansetron
- *CYP2C9, VKORC*1 – warfarin--UPDATE
- *CYP2D6, CYP2C19* – TCAs--UPDATE

https://cpicpgx.org/resources/

2017

- *CYP2D6* – tamoxifen
- *HLA-B* – carbamazepine—UPDATE
- *DPYD* -- 5FU / capecitabine—UPDATE-in review

2018

- *RYR1/CACNA1S*– inhaled anesthetics
- *TPMT/NUDT15* – thiopurines—UPDATE

2019

- *CYP2B6*—efavirenz-published
- *CYP2D6*—atomoxetine-published
- *CYP2C9*/NSAIDS-published

2020

- *CYP2C19*/PPI-published
- *CYP2C9*/HLA-phenytoin—UPDATE-published
- *CYP2D6*/opioids-UPDATE
- *CYP2C19*/clopidogrel-UPDATE
- *mtRNR1*/aminoglycosides
- *SLCO1B1*/statins-UPDATE
- *G6PD*/rasburicase -UPDATE (will include additional drugs)
- *CYP2D6-CYP2C19*/SSRI-UPDATE

25 guidelines; 20 genes and > 60 drugs

CPIC™ Clinical Pharmacogenetics Implementation Consortium

- *TPMT, NUDT15*
  - MP, TG, azathioprine
- *CYP2D6*
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs, tamoxifen, SSRIs, ondansetron, tropisetron, atomoxetine
- *CYP2C19*
  - TCAs, clopidogrel, voriconazole, SSRIs, PPIs
- *VKORC1*
  - Warfarin
- *CYP2C9*
  - Warfarin, phenytoin, NSAIDs
- *CYP4F2*
  - Warfarin
- *HLA-B*

  --Allopurinol, CBZ, Oxcarbazepine, abacavir, phenytoin
- *HLA-A*
  - CBZ

- *CFTR*

  -- Ivacaftor
- *DPYD*
  - 5FU, capecitabine, tegafur
- *G6PD*
  - Rasburicase
- *UGT1A1*
  - Atazanavir
- *SLCO1B1*
  - Simvastatin
- *IFNL3 (IL28B)*
  - Interferon
- *CYP3A5*
  - Tacrolimus
- *CYP2B6*
  - Efavirenz
- *RYR1, CACNA1S*
  - Inhaled anesthetics
- *mtRNR1* (in progress)
  - aminoglycosides

https://cpicpgx.org/guidelines/

https://cpicpgx.org/resources/

CPIC

- Interested in joining?
  - https://cpicpgx.org/members/
- Over 400 members from 35 countries of varying disciplines
- Monthly calls
- Working groups and membership review

PharmGKB

https://www.pharmgkb.org/

- Established 2001
- Knowledge resource that includes:
  - Clinical guidelines
  - Drug labeling
  - Clinically actionable gene-drug associations
  - Genotype-phenotype relationships
  - Clinical and variant annotations -> unique to this resource

BACK TO THE FDA…

- Dosing guidance
- Caution/alert
- Table of Pharmacogenomic Biomarkers in Drug Labeling
  - https://www.fda.gov/media/124784/download
- Table of Pharmacogenetic Associations:
  - https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

PHARMACOGENETIC TESTING
(lets dive in!)

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HOW ARE PATIENTS TESTED?

- Blood
- Saliva or buccal cells (whole saliva, cheek swab, mouthwash rinse)
- PGX test does NOT need FDA approval
  - PGX testing site does need to meet CLIA requirements (non-waived test)
- POC testing is available for CYP2C19 (<60 minute run time)
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6709578/- 2016 summary of POC challenges
  - 2C19, 2C9, 2D6, VKORC1, and oncologic assays most common

IMPLICATIONS OF USING THIS IN OFFICE/INPATIENT

- Workflow
- Clarity to patient
- Where is information stored in EMR
- How is information shared between providers
- Patient data collection and storage
- Clinical decision support

HOW MUCH DOES IT COST?

- Costs range from 100-999$
- CPT codes available for testing for SPECIFIC medications
  - Ex: clopidogrel, 81225
- PGX test determined to be medically necessary?
- Reimbursement for consultations or interventions not currently established

ANYBODY CURRENTLY USING
PGX TESTING IN THEIR PRACTICE?
(Ill share if you do!)

