Genius Genes: A Helpful Guide to Understand & Interpret Psychopharmacogenomic Tests

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Disclosures

The presenters have no relevant conflict of interests to disclose regarding the content of this presentation.

Goals and Objectives

- Discuss background, pros, and cons of testing
- Review pharmacodynamic versus pharmacokinetic principles
- Practice applying sample test results to hypothetical patient cases

Stephen Warnick Jr., MD

Part I : Background

- What is pharmacogenomic testing?
- Pros
- Cons

What is pharmacogenetic testing?

Reason to test #1:

- Genetic variants are extremely common
  - If you look…. You will find….
    - Well over 100 distinct CYP2D6 variants discovered
    - In one study, about 70% had at least one actionable variant with respect to psychiatric medication

Mrazek, DA; Psychiatric pharmacogenomic testing in clinical practice, Dialogues in Clinical Neuroscience; 12;69-76 (2010)
Gross T & Daniel J, Overview of pharmacogenomic testing in clinical practice, Mental Health Clinician; 2018;8:235-241.

Reason to test #2:

accessdata.fda.gov

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH TEGRETOL. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH TEGRETOL. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH TEGRETOL UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE **WARNINGS** AND **PRECAUTIONS, LABORATORY TESTS**).

- FDA includes some genetic testing in package inserts
  - More than 200 medicines have pharmacogenomic information in FDA label
    - 40 of these are neuropsychiatric medications
      - Ex: HLA for Carbamazapine
      - Ex: HLA-B*5701 for abacavir

Gross T & Daniel J, Overview of pharmacogenomic testing in clinical practice, Mental Health Clinician; 2018;8:235-241.

Reason to test #3:

- Potential cost savings
  - RCT showed with $1,036 savings per patient/year for meds [1]
  - Retrospective study showing more visits to doctor, increase in work absence, and higher healthcare costs for patients not genetically matched to their meds.[2]

Winner JG, Carhart JM, Altar CA, Goldfarb S, Allen JD, Lavezzari G, Parsons KK, Marshak AG, Garavaglia S, Dechairo BM. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Curr Med Res Opin. 2015;31(9):1633-43.
Winner JG, Allen JD, Anthony Altar C, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry. 2013 Mar; (3(3):e242.

Reason to test #4:

- Patient safety

Pharmacogenetics of Neonatal Opioid Toxicity Following Maternal Use of Codeine During Breastfeeding: A Case–Control Study

P Madadi[1,2], CJD Ross[3], MR Hayden[3], BC Carleton[4], A Gaedigk[5], JS Leeder[5] and G Koren[1,2,6]

A large number of women receive codeine for obstetric pain while breastfeeding. Following a case of fatal opioid poisoning in a breastfed neonate whose codeine prescribed mother was a CYP2D6 ultrarapid metabolizer (UM), we examined characteristics of mothers and infants with or without signs of central nervous system (CNS) depression following codeine exposure while breastfeeding in a case–control study. Mothers of symptomatic infants ($n = 17$) consumed a mean 59% higher codeine dose than mothers of asymptomatic infants ($n = 55$) (1.62 (0.79) mg/kg/day vs. 1.02 (0.54) mg/kg/day; $P = 0.004$). There was 71% concordance between maternal and neonatal CNS depression. Two mothers whose infants exhibited severe neonatal toxicity were CYP2D6 UMs and of the *UGT2B7*2/*2* genotype. There may be a dose–response relationship between maternal codeine use and neonatal toxicity, and strong concordance between maternal-infant CNS depressive symptoms. Breastfed infants of mothers who are CYP2D6 UMs combined with the *UGT2B7*2/*2* are at increased risk of potentially life-threatening CNS depression.

Madadi P, Ross CJD, Hayden MR et al, Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breast feeding: a case control study, *Clinical Pharmacology & Therapeutics* (2008); **85**, 1, 31–3

Reason **not** to test #1:

- Added cost to treatment
  - Insurance coverage varies (sliding scale for some – but is best use of resources)?
  - Overall cost effectiveness data is conflicting
    - Need more INDEPENDENT data (positive data from testing companies)

Rosenblat J, Lee Y, McIntyre R. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systemic review of clinical trials and cost-effectiveness studies. J Clin Psych. 2017: 78 (6);720-729.
Groessel E, Tally S, Hillary N, Mariel A, Graces J. Cost-effectiveness of a pharmacogenetic test to guide treatment for major depressive disorder. J Managed Care Spec Pharm. 2018: 24(8); 726-734.

Reason **not** to test #2:

- Less about 'perfect' drug and more about which medicines to avoid
  - So is this useful to treatment naïve patients?

Reason **not** to test #3:

- Lack of comfort in interpreting results
  - Studies have found less than 15% of pharmacists and primary care clinicians are comfortable in interpreting testing results and counseling patients

Frigon MP, Blackburn ME, Dubois-Bouchard C et al, Pharmcogenetic testing in primary care practice: opinions of physicians, pharmacists, and patients, 2019; 20:589-598

Reason **not** to test #4:

- High degree of variability between testing company panels
  - Need to know what you are interpreting
    - One comparison using 20 test panels found no two panels included all of the same 2D6 or 2C19 alleles
    - When 4 test panels were compared for the same 14 genes the agreement on antidepressant recommendations was only 56%

Bousman CA, et al. BMC *Psychiatry*. 2017;17:60.
Bousman CA, et al. *Pharmacogenomics J*. 2018;18:613-622.
Bousman CA, et al. *Pharmacogenet Genomics*. 2017;27:387-393.
Rosenblat JD, et al. *J Affect Disord*. 2018;241:484-491.

Reason **not** to test #5

- Do not improve clinical outcomes for all patients
  - Studies done by gene testing show improvements
  - Others show less robust or no improvement
  - Maybe concordance in using for moderate-to-severe patients with depression

Drozda K, Muller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. Pharmacotherapy. 2014;34:166-184.
Rosenblat J, Lee Y, McIntyre R. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? A systemic review of clinical trials and cost-effectiveness studies. J Clin Psych. 2017: 78 (6);720-729.

