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Continuing Education for Rehabilitation Professionals

Personalized Medicine: Pharmacogenomics Testing and Applications In Clinical Practice

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Objectives

1. Define pharmacogenomics and other key terms for basic understanding of genetics and personalized medicine.

2. Describe how variations in genes affect individual response to psychiatric medications.

3. Learn to interpret pharmacogenomics testing results and to use that information to guide clinical decision-making.

4. Provide resources for guidelines, further information, and application of pharmacogenomics testing in practice

What is Personalized Medicine?

- NIH: National Genome Research Institute:

Personalized medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen. Personalized medicine is being advanced through data from the Human Genome Project.

Retrieved from: https://www.genome.gov/genetics-glossary/Personalized-Medicine

What is Precision Medicine?

- According to the Precision Medicine Initiative, precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This approach will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people. It is in contrast to a one-size-fits-all approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.

- Data Driven

Retrieved from: https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

Pharmacogenomics

“Pharmacogenomics is the study of how genes affect a person’s response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person’s genetic makeup.”

Retrieved from:
https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics

Pharmacogenomics

AVOID	MAXIMIZE	SELECT
Adverse Drug Reactions	Drug efficacy	Responsive Patients

Why it matters?

- Drugs don't work the same way for everyone.
- It can be difficult to predict response to a drug.
- Adverse drug reactions are a significant cause of hospitalizations and deaths in the United States.
- With the knowledge gained from the Human Genome Project, researchers are learning how inherited differences in genes affect the body’s response to medications.

Single Nucleotide Polymorphisms

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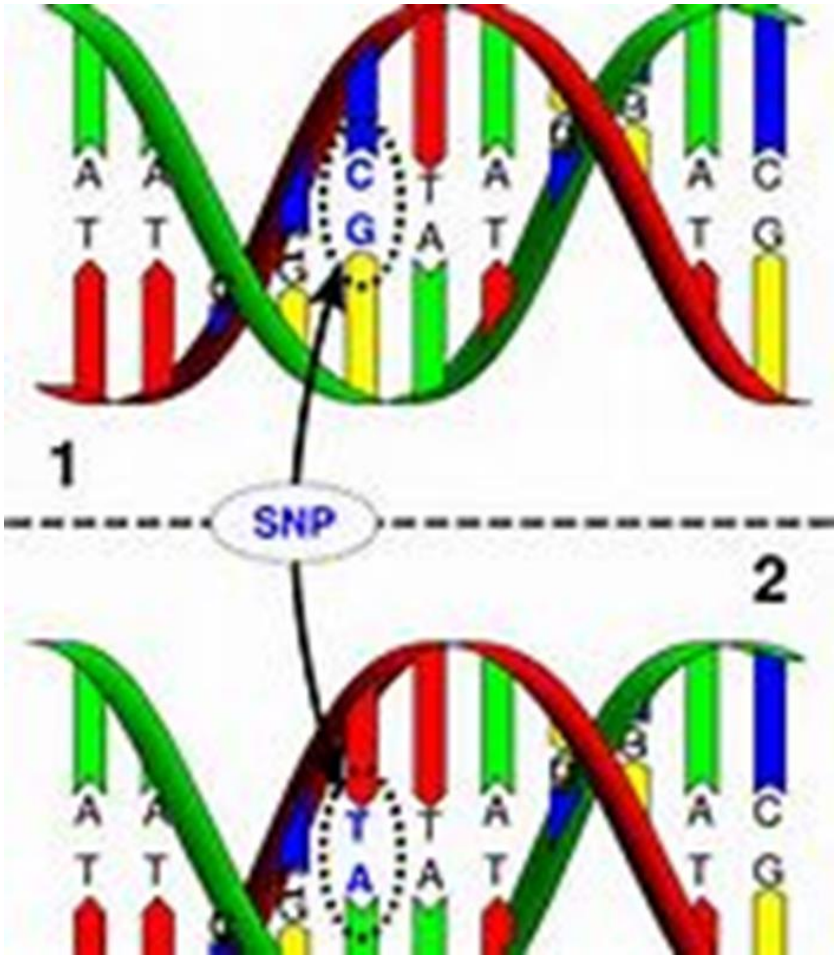
- Single nucleotide polymorphisms, frequently called SNPs are the most common type of genetic variation among people.
- Most SNPs have no effect on health or development.
- Some of these genetic differences have proven to be important in the study of human health.
- SNPs that may help predict an individual's response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases.
- SNPs can also be used to track the inheritance of disease genes within families



- Natural variations (DNA polymorphisms) play a role in our risk of getting or not getting certain diseases
- External factors such as environment, diet, and exercise, along with polymorphisms can also determine an individual's risk for disease
- Natural genetic variations can, in part, determine drug efficacy
- Variations in DNA can lead to differences in pharmacodynamics and pharmacokinetics in the individual patient
- Based on the patient's individual genetic expression, biomarkers and DNA microarrays can help detect the best medication for the patient.