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REPORTING EXAMPLES

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III. GENE DRUG INTERACTION SUMMARY

CLASS	MEDICATION	PHARMACODYNAMIC ASSOCIATIONS	PHARMACODYNAMIC GENE	DRUG EXPOSURE	PHARMACOKINETIC GENE
	ANTIDEPRESSANTS				
SSRIs	**Citalopram** (Celexa®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2C19, P-gp
SSRIs	**Escitalopram** (Lexapro®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2C19, P-gp
SSRIs	**Fluoxetine** (Prozac®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 2C9
SSRIs	**Fluvoxamine** (Luvox®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, 1A2, P-gp
SSRIs	**Paroxetine** (Paxil®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF	↑	2D6, P-gp
SSRIs	**Sertraline** (Zoloft®)	Lower odds of remission or response and increased side effects in Caucasians Higher odds of remission or response in Asians	SLC6A4,BDNF		2C19, 2B6
	Desvenlafaxine (Pristiq®)				

GENOMIND® PROFESSIONAL PGx™

ATIONS

NS	GUIDE	CLINICAL IMPACT
*6A4) is a synaptic transporter protein responsible for g this transporter to produce a therapeutic response **er likelihood of remission and increased side effect risk** sed cortisol release in response to stress		**Assess alternatives to SSRIs** in Caucasians **Therapeutic options: SNRIs** or other **non-SSRI antidepressants** may be considered if clinically indicated
c Factor (BDNF)** is a protein involved in neuronal* sticity n that **Met carriers of *Caucasian ancestry may have a **o SSRIs**, and **improved response to SNRIs or TCAs.** udies need to confirm these findings **Met carriers of *Asian ancestry*** may have an **improved** linked to improvements in cognition and stress response, **showing a more pronounced response**		**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate **Ethnicity dependent antidepressant response**
MTHFR C677T: C/T A1298C: A/C [Low to intermediate activity]	***Methylenetetrahydrofolate Reductase (MTHFR)** is an enzyme responsible for the conversion of folic acid to methylfolate which is a cofactor needed for serotonin, norepinephrine, and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • **L-methylfolate supplementation** of SSRIs and SNRIs may result in greater symptom reduction compared to SSRIs/SNRIs alone in major depressive disorder • L-methylfolate may be an effective monotherapy for patients with major depressive disorder	**Therapeutic options: L-methylfolate** may be used if clinically indicated