Chris White, MD, JD, MHA

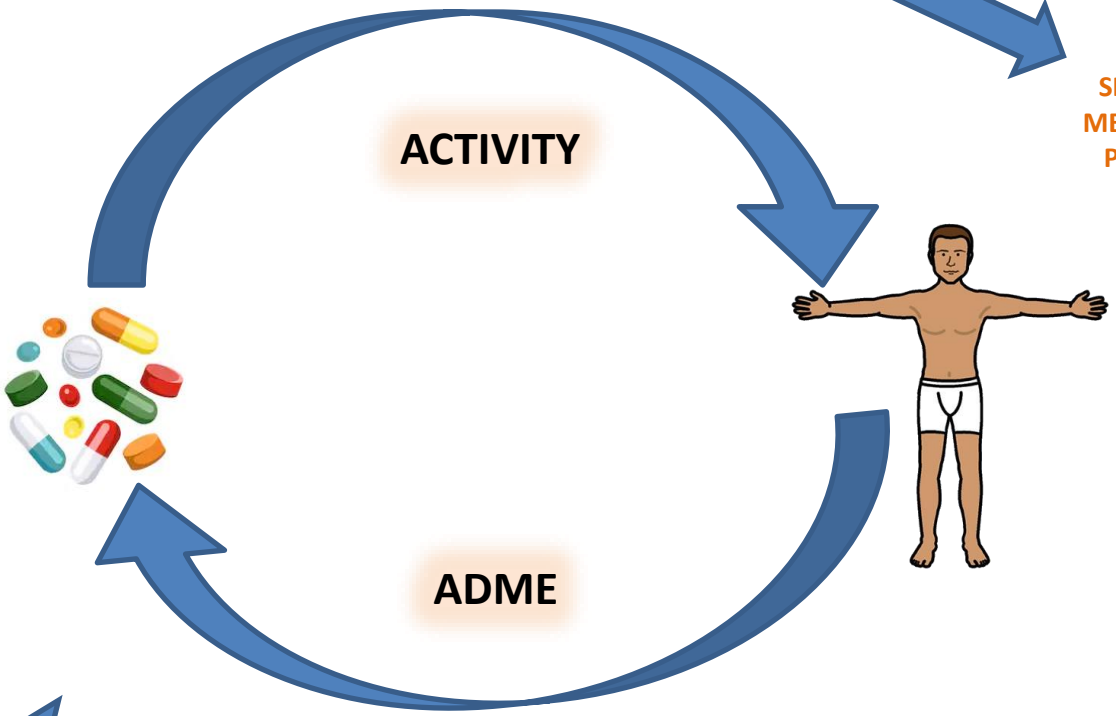
Part II : Let's get Basic....

- Pharmacokinetic overview
- Pharmacodynamic overview

Pharmacodynamics

"What a Drug Does to the Body"