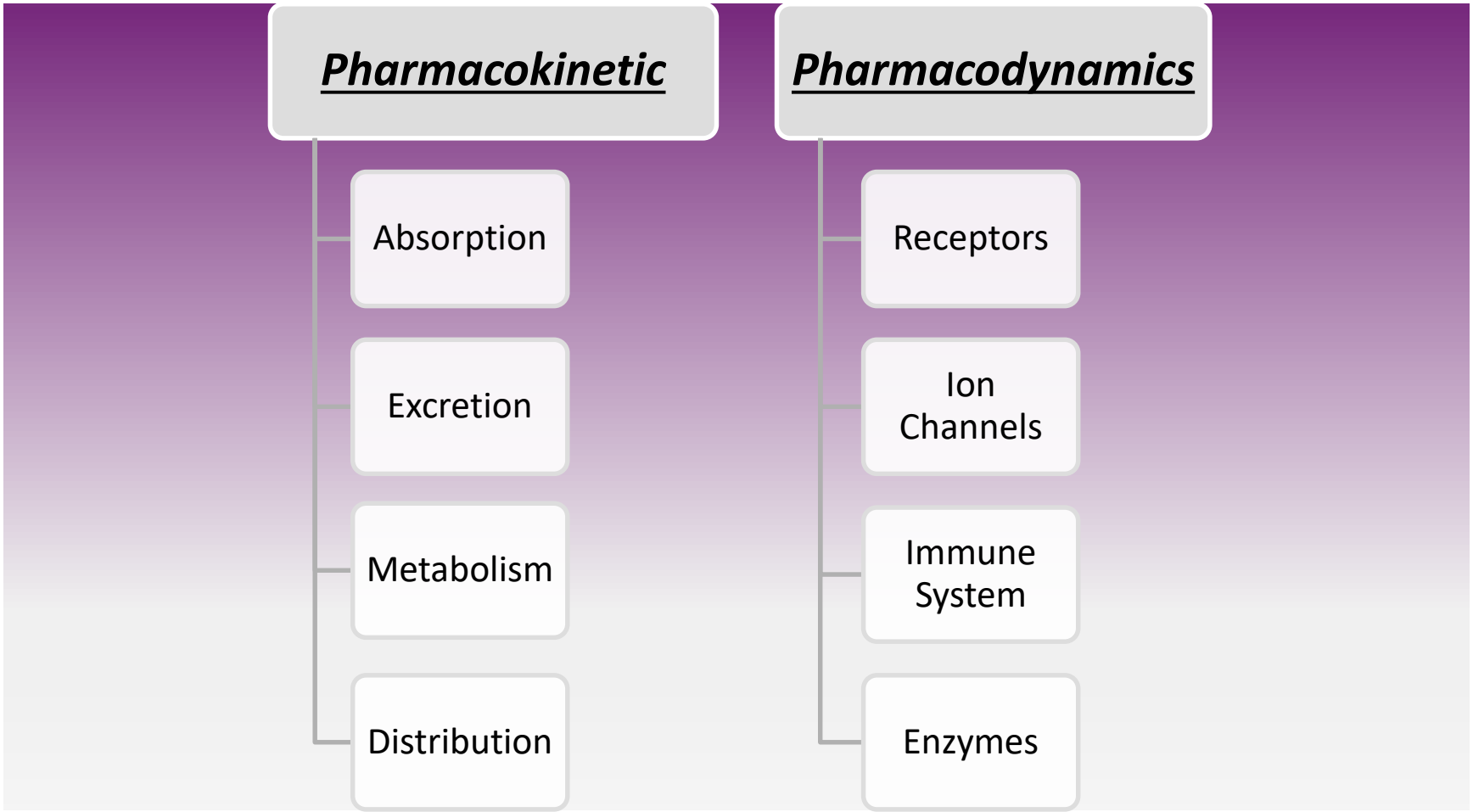
Pharmacokinetics vs Pharmacodynamics

Pharmacokinetics:

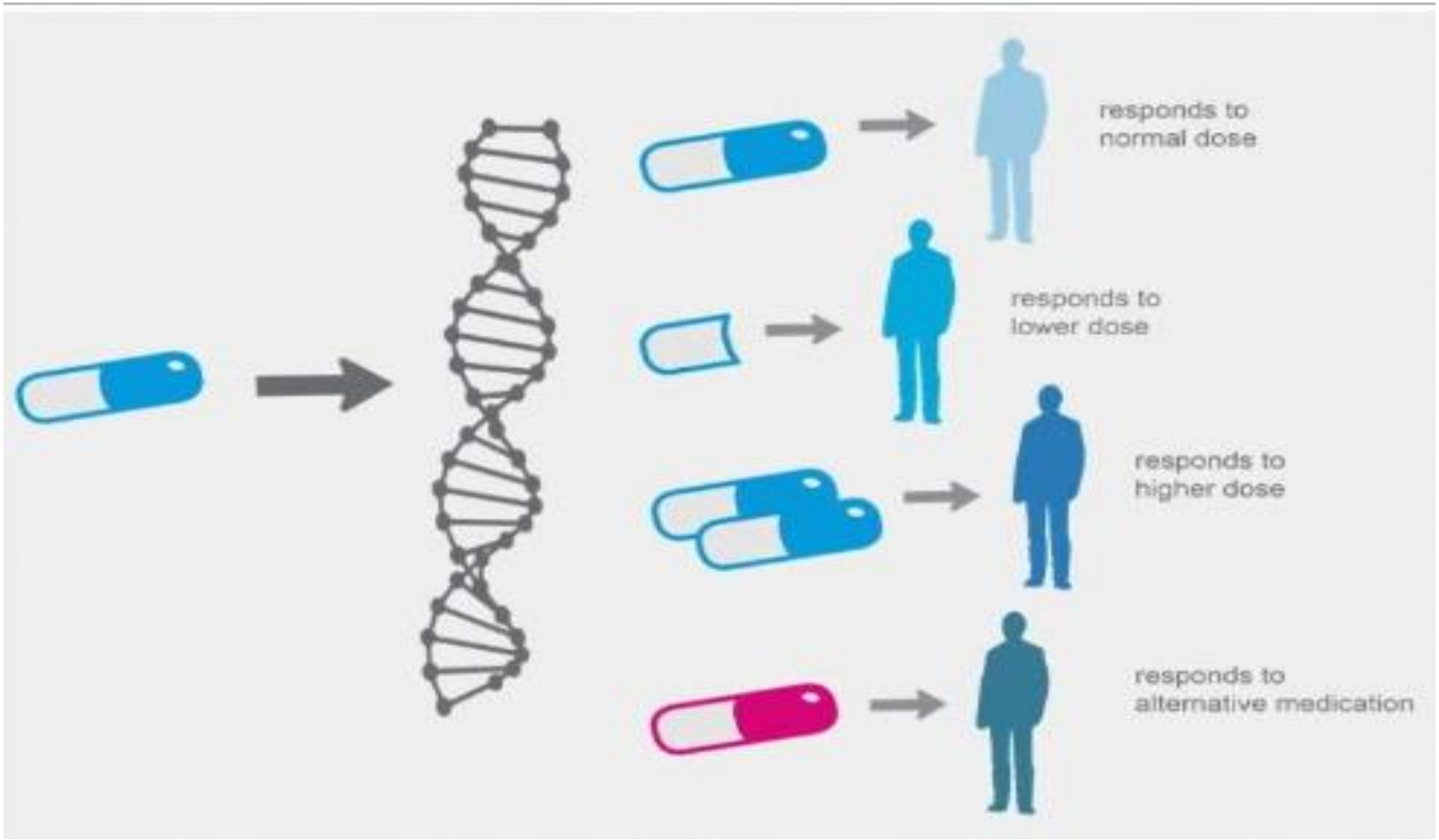
- What the body does to the drug: getting the drug in and back out:
- Impact of gene variation on active vs pro-drugs.
- Factors that influence the concentration of the drug that reaches the target. Where in the pharmacological pathway the variants impact

Pharmacodynamics: What the drug does to the body. Factors at the target or "downstream" that can influence drug response.