GENOMIND

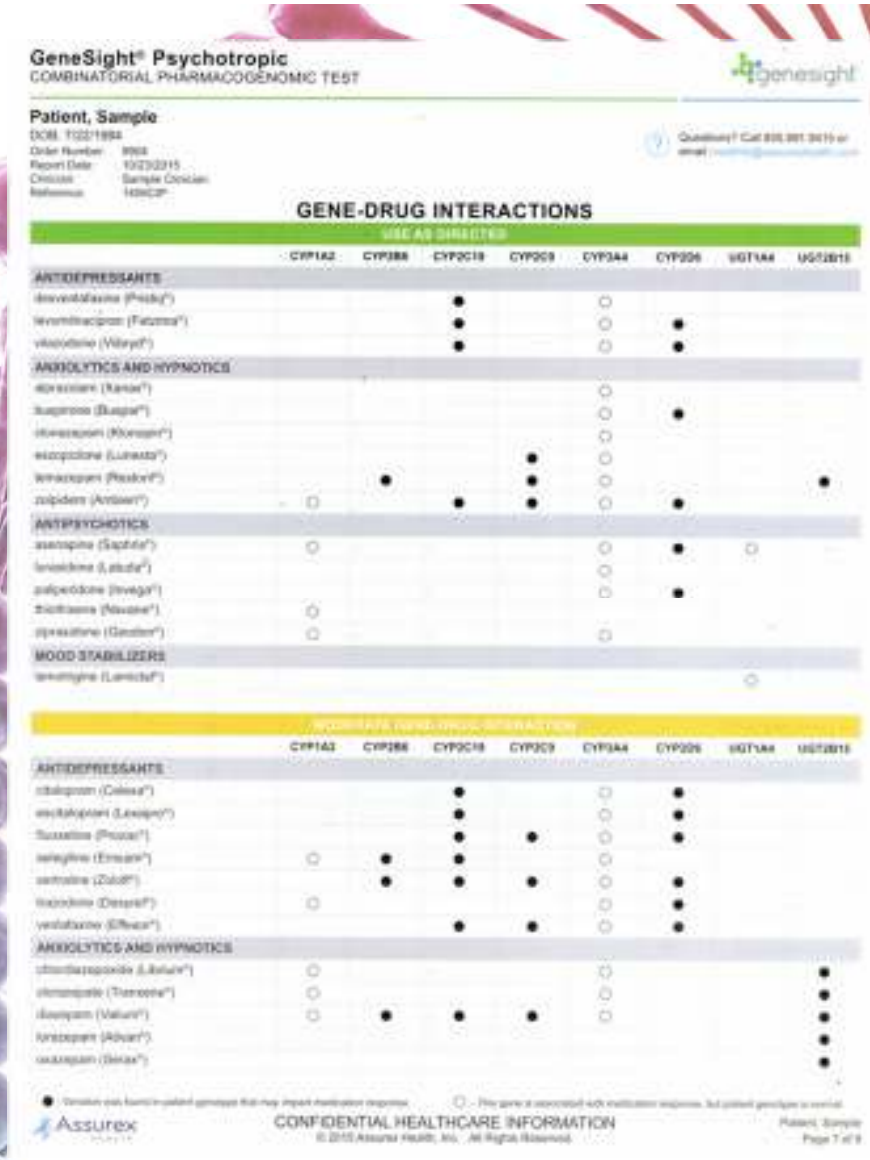
www.genomind.com

Drug Interaction Summary:

This summary provides a listing of implications for psychotropic and pain medications specific to your patient's genetic profile

	Medication	Primary metabolizing enzyme(s)	Use as Directed: No known gene-drug interactions	Therapeutic Options: Options which may be used if clinically indicated	Use with Caution: CYP450 Serum levels may be ↑ (reduced dose may be required)	Use with Caution: CYP450 Serum levels may be ↓ (increased dose may be required)	Use with Caution: Increased risk for adverse events or poor response
	Antidepressants			SLC6A4			SLC6A4
SSRIs	Citalopram (Celexa®)	2C19, 3A4/5			✓		✓
SSRIs	Escitalopram (Lexapro®)	2C19, 2D6			✓		✓
SSRIs	Fluoxetine (Prozac®)	2D6, 2C9					✓
SSRIs	Fluvoxamine (Luvox®)	2D6, 1A2					✓
SSRIs	Paroxetine (Paxil®)	2D6					✓
SSRIs	Sertraline (Zoloft®)	–					✓
SNRIs	Desvenlafaxine (Pristiq®)	–	✓	✓			
SNRIs	Duloxetine (Cymbalta®)	1A2, 2D6	✓	✓			
SNRIs	Levomilnacipran (Fetzima®)	3A4/5	✓	✓			
SNRIs	Venlafaxine (Effexor®) [1]	2D6, 2C19		✓	Indeterminate [2]		
Atypicals	Bupropion (Wellbutrin®)	2D6		✓	✓		
Atypicals	Mirtazapine (Remeron®)	2D6, 3A4/5, 1A2	✓	✓			
Atypicals	Trazodone (Desyrel®, Oleptro®)	3A4/5	✓	✓			
Atypicals	Vilazodone (Viibryd®)	3A4/5	✓	✓			
Atypicals	Vortioxetine (Brintellix®)	2D6	✓	✓			
TCAs	Amitriptyline (Elavil®)	2D6, 2C19			✓		
TCAs	Amoxapine	2D6	✓				
TCAs	Clomipramine (Anafranil®)	2D6, 2C19, 1A2			✓		
TCAs	Desipramine (Norpramin®)	2D6	✓				
TCAs	Doxepin (Sinequan®)	2D6	✓				
TCAs	Imipramine (Tofranil®)	2D6, 2C19			✓		
TCAs	Nortriptyline (Pamelor®)	2D6	✓				

ICES



GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9268
Report Date: 10/23/2315
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 800.381.3415 or email

GENE-DRUG INTERACTIONS

USE AS DIRECTED

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
desvenlafaxine (Pristiq®)			●		○			
levomilnacipran (Fetzima®)			●		○	●		
vilazodone (Viibryd®)			●		○	●		
ANXIOLYTICS AND HYPNOTICS								
alprazolam (Xanax®)					○			
buspirone (Buspar®)					○	●		
clonazepam (Klonopin®)					○			
eszopiclone (Lunesta®)				●	○			
temazepam (Restoril®)		●		●	○			●
zolpidem (Ambien®)	○		●	●	○	●		
ANTIPSYCHOTICS								
asenapine (Saphris®)	○				○	●	○	
lurasidone (Latuda®)					○			
paliperidone (Invega®)					○	●		
thiothixene (Navane®)	○							
ziprasidone (Geodon®)	○				○			
MOOD STABILIZERS								
lamotrigine (Lamictal®)							○	

MODERATE GENE-DRUG INTERACTION

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
citalopram (Celexa®)			●		○	●		
escitalopram (Lexapro®)			●		○	●		
fluoxetine (Prozac®)			●	●	○	●		
selegiline (Emsam®)	○	●	●		○			
sertraline (Zoloft®)		●	●	●	○	●		
trazodone (Desyrel®)	○				○	●		
venlafaxine (Effexor®)			●	●	○	●		
ANXIOLYTICS AND HYPNOTICS								
chlordiazepoxide (Librium®)	○				○			●
clonazepam (Klonopin®)	○				○			●
diazepam (Valium®)	○	●	●	●	○			●
lorazepam (Ativan®)								●
oxazepam (Serax®)								●

● Variation was found in patient genotype that may impact medication response. ○ This gene is associated with medication response, but patient genotype is normal.