TARGET ORGAN
RECEPTOR
PROTEIN
SIGNALING PATHWAY
MECHANISM OF ACTION
PHYSIOLOGIC EFFECT
DOSE-RESPONSE

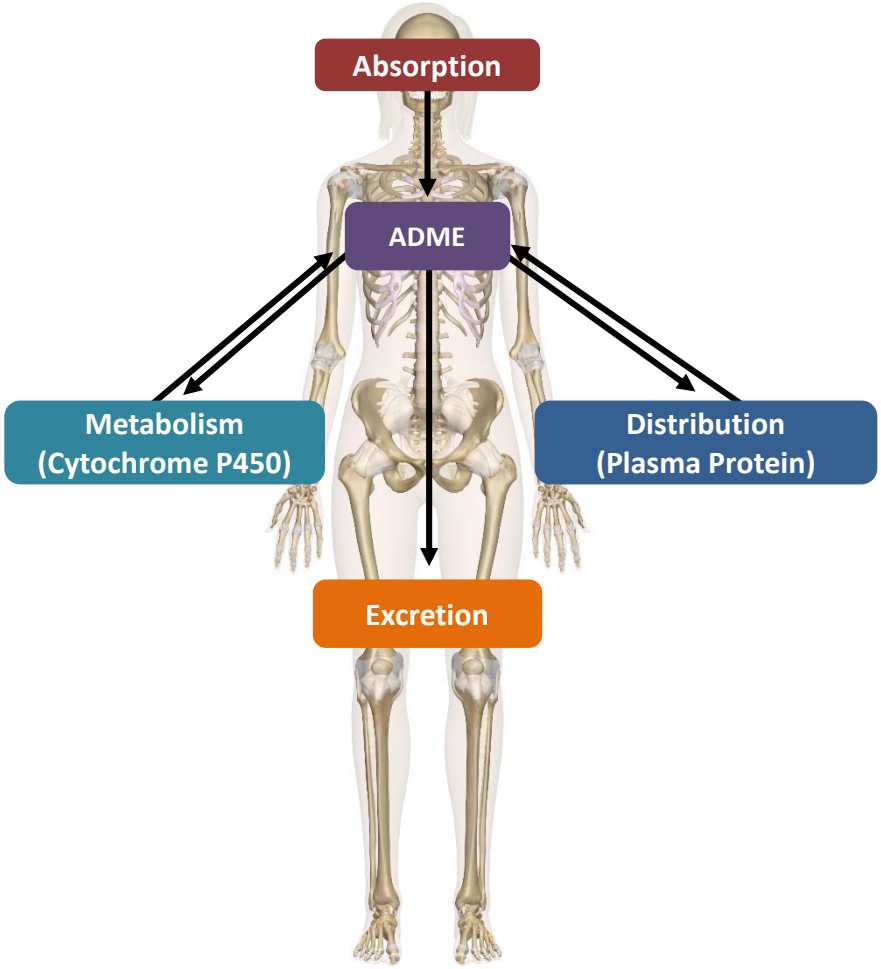


ADMINISTRATION
ABSORPTION
DISTRIBUTION
METABOLITE
EXCRETION
URINE
PLASMA DRUG CONCENTRATION

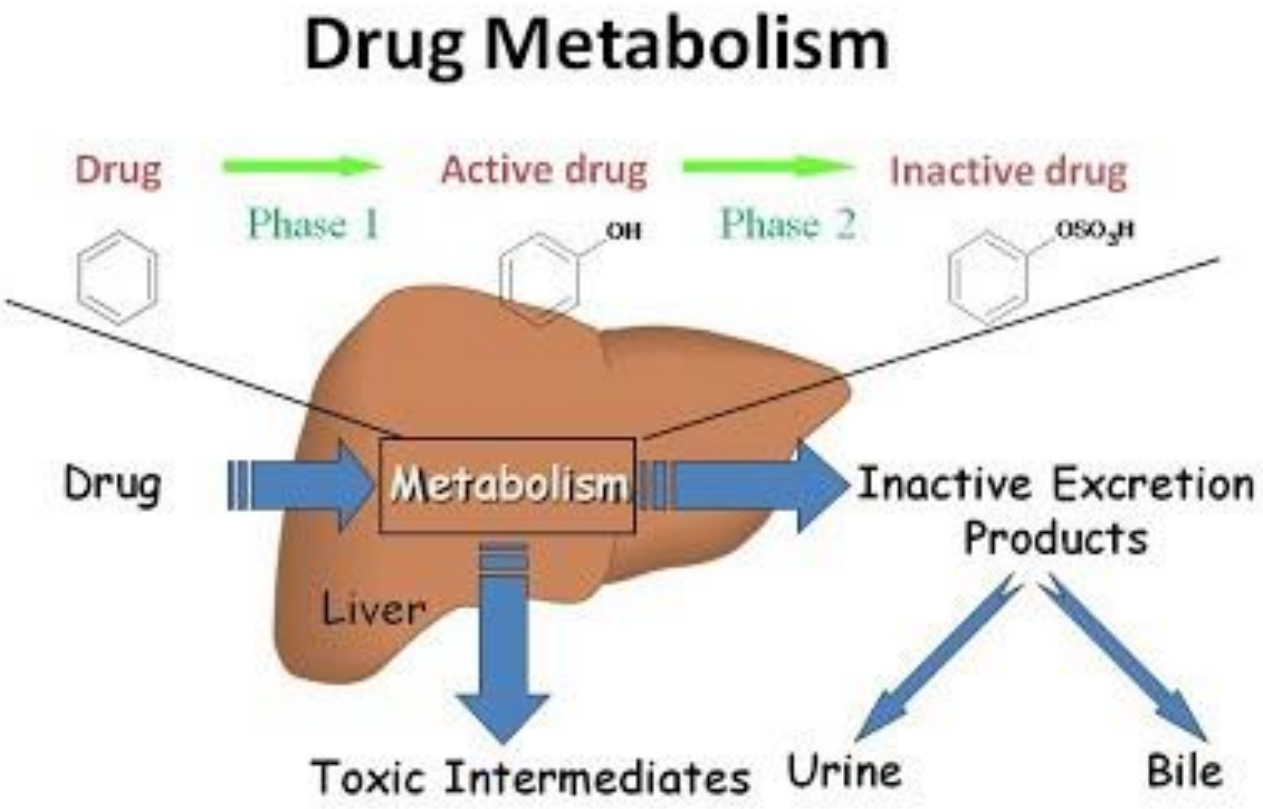
Pharmacokinetics

"What the Body Does to a Drug"