Genetic Polymorphisms



Individual Response



Pharmacologic Variability

- Genetics:
  Polymorphisms – Receptors, transporters, and enzymes
- Lifestyle:
  Diet, Alcohol, tobacco use, other drug therapy/supplements
- Reduced Drug Elimination/Pathology:
  Hepatic Function, Renal Function
- Physiology:
  Sex, Age

SHOULD I ORDER A PHARMACOGENOMICS TEST?

Ask: What will I do with the results? Will it impact how I treat my patient?

Pre-emptive Approach: "Screening" Test everyone (Used in larger research-focused health centers such as Mayo Clinic, Mount Sinai, St. Jude, University of Chicago)

Case-Based Approach: Planning on starting a new medication

- Guide dosage selection, drug selection, ensure drug efficacy
- Avoid serious adverse reactions such as a known drug-gene relationships associated with severe toxicity (HLA-B*58:01 allele have an increased risk of Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TENS) when treated with lamotrigine or allopurinol.

Reflexive Approach:

- Unexplained sensitivities or toxicities
- History of multiple medication trials with poor efficacy
- Assistance in making a more informed decision on medication selection or dose (i.e. antidepressant, delayed onset, cost of medications, etc.)

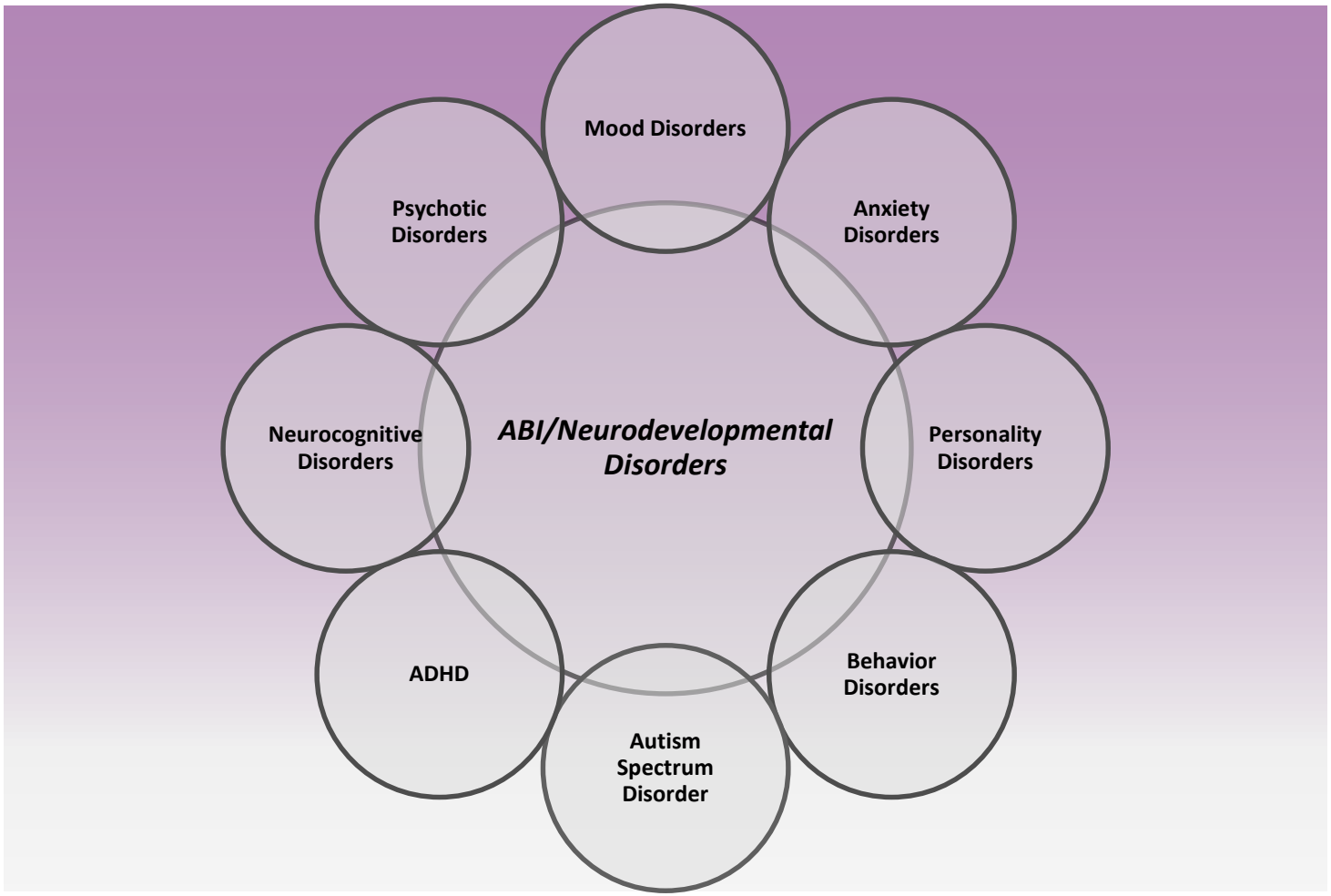
What does this have to do with psychiatry and ABI?