Assurex Health

CONFIDENTIAL HEALTHCARE INFORMATION

genesight

GeneSight Psychotropic Results

assurex Health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9268
Report Date: 1/24/2014

Antidepressants

USE AS DIRECTED

bupropion (Wellbutrin®)
desvenlafaxine (Pristiq®)
levomilnacipran (Fetzima®)
vilazodone (Viibryd®)
vortioxetine (Brintellix®)

USE WITH CAUTION

citalopram (Celexa®) [2,4]
clomipramine (Anafranil®) [3]
desipramine (Norpramin®) [1]
doxepin (Sinequan®) [3]
duloxetine (Cymbalta®) [1]
escitalopram (Lexapro®) [2,4]
fluoxetine (Prozac®) [1,4]
fluvoxamine (Luvox®) [1,4]
mirtazapine (Remeron®) [1]
nortriptyline (Pamelor®) [1]
sertraline (Zoloft®) [1,4]
trazodone (Desyrel®) [3]
venlafaxine (Effexor®) [3]

USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

amitriptyline (Elavil®) [1,6]
imipramine (Tofranil®) [1,6]
paroxetine (Paxil®) [1,4,6]
selegiline (Emsam®) [2]

Antipsychotics

USE AS DIRECTED

asenapine (Saphris®)
clozapine (Clozaril®)
fluphenazine (Prolixin®)
haloperidol (Haldol®)
lurasidone (Latuda®)
olanzapine (Zyprexa®)
paliperidone (Invega®)
quetiapine (Seroquel®)
thiothixene (Navane®)
ziprasidone (Geodon®)

USE WITH CAUTION

aripiprazole (Abilify®) [1]
chlorpromazine (Thorazine®) [1]
iloperidone (Fanapt®) [1]
perphenazine (Trilafon®) [3]
risperidone (Risperdal®) [1]
thioridazine (Mellaril®) [3,6]

USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

Report will be different for each person

[1]: Serum level may be too high, lower doses may be required.
[2]: Serum level may be too low, higher doses may be required.
[3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.
[4]: Genotype may impact drug mechanism of action and result in reduced efficacy.
[6]: Use of this drug may increase risk of side effects.
[6]: FDA label identifies a potential gene-drug interaction for this medication.

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ONEOME

Gene and phenotype summary (cont.)

COMT	rs4680 GG	High activity (warning icon)	**High activity** The COMT GG (Val/Val) genotype is predicted to yield higher COMT activity than the AA (Met/Met) or GA (Val/Met) genotypes at rs4680.
DPYD	*1/*2A	Atypical (hand icon)	**DPD activity score: 1** Genotype consistent with partial reduction of dihydropyrimidine dehydrogenase (DPD) activity with an activity score of 1, or an intermediate metabolizer phenotype. Partial DPD activity is associated with an increased risk of severe, life-threatening, or fatal adverse reactions related to the administration of certain medications.
DRD2	rs1799978 GG	Atypical (hand icon)	**Reduced receptor expression** Homozygous variant dopamine receptor D2 (DRD2) rs1799978 GG genotype is consistent with reduced receptor expression.
F2	rs1799963 GG	Typical (check icon)	**Normal risk** Normal risk of thrombosis associated with Factor II (prothrombin). Other genetic and clinical factors contribute to the risk for thrombosis.
F5	rs6025 GG	Typical (check icon)	**Normal risk** Normal risk of thrombosis associated with Factor V. Other genetic and clinical factors contribute to the risk for thrombosis.
GRIK4	rs1954787 CC	Typical (check icon)	**Normal receptor function** Glutamate ionotropic receptor kainate type subunit 4 (GRIK4) genotype is consistent with normal receptor function.
HLA-A	Negative	Typical (check icon)	**Normal risk** Negative for the presence of the HLA-A*31:01 allele. Normal risk of hypersensitivity induced by certain medications, and possibly others of structural similarity. Hypersensitivity and severe cutaneous reactions may occur regardless of the presence of the HLA-A*31:01 allele. In particular the presence of the HLA-B*15:02 allele is associated with severe cutaneous reactions induced by certain medications.
HLA-B	Negative	Typical (check icon)	**Normal risk** Negative for presence of the HLA-B*15:02, HLA-B*57:01, and HLA-B*58:01 alleles. Normal risk of hypersensitivity, severe cutaneous reactions, and severe hepatotoxicity induced by certain medications. Hypersensitivity, severe cutaneous reactions, and severe hepatotoxicity may occur regardless of the presence of HLA-B*15:02, HLA-B*57:01, or HLA-B*58:01 alleles. In particular, the presence of the HLA-A*31:01 allele is associated with hypersensitivity reactions induced by a certain medication, and possibly other medications of structural similarity.
HTR2A	rs7997012 AA	Typical (check icon)	**Intron 2 genotype AA** Homozygous wild-type HTR2A (5-hydroxytryptamine receptor 2A) genotype is consistent with normal HTR2A receptor function.