Pharmacokinetic A

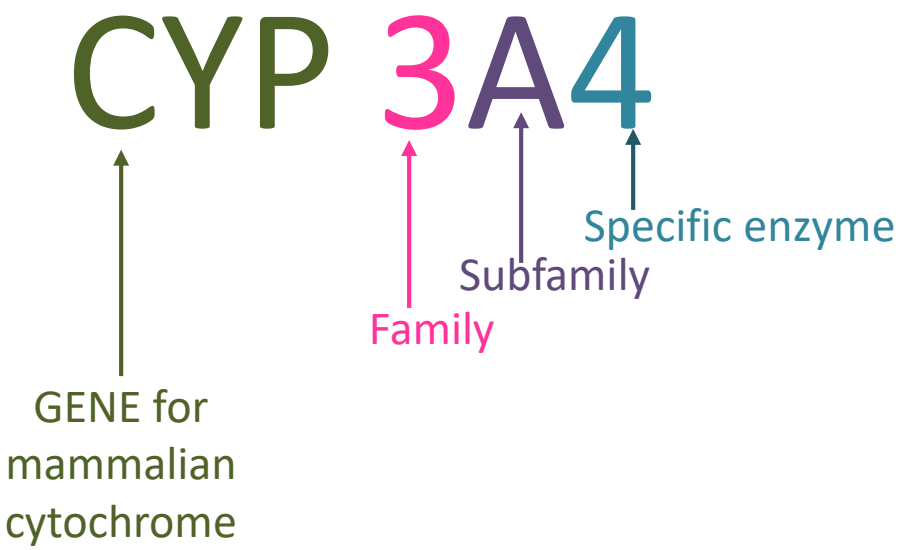


Pharmacokinetic B

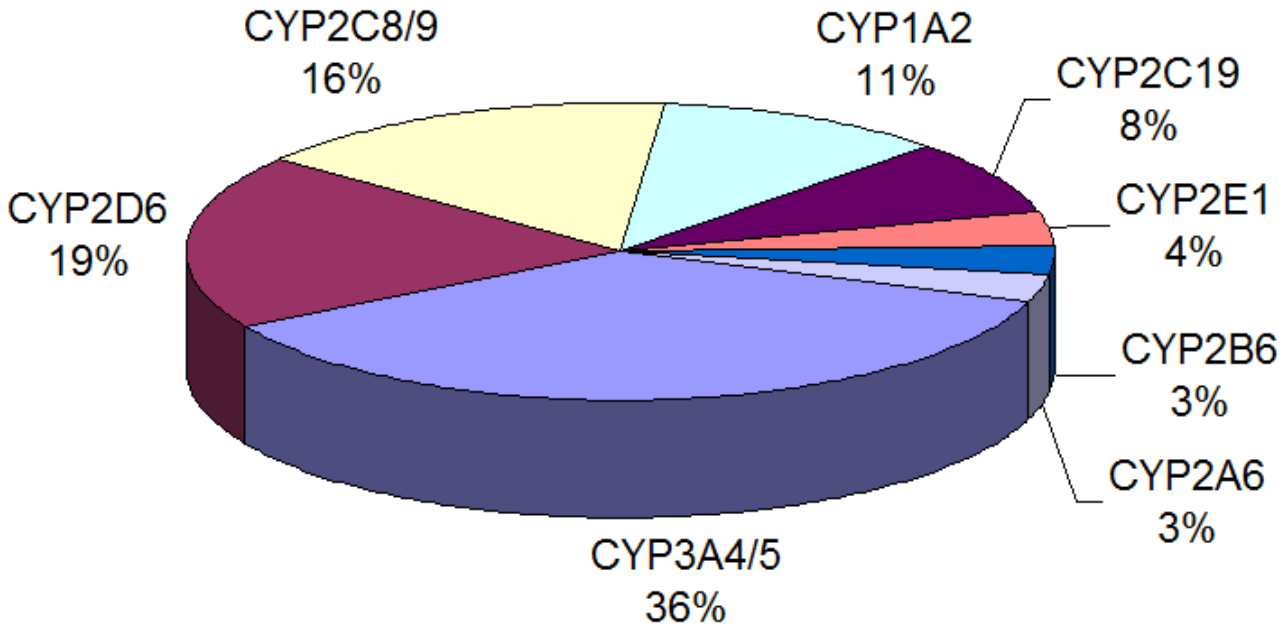


Pharmcokinetic C

Cytochrome P450 Nomenclature

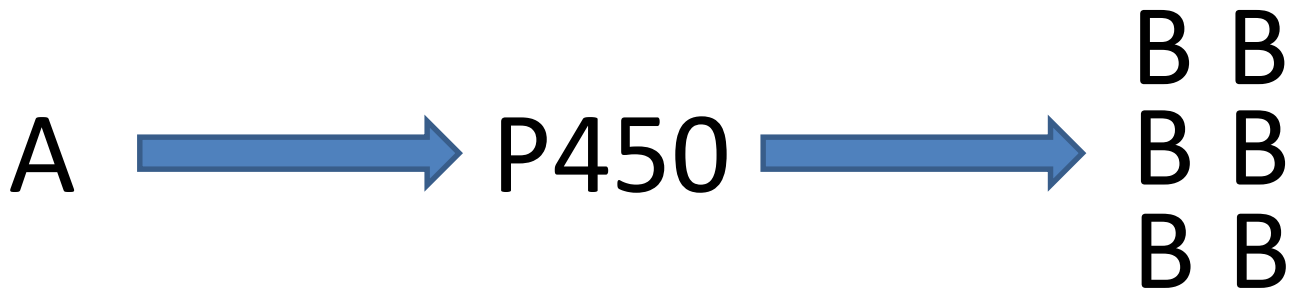


Pharmacokinetic D



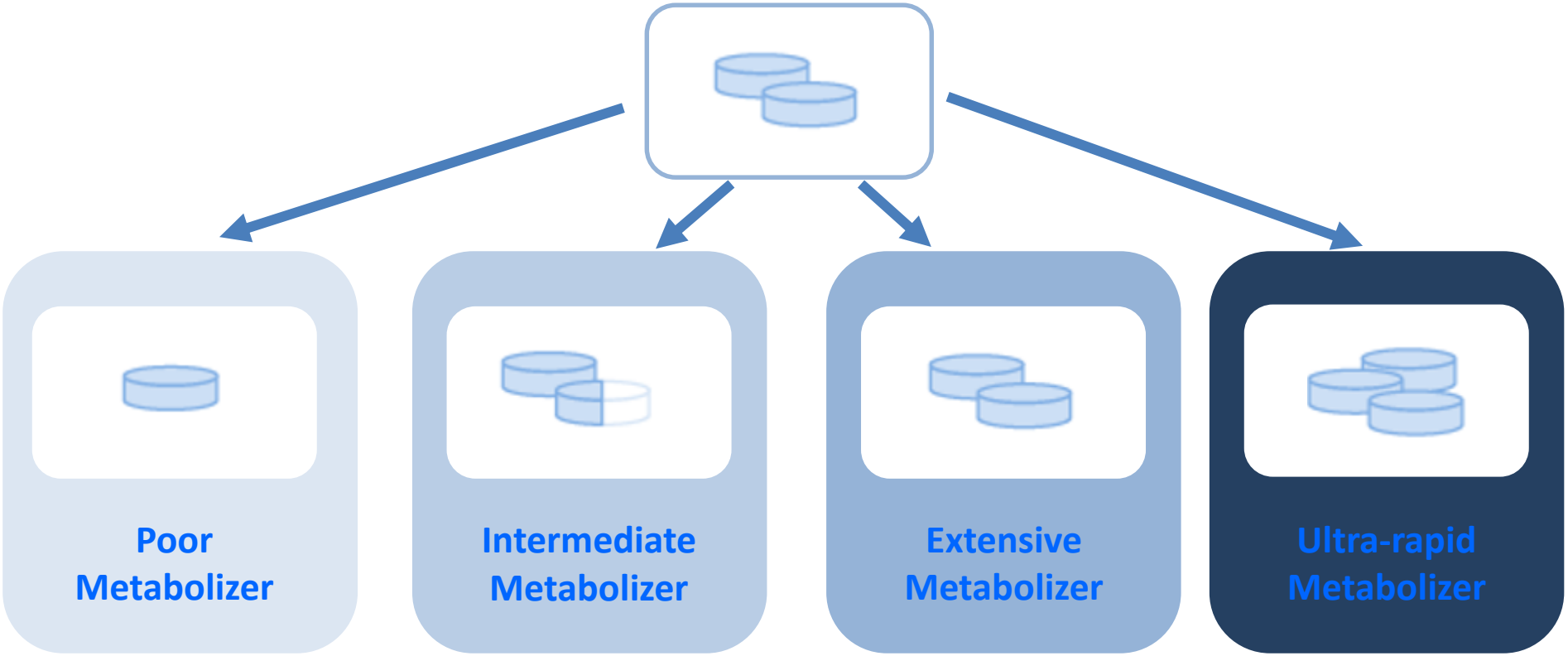
Pharmacokinetic E: Induction vs Inhibition