Mental Health and Acquired Brain Injury

Factors that may adversely influence the mental health of a person with brain injury can be seen at a number of levels:

- Direct effects of brain injuries (eg. cognitive and motor disturbances, emotional disorders, increased impulsivity, depression, rigidity, hyperactivity) may precipitate mental health difficulties.
- Longer-term implications of the effects of brain injury may result in profound personality changes.
- Changes in capabilities and competencies post injury may increase the likelihood of depression for people with ABI. Suicide rates are 2-3 X higher among people with brain injuries than the general population, especially in the first 6 months post injury.
- Brain injury is often a catastrophic, life-changing event for individuals and their families. This may predispose them to significant depressive reactions and feelings of social isolation, helplessness and hopelessness.
- Pre-injury social functioning, alcohol use, previous psychiatric problems and family history, all influence mental health.

Psychiatric/Mental Health Co-morbidity in ABI/Neurodevelopmental Disorders



Challenges in prescribing

- Incomplete records
- Individual may be a poor historian/ Family or guardian may not know history
- Disjointed and interrupted treatment history
- Unknown family history
- Poor insight
- Inability to identify or verbalize treatment response and/or side effects
- Polypharmacy
- Multimorbidity

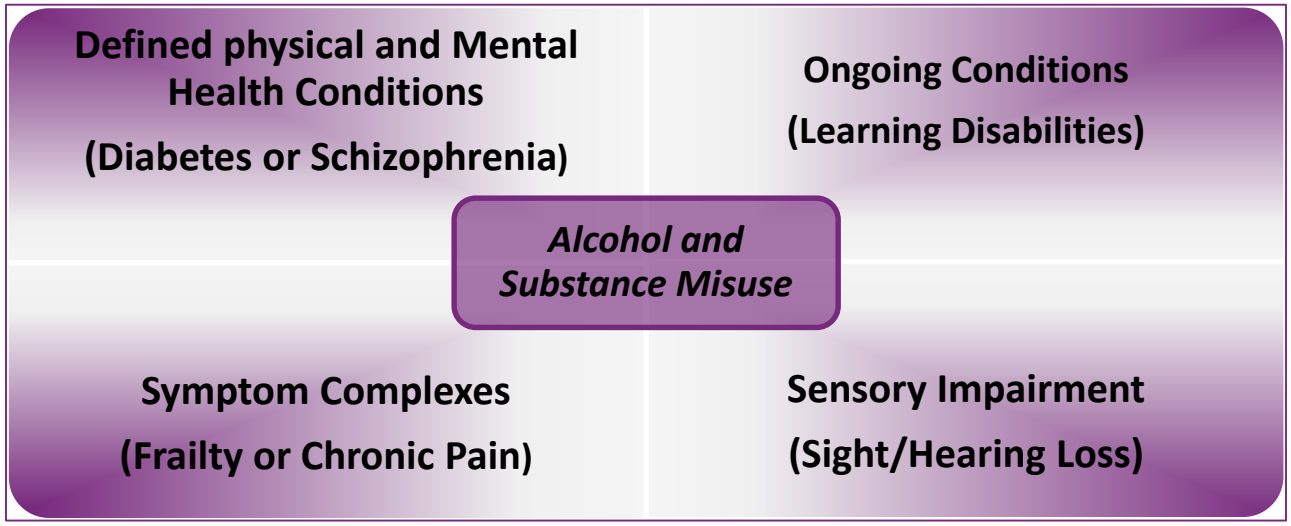
Polypharmacy

Individuals in residential treatment facilities:

- Have severe and chronic disorders
- Have received a variety of treatments in the past and are often taking several psychotropic medications
- During brief hospital stays, medications are often used to quickly stabilize patients.
- During repeated admissions, medications often accumulate. New medications are added, while past medications may be continued for no apparent reason.
- For example, Connor et al. (1997) found polypharmacy in 60.3% of patients admitted to an RTF.
- One factor associated with polypharmacy was the number of previous psychiatric placements.

Multimorbidity

The presence of two or more long-term health conditions



Medication Safety in Polypharmacy: WHO
https://apps.who.int/iris/rest/bitstreams/1235792/retrieve

Other Drug-Drug Interactions

- A patient on several medications known to prolong the QT interval remains a risk for medication induced ‘Torsade de pointes’ despite having normal pharmacogenomics results.

- In the case of phenoconversion, an inhibitor or inducer may alter the function of an enzyme (fluoxetine, paroxetine)

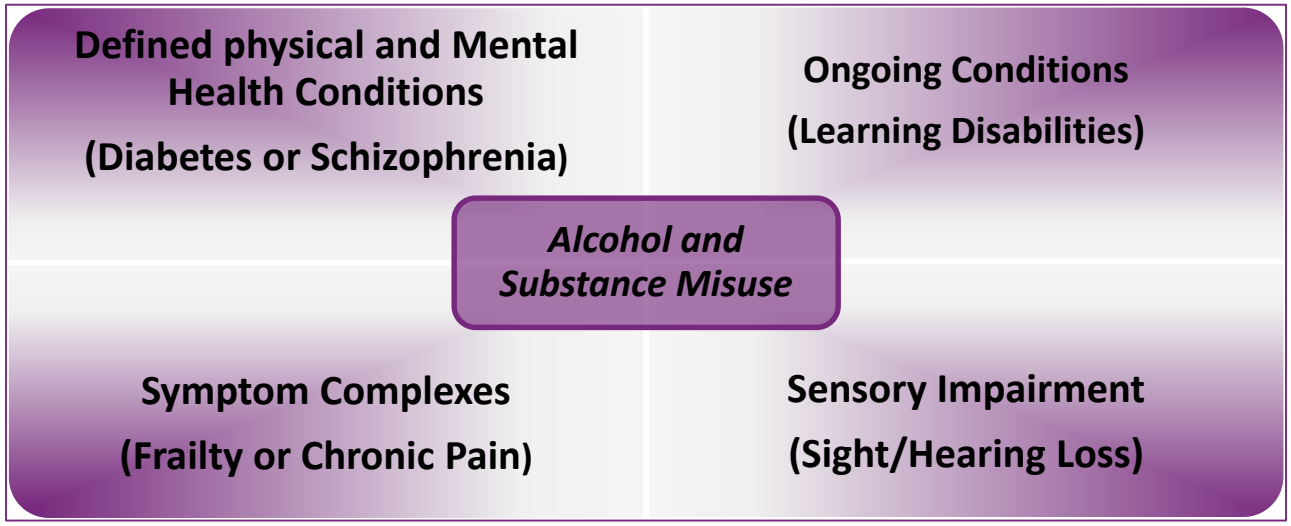
Case Study: Charles

56 year old Black male 6’ 0” 260lbs

- TBI r/t MVA 1984 and 2 additional ABIs r/t seizures 2018
- Impairments r/t head injuries: delayed speech, narcolepsy, psychomotor retardation, balance issues and mobility impairments with hx of falls
- Incarcerated r/t assault charges
- Schizoaffective Disorder-depressed with active auditory hallucinations
- Alcohol Use Disorder
- Hypertension
- Hyperlipidemia
- Angina Pectoris
- GERD
- Asthma
- Dystonia
- Chronic Low back pain, knee pain, arthralgia
- Insomnia
- Obesity
- Allergies: Latex, Bee Stings, Bananas