ONEOME

RightMed® Gene Report

Patient and report summary

Patient name: John Doe
Patient date of birth: [illegible]
OneOme report date: 2019-12-11

Ordering provider: Sample Doctor
Ordering facility: Healthcare Institution
Report type: Original

Phenotype icon legend for CYP genes

CYP phenotype, or metabolizer status, is determined by the total predicted activity of the gene based on the genotype, and is represented by a gauge icon. Total predicted activity which falls between phenotypes will be reported as a range phenotype.

Poor metabolizer
No to very low activity. Drugs converted to active metabolite(s) may have reduced efficacy. Active drugs converted to inactive metabolite(s) may cause side effects or toxicity.

Intermediate metabolizer
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.

Normal metabolizer
Normal level of activity. Drugs metabolized at a normal rate.

Rapid metabolizer
Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.

Ultrarapid metabolizer
Increased activity. Drugs converted to active metabolite(s) may cause side effects or toxicity. Active drugs converted to inactive metabolite(s) may lack efficacy.

Phenotype icon legend for other genes

Phenotype icons for other genes represent the extent of impact of the genotype on protein activity, expression, or function, and/or increased clinical impact (e.g., adverse event risk).

Atypical
Genotype indicates an absence of or major decrease in protein activity, expression, or function.

Atypical
Genotype indicates a moderate loss of or increase in protein activity, expression, or function.

Typical
Genotype indicates normal or typical protein activity, expression, or function.

NCES

PGX IN PRIMARY CARE

- Proton Pump Inhibitors and 2C19 *(new)*
- NSAIDs and 2C9 *(new)*
- Opioids and 2D6, OPRM1, and COMT *(new update)*
- Clopidogrel and 2C19
- TCAs and 2D6 and 2C19
- Ondansetron and 2D6
- Atomoxetine and 2D6
- SSRIs and 2D6 and 2C19
- SLCO1B1 Simvastatin (being updated and including more)
- HLA-B and HLA-A for allopurinol, carbamazepine and oxcarbazepine

WHAT ELSE IS OUT THERE?

- SLCO1B1-> decreased function = decreased simvastatin uptake into liver and decreased concentrations into plasma-> increased risk of myopathy
- VKOR-> decreased function = decreased vitamin k epoxide reductase enzyme activity -> smaller doses of warfarin required
  - 2C9 activity associated with warfarin metabolism-> reduced activity = decreased dose required

CANCER PHARMACOGENOMICS

- Tumor target drug therapies (HER2, BRAF, ALK, ROS1, EGRF)
- Germline genome-> inherited disease risk (BRCA)
- LOTS Of targeted precision PGX examples
  - Afatinib, alectinib crizotinib, erlotinib, gefitinib, pembrolzumab, and MORE!
    - Can obtain somatic test (blood or urine) of the cancer to determine variants

GENE-DRUG MEDIATED IMMUNE RESPONSE

- HLA-B*57:01-> predictive of immunologically mediated hypersensitivity reaction
  - Abacavir
- HLA-B*58:01-> SJS, TEN, ARF, etc.
  - Allopurinol
- HLA-B*15:02/HLA-A*31:01 -> SJS, TEN
  - Aromatic anticonvulsants (carbamazepine, phenytoin)

DRUG HYPERSENSITIVITY REACTIONS

- HLAs = human leukocyte antigens are part of the major histocompatibility complex
  - Present intracellular antigens to the immune system
  - Very Polymorphic!
- HLA-B*15:02 associated with SJS (30% mortality)
- Boxed warning: SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT

CPIC GUIDELINE

TABLE 1. HLA-B*15:02 FREQUENCY	
Country/ Region/Ethnicity	HLA-B*15:02 Allele Frequency
China	1-12%
Singapore	10-12%
Hong Kong	10-12%
Malaysia	6-8%
Thailand	6-8%
India	2-6%
Korea	0.5%
Japan	0.1%
African populations	0-0.02%
European populations	0-0.02%

- Carrier of HLA-B*1502
  - If carbamazepine-naïve do not use (strong)
  - If patient has used carbamazepine previously for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine (optional)
- FDA label for oxcarbazepine states “carrying the HLA-B*1502 allele may be at an increased risk of SJS/TEN with oxcarbazepine treatment”

…SO WHO SHOULD WE TEST?!

- Walden et all (Psychiatry Research, 2015) found that 134/163 physicians agreed or very much agreed that genetic testing may become part of psychiatric practice
- Similar findings from Thompson et al (Psychiatry Research, 2015)
- 2C19 prior to PCI (conflicting evidence)
- Thoughts from the audience…?

PATIENT CASE

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PATIENT F.C.

- F.C. is a 29 year old Caucasian male who presents to your primary care clinic to establish care
- He reports multiple “bad reactions” to medications in the past
- PMH: depression, anxiety, chronic low back pain, opioid use disorder, vitamin D deficiency
- Medications: naltrexone 50mg once daily, ibuprofen 400mg TID, sertraline 100mg daily, hydroxyzine 50mg TID PRN, vitamin D 1000mg daily

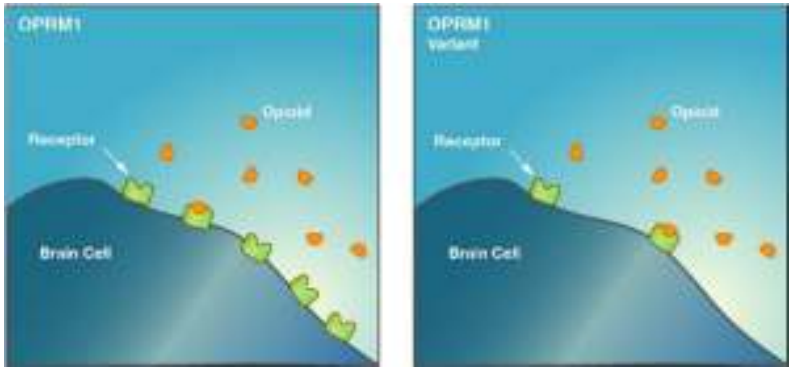
PATIENT F.C.

- F.C. has arthritic and neuropathic pain in his lower back
- He also complains of increased anxiety today (PHQ-9: 11 GAD-7: 14)
- He is open to PGX testing

PATIENT F.C.- PHARMACODYNAMICS

- SLC6A4 L(A)/S (intermediate activity)
- MTHFR C/C (intermediate activity)
- COMT Met/Met (low activity)
- OPRM1 G/G (decreased sensitivity to opioids)

OPRM1



- The gene for human mu-opioid receptors
  - Highly polymorphic → >200 variants
- Binds endogenous opioids (endorphins, enkephalins, and dynorphins)
  - Also, exogenous opioids (morphine, hydrocodone, oxycodone, etc.)
- It is involved in pain perception and opioid response
- Variations currently not linked to any condition or disease

HOW DOES THIS AFFECT MY PAIN PATIENT?

- 2019 meta-analysis from Yu et al. Clin J Pain 2019. -> GG allele more likely to require higher doses of opioids and the effect size is moderate (0.3 to 0.79)

- If AA genotype:
  - May likely respond better to opioids and require ***lower*** overall doses
  - Thus, opioids could potentially work better for appropriate candidates

- If GG genotype:
  - May likely not respond as well to opioid treatment and require ***higher*** overall doses
  - Thus, higher doses of opioids may be required

COMT

- Enzyme present on nerve terminals that is involved in metabolism of neuroamines
    - Including dopamine, norepinephrine, and epinephrine
- Can be involved in pain modulation, sensitivity, and opioid response
    - Descending pain pathway is sensitive to noradrenergic modulation
- Variations currently not linked to any condition or disease

Kaye AD et al. Pharmgenomics Pers Med. 2019;12:15-143

HOW DOES THIS AFFECT MY PAIN PATIENT?