Inducer

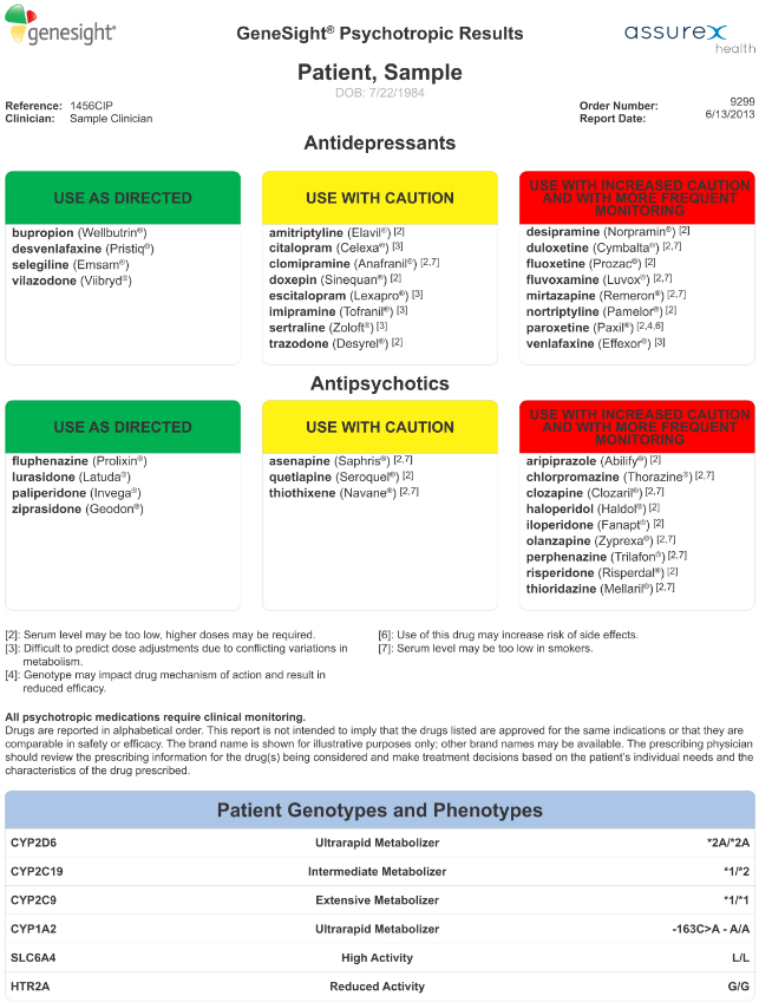


Inhibitor

Pharmacokinetic F: P450 Metabolizing Spectrum Names



Genesight Report Example



genesight

GeneSight® Psychotropic Results

assurex health

Patient, Sample

DOB: 7/22/1984

Reference: 1456CIP
Clinician: Sample Clinician

Order Number: 9299
Report Date: 6/13/2013

Antidepressants

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	**amitriptyline** (Elavil®) [2]	**desipramine** (Norpramin®) [2]
desvenlafaxine (Pristiq®)	**citalopram** (Celexa®) [3]	**duloxetine** (Cymbalta®) [2,7]
selegiline (Emsam®)	**clomipramine** (Anafranil®) [2,7]	**fluoxetine** (Prozac®) [2]
vilazodone (Viibryd®)	**doxepin** (Sinequan®) [2]	**fluvoxamine** (Luvox®) [2,7]
	escitalopram (Lexapro®) [3]	**mirtazapine** (Remeron®) [2,7]
	imipramine (Tofranil®) [3]	**nortriptyline** (Pamelor®) [2]
	sertraline (Zoloft®) [3]	**paroxetine** (Paxil®) [2,4,6]
	trazodone (Desyrel®) [2]	**venlafaxine** (Effexor®) [3]

Antipsychotics

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
fluphenazine (Prolixin®)	**asenapine** (Saphris®) [2,7]	**aripiprazole** (Abilify®) [2]
lurasidone (Latuda®)	**quetiapine** (Seroquel®) [2]	**chlorpromazine** (Thorazine®) [2,7]
paliperidone (Invega®)	**thiothixene** (Navane®) [2,7]	**clozapine** (Clozaril®) [2,7]
ziprasidone (Geodon®)		**haloperidol** (Haldol®) [2]
		iloperidone (Fanapt®) [2]
		olanzapine (Zyprexa®) [2,7]
		perphenazine (Trilafon®) [2,7]
		risperidone (Risperdal®) [2]
		thioridazine (Mellaril®) [2,7]

[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.
[7]: Serum level may be too low in smokers.

All psychotropic medications require clinical monitoring.
Drugs are reported in alphabetical order. 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.

Patient Genotypes and Phenotypes

CYP2D6	Ultrarapid Metabolizer	*2A/*2A
CYP2C19	Intermediate Metabolizer	*1/*2
CYP2C9	Extensive Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163C>A - A/A
SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