Multimorbidity

The presence of two or more long-term health conditions



Medication Safety in Polypharmacy: WHO
https://apps.who.int/iris/rest/bitstreams/1235792/retrieve

Medications upon admission

Amlodipine 5mg 1 tab PO q AM for hypertension
Avorstatin 20mg 1 tab PO q hs for hyperlipidemia
Diphenhydramine 50mg q hs for insomnia
Doxazosin 2mg q hs for hypertension
Metoprolol ER 100mg 3 tabs q AM for chronic left Diastolic Heart Failure
Fluticasone-salmeterol 230-21mcg 2 puffs bid
Furosemide 40mg daily for hypertension
Gabapentin 1200 mg tid for arthralgia
Lisinopril 40mg daily for hypertension
Hydralazine 50mg 1 tab PO bid for hypertension
Omeprazole 20mg ER 20mg daily for GERD
Risperidone 1mg q hs for schizophrenia
Trazodone 100mg q hs for insomnia
Venlafaxine EX 300mg q AM for depression
Acetaminophen 650mg q 4 hours PRN for knee pain
Cyclobenzaprine 10mg 1 tab PO PRN for muscle back spasm
Ibuprofen 600mg q 8 hours PRN for Arthralgia
Nitroglycerin SL 0.4mg 1 tab q 5 min up to 3 doses PRN for chest pain

Past Medications (per records available)

Diphenhydramine 50mg q hs
Risperidone 1 mg q AM and 3mg q hs
Trazodone 200mg q hs
Venlafaxine XR 300mg q AM
Fluoxetine 40mg q AM
Clonidine 0.1mg tid

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CHARLES

- Initial Insomnia
- Voices
- No Interest
- No Enjoyment
- No Motivation

STAFF

- Insomnia
- Napping during the day
- Flat Affect
- Irritability
- Low tolerance for peers
- Lack of Motivation

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

DOB:
Order Number:
Report Date:
Clinician:
Reference:

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED
desvenlafaxine (Pristiq®)
levomilnacipran (Fetzima®)
selegiline (Emsam®)
sertraline (Zoloft®)
vilazodone (Viibryd®)

MODERATE GENE-DRUG INTERACTION	
citalopram (Celexa®)	1
escitalopram (Lexapro®)	1
mirtazapine (Remeron®)	3,7
trazodone (Desyrel®)	3,7
duloxetine (Cymbalta®)	3,7,8
fluvoxamine (Luvox®)	3,7,8

SIGNIFICANT GENE-DRUG INTERACTION	
bupropion (Wellbutrin®)	1,6
fluoxetine (Prozac®)	1,6
venlafaxine (Effexor®)	1,6
amitriptyline (Elavil®)	1,6,8
clomipramine (Anafranil®)	1,6,8
desipramine (Norpramin®)	1,6,8
doxepin (Sinequan®)	1,6,8
imipramine (Tofranil®)	1,6,8
nortriptyline (Pamelor®)	1,6,8
vortioxetine (Trintellix®)	1,6,8
paroxetine (Paxil®)	1,4,6,8

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower 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.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed. Propranolol might be considered off-label when being used for neuropsychiatric disorders. Please consult the FDA drug label for specific guidelines regarding its use.

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ANXIOLYTICS AND HYPNOTICS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION
alprazolam (Xanax®)	**propranolol** (Inderal®)	3,7,8	
buspirone (BuSpar®)			
chlordiazepoxide (Librium®)			
clonazepam (Klonopin®)			
clorazepate (Tranxene®)			
diazepam (Valium®)			
eszopiclone (Lunesta®)			
lorazepam (Ativan®)			
oxazepam (Serax®)			
temazepam (Restoril®)			
zolpidem (Ambien®)			

CLINICAL CONSIDERATIONS

3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed. Propranolol might be considered off-label when being used for neuropsychiatric disorders. Please consult the FDA drug label for specific guidelines regarding its use.

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ANTIPSYCHOTICS

USE AS DIRECTED
asenapine (Saphris®)
cariprazine (Vraylar®)
lurasidone (Latuda®)
paliperidone (Invega®)
ziprasidone (Geodon®)

MODERATE GENE-DRUG INTERACTION	
fluphenazine (Prolixin®)	1
quetiapine (Seroquel®)	1
chlorpromazine (Thorazine®)	3,7
olanzapine (Zyprexa®)	3,7
clozapine (Clozaril®)	3,7,8
haloperidol (Haldol®)	3,7,8

SIGNIFICANT GENE-DRUG INTERACTION	
thiothixene (Navane®)	2,7
aripiprazole (Abilify®)	1,6,8
brexpiprazole (Rexulti®)	1,6,8
iloperidone (Fanapt®)	1,6,8
perphenazine (Trilafon®)	1,6,8
risperidone (Risperdal®)	1,6,8
thioridazine (Mellaril®)	3,7,9

CLINICAL CONSIDERATIONS

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.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
9: Per FDA label, this medication is contraindicated for this genotype.

All psychotropic medications require clinical monitoring.
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MOOD STABILIZERS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION	SIGNIFICANT GENE-DRUG INTERACTION
carbamazepine (Tegretol®) **lamotrigine** (Lamictal®) **oxcarbazepine** (Trileptal®) **valproic acid/divalproex** (Depakote®)		

NO PROVEN GENETIC MARKERS			
gabapentin (Neurontin®)	10	**topiramate** (Topamax®)	10
lithium (Eskalith®)	10		

CLINICAL CONSIDERATIONS

10: This medication does not have clinically proven genetic markers that allow it to be categorized.