- If COMT Met/Met genotype:
  - Lower metabolism of synaptic neuroamines
  - May likely respond better to opioids and require ***lower*** overall doses
  - Thus, opioids could potentially work better for appropriate candidates

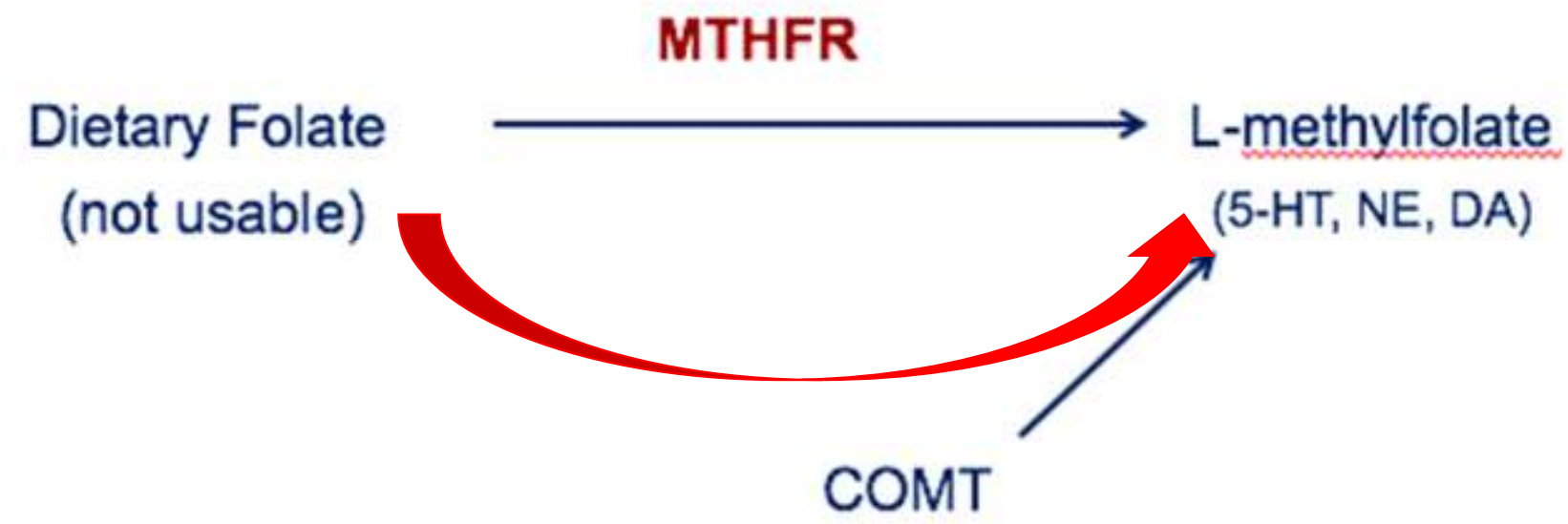
- If COMT Val/Val genotype:
  - May likely not respond as well to opioid treatment and require ***higher*** overall doses
  - Thus, higher doses of opioids may be required
  - Potentially could benefit from antidepressants?

MTHFR

- Catalyzes transformation of homocysteine to methionine
  - Body uses methionine as building block for proteins and neuroamines
  - Also allows for activation of dietary folate
- Similarly to COMT, can be involved in pain modulation, sensitivity, and opioid response
  - Descending pain pathway is sensitive to noradrenergic modulation
- 50-60% of individuals have reduced activity

Yigit S et al. Mol Vis. 2013;1626-1630.
Papakostas GI et al. Am J Psychiatry. 2012;169:1267-1274
Botto LD et al. Am J Epidemiol. 2000;161(9):862-877

HOW DOES THIS AFFECT MY PAIN PATIENT?



If MTHFR deficient, may consider supplement

MTHFR

- Unfortunately, there are not many studies that have attempted to associate C677T mutations with chronic pain conditions
- There have been several case studies and series that have noted some correlation in treating a C677T mutation with reduction in pain levels
    - Specifically by using L-methylfolate (active version of folate)
- There have been a multitude of studies showing an association between increased rates of depression, anxiety, bipolar disorder, and schizophrenia in those that are MTHFR poor metabolizers (677TT genotypes)

Wan et al. Transl Psychiatry. 2018;8:242.