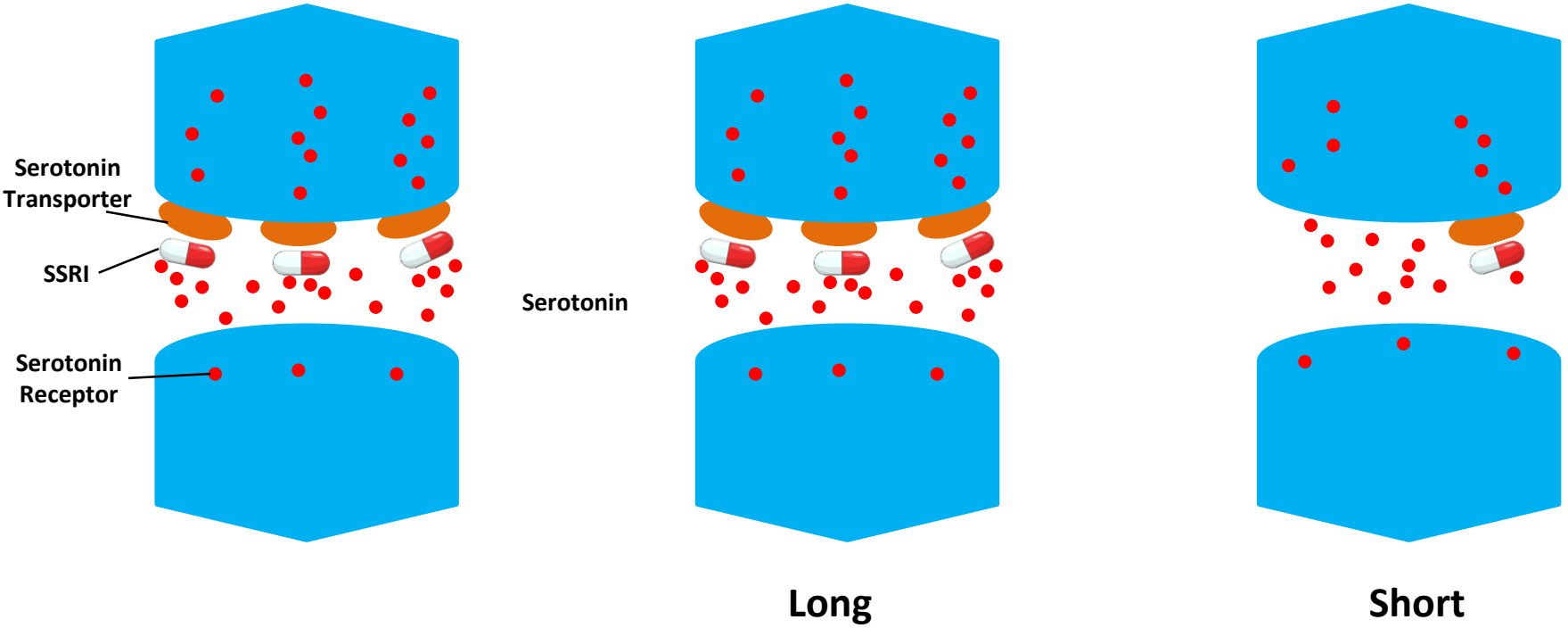
Genomind Report Example

GENOMIND

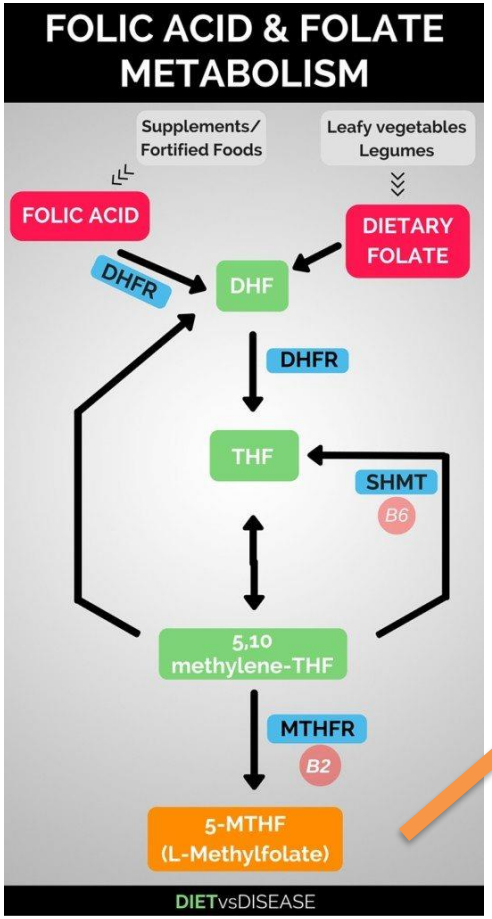
RESULTS REPORT: Pharmacokinetic Gene Variations; CYP450 Drug Metabolism

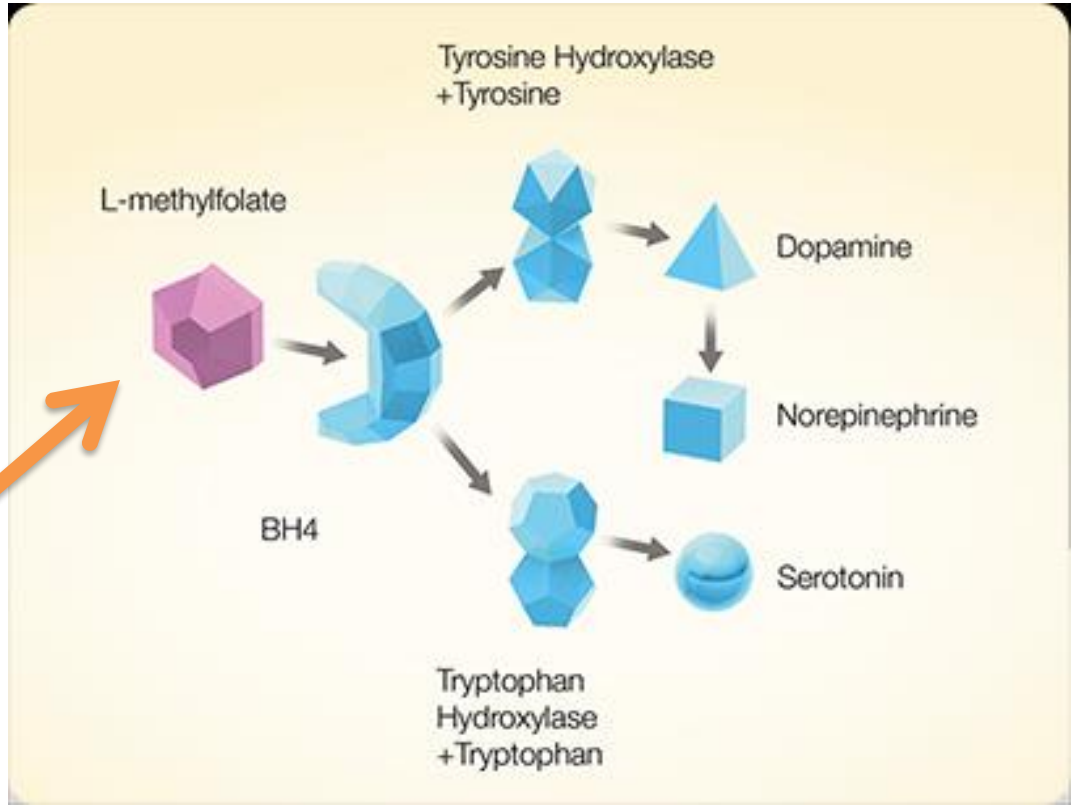
GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
CYP1A2 UM *1F/*1F [High activity **in the presence of inducers**]	***Ultrarapid Metabolizer:*** *↑ metabolism of drugs leading to ↓ serum levels and poorer efficacy* ***in the presence of inducers****. Possible adverse events associated with toxic metabolites* • A dose adjustment or alternate therapy may be necessary • CYP1A2 *1F is highly induced by certain substances including tobacco/marijuana smoke or other medications; if patient uses these substances, a higher dose of CYP1A2 substrates may be required (see the Genecept Assay Report Interpretation Guide for full list of inducers)	⚠	**Use caution** with medications metabolized by CYP1A2 when inducer is present *See Drug Interaction Summary for Details*
CYP2B6 IM *5/*5 [Intermediate activity]	***Intermediate metabolizer:*** *↑ risk of elevated serum levels, drug interactions, and ↓ production of active moieties* • A dose adjustment or alternate therapy may be necessary	⚠	**Use caution** with medications metabolized by CYP2B6 *See Drug Interaction Summary for details*
CYP2C9 EM *1/*1 [Normal activity]	*Variations in the CYP2C9 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP2C19 EM *1/*1 [Normal activity]	*Variations in the CYP2C19 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP2D6 EM *1/*3 [Normal activity]	*Variations in the CYP2D6 liver enzyme can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity	✓	There are no known gene-drug interactions for this genotype
CYP3A4 *1/*1 CYP3A5 *1/*6 [Normal activity]	*Variations in the CYP3A4/5 liver enzymes can result in altered drug metabolism and unexpected drug serum levels* • This genotype confers normal activity • CYP3A activity is determined by the sum activity of the CYP3A family of genes; in adults the most influential are CYP3A4 and 3A5	✓	There are no known gene-drug interactions for this genotype