All psychotropic medications require clinical monitoring.
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PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Normal Response**

L/L

This patient is homozygous for the long promoter polymorphism of the serotonin transporter gene. The long promoter allele is reported to express normal levels of the serotonin transporter. The patient is predicted to have a normal response to selective serotonin reuptake inhibitors.

HTR2A — **Increased Sensitivity**

G/G

This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.

HLA-B*1502 — **Lower Risk**

Not Present

This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

HLA-A*3101 — **Lower Risk**

A/A

This patient is homozygous for the A allele of the rs1061235 A>T polymorphism indicating absence of the HLA-A*3101 allele. This genotype suggests a lower risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.

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PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES (PK)

CYP1A2 — **Ultrarapid Metabolizer**

-3860G>A - G/A, -2467T>DELT - T/DELT, -163C>A - C/A

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal phenotype.

CYP2B6 — **Intermediate Metabolizer**

*1/*6

CYP2B6*1 allele enzyme activity: Normal
CYP2B6*6 allele enzyme activity: Reduced

This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

CYP2C19 — **Extensive (Normal) Metabolizer**

*1/*1

CYP2C19*1 allele enzyme activity: Normal
CYP2C19*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2C9 — **Extensive (Normal) Metabolizer**

*1/*1

CYP2C9*1 allele enzyme activity: Normal
CYP2C9*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

CYP2D6 — **Poor Metabolizer**

*4/*41 (DUPLICATION)

CYP2D6*4 allele enzyme activity: None
CYP2D6*41 allele enzyme activity: Reduced

This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

CYP3A4 — **Extensive (Normal) Metabolizer**

*1/*1

CYP3A4*1 allele enzyme activity: Normal
CYP3A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

UGT1A4 — **Extensive (Normal) Metabolizer**

*1/*1

UGT1A4*1 allele enzyme activity: Normal
UGT1A4*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

UGT2B15 — **Extensive (Normal) Metabolizer**

*1/*2

UGT2B15*1 allele enzyme activity: Normal
UGT2B15*2 allele enzyme activity: Reduced

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

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GENE-DRUG INTERACTIONS

USE AS DIRECTED	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
desvenlafaxine (Pristiq®)			○		○			
levomilnacipran (Fetzima®)			○		○	●		
selegiline (Emsam®)	●	●	○		○			
sertraline (Zoloft®)		●	○	○	○	●		
vilazodone (Viibryd®)			○		○	●		
ANXIOLYTICS AND HYPNOTICS								
alprazolam (Xanax®)					○			
buspirone (BuSpar®)					○	●		
chlordiazepoxide (Librium®)	●				○			○
clonazepam (Klonopin®)					○			
clorazepate (Tranxene®)	●				○			○
diazepam (Valium®)	●	●	○	○	○			○
eszopiclone (Lunesta®)				○	○			
lorazepam (Ativan®)								○
oxazepam (Serax®)								○
temazepam (Restoril®)		●		○	○			○
zolpidem (Ambien®)	●		○	○	○	●		
ANTIPSYCHOTICS								
asenapine (Saphris®)	●				○	●	○	
cariprazine (Vraylar®)					○	●		
lurasidone (Latuda®)					○			
paliperidone (Invega®)					○	●		
ziprasidone (Geodon®)	●				○			
MOOD STABILIZERS								
carbamazepine (Tegretol®)		●			○			
lamotrigine (Lamictal®)							○	
oxcarbazepine (Trileptal®)								
valproic acid/divalproex (Depakote®)		●		○			○	

MODERATE GENE-DRUG INTERACTION	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
citalopram (Celexa®)			○		○	●		
duloxetine (Cymbalta®)	●					●		
escitalopram (Lexapro®)			○		○	●		
fluvoxamine (Luvox®)	●					●		
mirtazapine (Remeron®)	●			○	○	●		

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

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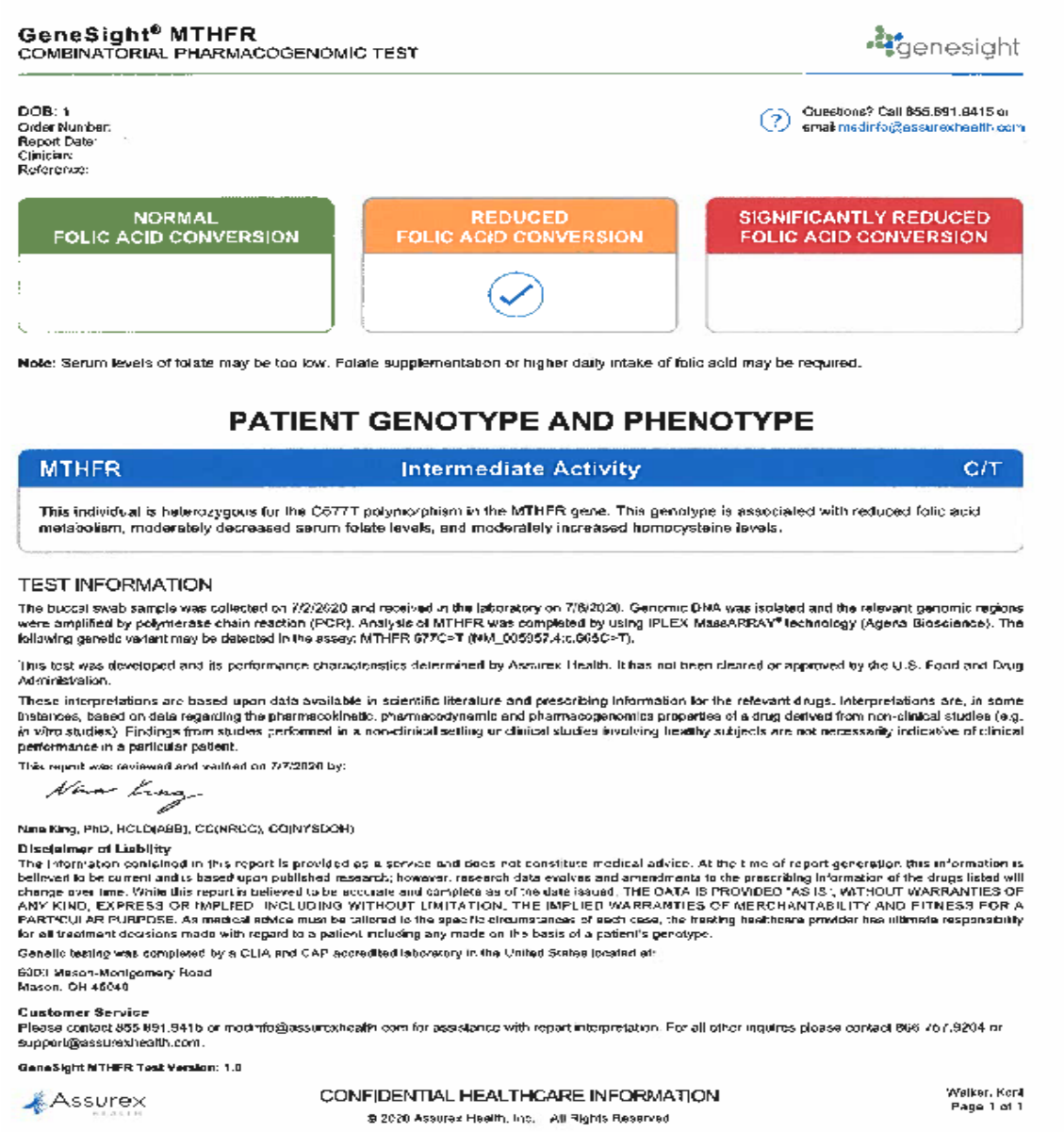
GENE-DRUG INTERACTIONS