PATIENT F.C.- PHARMACOKINETICS

- CYP2C19 *2/*2 (poor metabolizer)
- CYP2C9 *1/*2 (intermediate AS 1.5)
- CYP2D6 *1/*4 (intermediate activity)
- HLA-B*15:02 positive
- CYP1A2 normal
- CYP2B6 normal
- CYP3A4 normal

ANXIETY/DEPRESSION

- SLC6A4- may be at an increased risk for GI side effects with SSRI use
- MTHFR- supplementation of l-methylfolate
- 2C19 and 2D6 relevant for antidepressant use
  - https://files.cpicpgx.org/data/guideline/publication/SSRI/2015/25974703.pdf
- Sertraline- greatly reduced metabolism when compared to extensive metabolizers-> higher plasma concentrations may increase side effects

OTHER NOTES FOR F.C.

- Best NSAID to recommend for this patient-> may have higher than normal risk of adverse events related to ibuprofen use compared with normal CYP2C9 metabolism
  - Consider diclofenac, indomethacin, nabumetone, or naproxen
- *AVOID opioids due to history of OUD and on naltrexone therapy
  - Conflicting OPRM1 and COMT phenotypes
  - OPRM1- patient may experience decreased analgesia with opioids vs.
  - COMT- patient may achieve analgesia with lower doses of opioids

OTHER NOTES FOR F.C.

- Best PPI to recommend for this patient-> increased plasma concentration of PPI compared with normal CYP2C19 metabolism
  - Consider esomeprazole or rabeprazole
- Clopidogrel recommendation for this patient -> significantly reduced active clopidogrel metabolite formation compared with normal CYP2C19 metabolism
  - Consider prasugrel or ticagrelor

PATIENT F.C. SUMMARY

- D/c sertraline and starting duloxetine (taper)
- Start L-methylfolate 15mg daily
- D/c ibuprofen and start naproxen
- HLA-B*15:02 positive -> DOCUMENT
- LOTS of options here!

THE ROLE OF A PHARMACIST

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WE ARE THE DRUG EXPERTS!

Pharmacist-Provided Pharmacogenetic Point-of-Care Testing Consultation Service: A Time and Motion Study

David R. Bright, PharmD, BCACP, Michael E. Klepser, PharmD, FCCP, FIDP, Logan Murry, PharmD, more... Show all authors

First Published February 2, 2018 | Research Article | Check for updates
https://doi.org/10.1177/8755122518756651

Article information

Abstract

Background: With recent advances in pharmacogenomics (PGx) comes the potential to customize medication use based on genetic data. Support for PGx has found practical limitations in terms of workflow and turnaround time of a test. However, with the expansion of point-of-care testing (POCT) in pharmacy practice models comes opportunity for PGx testing in the pharmacy setting. **Objective:** The purpose of this study is to quantify the amount of time spent during each step of a PGx POCT encounter in a community pharmacy setting. **Methods:** A time and motion study was conducted using a mock community pharmacy space for a simulated PGx-focused encounter to manage antiplatelet therapy following hospital discharge. PGx POCT was conducted using the Spartan RX instrument. Simulated patient encounters were divided into 7 categories. Time spent in each step, as well as total time spent, was tracked. **Results:** A total of 54 simulated PGx POCT encounters took place with an average time of 9.49 minutes (SD ± 1.38 minutes). Instrument run time adds 60 minutes to the total time required to obtain a result. Duties that could be

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- Physicians' knowledge and attitudes regarding POC Pharmacogenetic Testing: A Hospital Based Cross Sectional Study
- Muflih S, Alshogran OY, Al-Azzam S, Al-Taani G, Khader YS. Physicians' Knowledge and Attitudes Regarding Point-of-Care Pharmacogenetic Testing: A Hospital-Based Cross-Sectional Study. *Pharmgenomics Pers Med*. 2021;14:655-665 https://doi.org/10.2147/PGPM.S307694
- 200 MDs perceived knowledge of the role of PGx testing in therapeutic decision-making was rated as "Excellent" (1.9%), "Very Good" (19.4%), "Good" (34.4%), "Fair" (32.5%), and "Poor" (11.9%)
- Physicians' actual knowledge of PGx testing was adequate (mean=3.56 out of 7, SD=1.2), but their attitudes were generally favorable (mean=3.64 out of 5.00, SD=0.52)

WE ARE THE DRUG EXPERTS!

- ACPE standards to now include in our curriculum
  - NOT currently in standards for MD or NP programs
- Role of genetic counseling
  - CDTM or MTM opportunities
- Expanding role of clinical pharmacist
- WE ARE THE DRUG EXPERTS!

5 Great Modules. 5 Great Dates.

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OR

5/9: Clinical Implementation in Medicine (3 CME credits) OPTION 2

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A Pharmacist's Introduction to Clinical Pharmacogenomics

Jacqueline Cleary, PharmD, BCACP
Assistant Professor of Pharmacy Practice
Albany College of Pharmacy and Health Sciences

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