Pharmacodynamics Gene #1: Serotonin Transporter SLC6A4

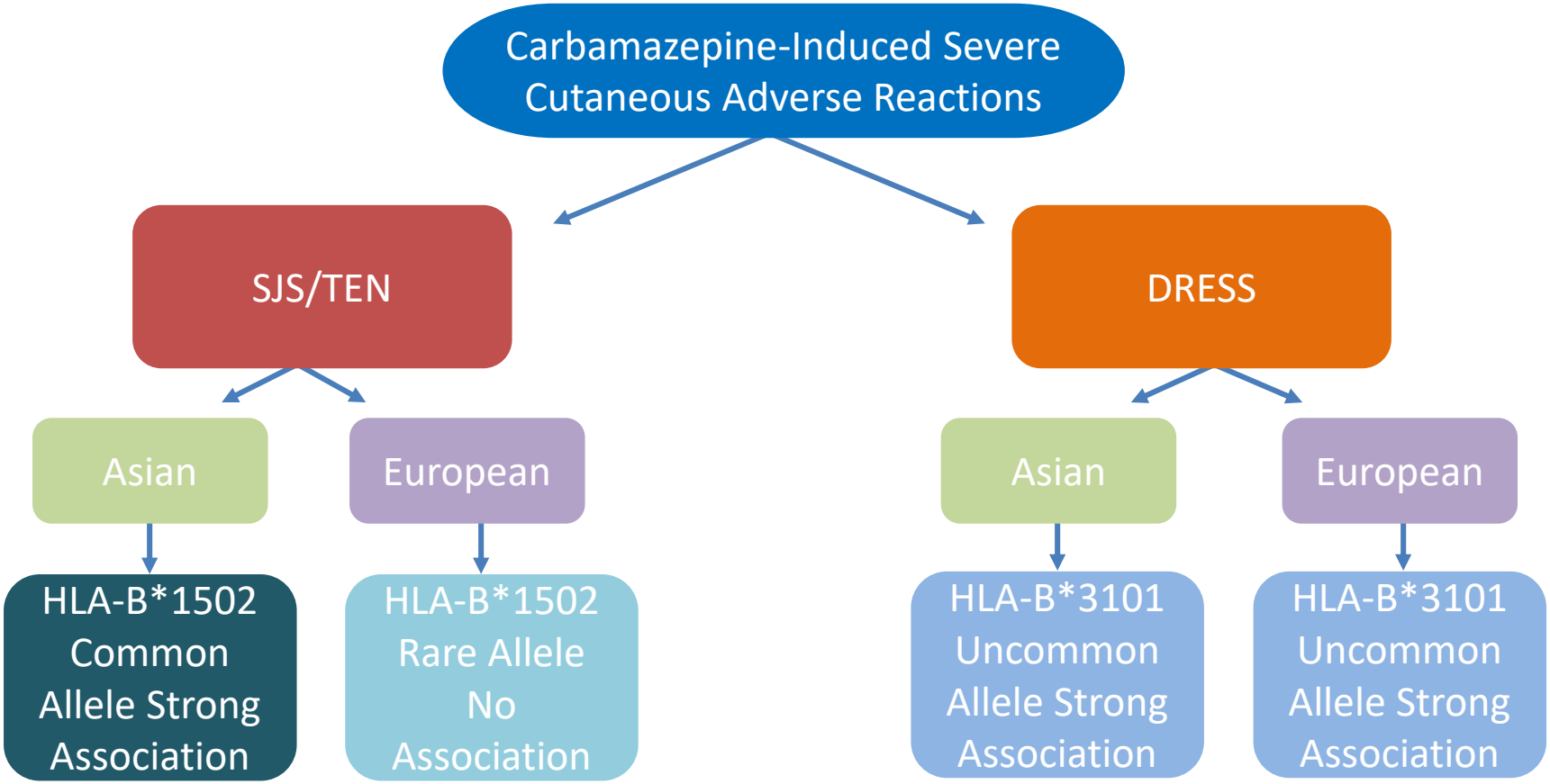


Pharmacodynamics Gene #2: Folic Acid MTHFR





Pharmacodynamics Gene #3: HLA



Genesight Report Example

PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

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 — **Higher Risk**
Present

This patient carries the HLA-B*1502 allele, which suggests higher risk of serious dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), when taking certain mood stabilizers.

HLA-A*3101 — **Higher Risk**
A/T

This patient is heterozygous for the A allele and the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher 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.