MODERATE GENE-DRUG INTERACTION	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
trazodone (Desyrel®)	●				○	●		
ANXIOLYTICS AND HYPNOTICS								
propranolol (Inderal®)	●					●		
ANTIPSYCHOTICS								
chlorpromazine (Thorazine®)	●				○	●		
clozapine (Clozaril®)	●				○	●	○	
fluphenazine (Prolixin®)	●		○	○	○	●		
haloperidol (Haldol®)	●				○	●	○	
olanzapine (Zyprexa®)	●				○	●	○	
quetiapine (Seroquel®)					○	●		

SIGNIFICANT GENE-DRUG INTERACTION	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
amitriptyline (Elavil®)	●		○	○	○	●	○	
bupropion (Wellbutrin®)		●			○	●		
clomipramine (Anafranil®)	●		○		○	●		
desipramine (Norpramin®)						●		
doxepin (Sinequan®)	●		○	○	○	●	○	
fluoxetine (Prozac®)			○	○	○	●		
imipramine (Tofranil®)	●		○		○	●		
nortriptyline (Pamelor®)						●		
paroxetine (Paxil®)					○	●		
venlafaxine (Effexor®)			○	○	○	●		
vortioxetine (Trintellix®)		●	○	○	○	●		
ANTIPSYCHOTICS								
aripiprazole (Abilify®)					○	●		
brexpiprazole (Rexulti®)					○	●		
iloperidone (Fanapt®)					○	●		
perphenazine (Trilafon®)	●		○		○	●		
risperidone (Risperdal®)					○	●		
thioridazine (Mellaril®)	●		○		○	●		
thiothixene (Navane®)	●							

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



GeneSight® MTHFR
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

DOB: 1
Order Number:
Report Date:
Clinician:
Reference:

Questions? Call 855.891.8415 or
email medinfo@assurexhealth.com

NORMAL FOLIC ACID CONVERSION	REDUCED FOLIC ACID CONVERSION	SIGNIFICANTLY REDUCED FOLIC ACID CONVERSION
	✓	

Note: Serum levels of folate may be too low. Folate supplementation or higher daily intake of folic acid may be required.

PATIENT GENOTYPE AND PHENOTYPE

MTHFR	Intermediate Activity	C/T

This individual is heterozygous for the C677T polymorphism in the MTHFR gene. This genotype is associated with reduced folic acid metabolism, moderately decreased serum folate levels, and moderately increased homocysteine levels.

TEST INFORMATION

The buccal swab sample was collected on 7/2/2020 and received in the laboratory on 7/6/2020. Genomic DNA was isolated and the relevant genomic regions were amplified by polymerase chain reaction (PCR). Analysis of MTHFR was completed by using iPLEX MassARRAY® technology (Agena Bioscience). The following genetic variant may be detected in the assay: MTHFR 677C>T (NM_005957.4:c.665C>T).

This test was developed and its performance characteristics determined by Assurex Health. It has not been cleared or approved by the U.S. Food and Drug Administration.

These interpretations are based upon data available in scientific literature and prescribing information for the relevant drugs. Interpretations are, in some instances, based on data regarding the pharmacokinetic, pharmacodynamic and pharmacogenomics properties of a drug derived from non-clinical studies (e.g. *in vitro* studies). Findings from studies performed in a non-clinical setting or clinical studies involving healthy subjects are not necessarily indicative of clinical performance in a particular patient.

This report was reviewed and verified on 7/7/2020 by:

Nana King, PhD, HCLD(ABB), CC(NRCC), CC(NYSDOH)

Disclaimer of Liability
The information contained in this report is provided as a service and does not constitute medical advice. At the time of report generation this information is believed to be current and is based upon published research; however, research data evolves and amendments to the prescribing information of the drugs listed will change over time. While this report is believed to be accurate and complete as of the date issued, THE DATA IS PROVIDED "AS IS", WITHOUT WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. As medical advice must be tailored to the specific circumstances of each case, the treating healthcare provider has ultimate responsibility for all treatment decisions made with regard to a patient including any made on the basis of a patient's genotype.

Genetic testing was completed by a CLIA and CAP accredited laboratory in the United States located at:

6801 Mason-Montgomery Road
Mason, OH 45040

Customer Service
Please contact 855.891.9416 or medinfo@assurexhealth.com for assistance with report interpretation. For all other inquiries please contact 866.767.9204 or support@assurexhealth.com.

GeneSight MTHFR Test Version: 1.0

Assurex HEALTH

CONFIDENTIAL HEALTHCARE INFORMATION

DOB:
Order Number:
Report Date:
Clinician:
Reference:

Questions? Call 855.891.9415 or
email medinfo@assurexhealth.com

ANTIPSYCHOTICS

USE AS DIRECTED
asenapine (Saphris®)
cariprazine (Vraylar®)
lurasidone (Latuda®)
paliperidone (Invega®)
ziprasidone (Geodon®)

MODERATE GENE-DRUG INTERACTION	
fluphenazine (Prolixin®)	1
quetiapine (Seroquel®)	1
chlorpromazine (Thorazine®)	3,7
olanzapine (Zyprexa®)	3,7
clozapine (Clozaril®)	3,7,8
haloperidol (Haldol®)	3,7,8

SIGNIFICANT GENE-DRUG INTERACTION	
thiothixene (Navane®)	2,7
aripiprazole (Abilify®)	1,6,8
brexpiprazole (Rexulti®)	1,6,8
iloperidone (Fanapt®)	1,6,8
perphenazine (Trilafon®)	1,6,8
risperidone (Risperdal®)	1,6,8
thioridazine (Mellaril®)	3,7,9

CLINICAL CONSIDERATIONS

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.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.
9: Per FDA label, this medication is contraindicated for this genotype.

All psychotropic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed. Propranolol might be considered off-label when being used for neuropsychiatric disorders. Please consult the FDA drug label for specific guidelines regarding its use.

Medications upon admission

Amlodipine 5mg 1 tab PO q AM for hypertension
Avorstatin 20mg 1 tab PO q hs for hyperlipidemia
Diphenhydramine 50mg q hs for insomnia
Doxazosin 2mg q hs for hypertension
Metoprol ER 100mg 3 tabs q AM for chronic left Diastolic Heart Failure
Fluticasone-salmeterol 230-21mcg 2 puffs bid
Furosemide 40mg daily for hypertension
Gabapentin 1200 mg tid for arthralgia
Lisinopril 40mg daily for hypertension
Hydralazine 50mg 1 tab PO bid for hypertension
Omeprazole 20mg ER 20mg daily for GERD
Risperidone 1mg q hs for schizophrenia
Trazodone 100mg q hs for insomnia
Venlafaxine EX 300mg q AM for depression
Acetaminophen 650mg q 4 hours PRN for knee pain
Cyclobenzaprine 10mg 1 tab PO PRN for muscle back spasm
Ibuprofen 600mg q 8 hours PRN for Arthralgia
Nitroglycerin SL 0.4mg 1 tab q 5 min up to 3 doses PRN for chest pain

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

DOB:
Order Number:
Report Date:
Clinician:
Reference:

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED
desvenlafaxine (Pristiq®)
levomilnacipran (Fetzima®)
selegiline (Emsam®)
sertraline (Zoloft®)
vilazodone (Viibryd®)

MODERATE GENE-DRUG INTERACTION	
citalopram (Celexa®)	1
escitalopram (Lexapro®)	1
mirtazapine (Remeron®)	3,7
trazodone (Desyrel®)	3,7
duloxetine (Cymbalta®)	3,7,8
fluvoxamine (Luvox®)	3,7,8

SIGNIFICANT GENE-DRUG INTERACTION	
bupropion (Wellbutrin®)	1,6
fluoxetine (Prozac®)	1,6
venlafaxine (Effexor®)	1,6
amitriptyline (Elavil®)	1,6,8
clomipramine (Anafranil®)	1,6,8
desipramine (Norpramin®)	1,6,8
doxepin (Sinequan®)	1,6,8
imipramine (Tofranil®)	1,6,8
nortriptyline (Pamelor®)	1,6,8
vortioxetine (Trintellix®)	1,6,8
paroxetine (Paxil®)	1,4,6,8

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower 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.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed. Propranolol might be considered off-label when being used for neuropsychiatric disorders. Please consult the FDA drug label for specific guidelines regarding its use.

Legal and Ethical Implications

- Potential legal and ethical questions always arise with new technology and treatment options
- Who should have access to a person’s genetic profile?
- How will we protect genetic privacy and prevent genetic discrimination in the workplace and in our health care?
- How will we as consumers use genetic information to our benefit?

Pharmacogenomics Resources

Neuro Restorative™
Rebuilding Lives. Restoring Hope.

Guidelines and Resources

- PharmGKB (PharmGKB.org) : Pharmacogenomics Knowledge Base
- CPIC (CpicPGx.org): Clinical Pharmacogenetics Implementation Consortium: provides evidence-based guidelines.

- FDA: Provides specific pharmacogenomics/drug-gene interaction in the drug labeling.

Research

- PGRN.org: Pharmacogenomics Research Network
- PharmVar.org
- www.ncbi.nlm.nih.gov/ClinVar
- https://gnomad.broadinstitute.org

Drug Labeling

FDA Drug labeling may contain information on genomic biomarkers:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes
- FDA Label database features allow navigation of drug labeling information. A total of 261 drugs and 362 drug–biomarker pairs (DBPs) were identified. DBPs can be categorized into Indication, Safety, Dosing and Information.

Retrieved from: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Limitations of Testing

- Reimbursement pathway of testing not established
- Ethical issues with genetic testing and data sharing
- Integration of pharmacogenomics, personalized medicine, and the payer and regulatory environment is still ongoing
- Clinician are generally not educated concerning available tests, associate drugs, and outcomes
- The response to a medication may be a result of the interactions of multiple genes

Review

- Pharmacogenomics is the study of how genes affect a person's response to drugs.
- Precision Medicine is data driven and takes into account variability in genes, environment, and lifestyle.
- The goal of pharmacogenomics testing is to avoid adverse side effects, maximize drug efficacy, and select responsive patients.
- Pharmacogenomic testing can improve pharmacotherapy by identifying patients at an increased risk of having no response when prescribed a medication, and/or at an increased risk of experiencing drug-induced toxicities.
- Useful resources for finding how genetic variations affect response to medications are: PharmGKB, CPIC (Clinical Pharmacogenetics Implementation Consortium), and FDA Table of Pharmacogenomic Biomarkers in Drug Labeling.
- One primary limitation of pharmacogenomic testing is that clinicians are not generally educated concerning available tests, associated drugs, and outcomes.