Genomind Report Example

GENOMIND www.genomind.com

RESULTS REPORT: Pharmacodynamic Gene Variations; Drug Target Sites

Use caution with related therapies | Therapeutic options | No known gene-drug interaction

GENE RESULT	THERAPEUTIC IMPLICATIONS	INTERACTION	CLINICAL IMPACT
Serotonin Transporter (SLC6A4) S/S [High risk of non-response]	*SLC6A4 is a presynaptic transmembrane protein responsible for serotonin reuptake* • SSRIs act by blocking this transporter to produce a therapeutic response • Higher risk of poor response, slow response or intolerance to SSRIs; potential increased risk for PTSD and reduced stress resilience • Therapeutic options such as atypical antidepressants or SNRIs may be used as clinically appropriate	⚠ 💡	**Use caution** with SSRIs **Therapeutic options: atypical antidepressants** or **SNRIs** may be used if clinically indicated
Calcium Channel (CACNA1C) A/A [Highest risk of altered neuronal signaling]	*CACNA1C is a subunit of L-type voltage gated calcium channels which is involved in excitatory signaling in the brain* • Abnormal calcium signaling may be clinically associated with conditions characterized by mood instability or lability	💡	**Therapeutic options: atypical antipsychotics, mood stabilizers** and/or **omega-3 fatty acids** may be used if clinically indicated
Melanocortin 4 Receptor (MC4R) A/A [High weight gain risk]	*MC4R is a receptor that plays a central role in the control of food intake* • Risk of increased weight gain and BMI in healthy individuals and this risk may be further exacerbated with atypical antipsychotics **High risk**: Clozapine; Olanzapine; **Medium risk**: Aripiprazole; Iloperidone; Paliperidone; Quetiapine; Risperidone **Lower risk**: Asenapine; Brexpiprazole; Cariprazine; Lurasidone; Ziprasidone	⚠	**Use caution** with atypical antipsychotics
Methylenetetrahydro-folate Reductase (MTHFR) C677T: T/T A1298C: A/C [Low activity]	*MTHFR is an enzyme responsible for the conversion of folic acid to methylfolate which is a precursor needed for serotonin, norepinephrine and dopamine synthesis* • Risk for reduced MTHFR enzyme activity and reduced methylfolate production • Folic acid-based supplementation of SSRIs and SNRIs show superior symptom reduction and medication adherence compared to SSRIs/SNRIs alone in Major Depressive Disorder	💡	Higher intake of folic acid based interventions may be required **Therapeutic options: l-methylfolate** may be used if clinically indicated
Brain-derived Neurotrophic Factor (BDNF) Met/Met	*BDNF is a protein involved in neuronal development and neural plasticity* • Potential risk for increased depression symptoms, impaired working memory, and altered stress response • Studies have shown that Met carriers may have less satisfactory response to SSRIs in Caucasians, but not Asians, however larger studies need to be conducted to confirm these findings • Exercise has been linked to improvements in cognition, and recent studies show that Met allele carriers may demonstrate enhanced effects of exercise on working memory compared to Val/Val patients	💡	**Therapeutic options:** increased levels of **physical activity/exercise** if clinically appropriate

Kevin Brazill, DO, MS

Part III : Let's apply it to some *patients*…

- Patient Case #1 : Gordon
- Patient Case #2 : Hannah

Gordon

- 58 yr old Asian male diagnosed w/ schizoaffective disorder.
- Hx of 7 inpatient hospitalizations, multiple 1st and 2nd gen antipsychotic medications, mood stabilizers, and SSRIs, SNRIs, and TCAs over 30 year life course of illness. Involved in day programming, case management and therapy.
- Social: lives in group home, CM and pt interested in completing work training with eventual semi-independent living.

Gordon

- Current medication regimen from psych hospital:
  - Carbamazapine 400 mg BID
  - Risperidone 2 mg BID
  - Citalopram 40 mg QD
  - Benztropine 0.5 mg BID
  - Propranolol 20 mg TID
  - Insulin (Lantus) 20 units SQ HS
  - Metformin 1000 mg BID
  - Losartan 100 mg QD

Gordon

Gordon reports that he "just doesn't feel right". He says:

- "I'm always tired, even when I wake up after sleeping all night, I want to go right back to bed."
- "My mouth is so dry it feels like my teeth are stuck to my tongue."
- "I keep hearing my dad say: 'Gordo! You're a stupid idiot!'"
- "I'm either hungry or nauseous all the time and I'm fatter than ever."

Gordon

- Insurance: Medicare. Cost: $0
- Genetic test: Genesight
- Results
  - SLC6A4 => S/S => 'small vacuum cleaners' => Poor SSRI response
  - MTHFR => T677T => likely high homocysteine => Supplement with L-methylfolate
  - HLA-B 1502 => increased risk of SJS with carbamazapine
  - CYP2C19 => Ultra rapid metabolizer
  - CYP2D6 => Poor Metabolizer

- Knowing these things, what can we do to help Gordon?

Gordon

- Selected psychiatric medications from psych hospital:
  - Carbamazapine 400 mg BID -- ## HLA Issue, further depletes folate raising cardiac risk ##
  - Risperidone 2 mg BID -- ## poor 2D6, pro-drug ##
  - Citalopram 40 mg QD -- ## 2C19 lowers & 2D6 raises, SLC6A4 suggests poor SSRI response, MTHFR suggests need for L-methylfolate supplementation ##

Hannah

- 22 year old caucasian woman diagnosed with MDD, recurrent, severe w/o psychosis and GAD.
- Hx of one inpatient hospitalization for SA at age 20, ongoing outpatient therapy (IOP and weekly psychotherapy) and multiple trials of SSRIs and benzodiazepines.
- Social: part-time college student, lives with parents, unable to work due to mental illness, smokes 2ppd

Hannah

- Current medication regimen:
  - Duloxetine 60mg daily
  - Buspirone 10 mg TID
  - Lorazepam 0.5 mg BID PRN severe anxiety
  - Aripiprazole 2 mg daily

Hannah

Hannah reports, “Nobody I know is this anxious and I don’t feel like it’s ever going to get better. She says:

- “I had to drop two classes and now I’m only taking 6 credits and I can barely make myself go to school.”
- “I had to quit my job because my boss told me I wasn’t doing a good job.”
- ”My libido is like… zilch. I have zero interest in sex.”
- “Besides feeling anxious *all the time*, I don’t have any other emotions. I’m like a zombie.”

Hannah

- Insurance: Health Alliance (private). Cost: $150
- Genetic test: Genecept (Genomind)
- Results
  - SLC6A4 S/S => SSRIs less effective
  - MTHFR => Intermediate enzyme activity
  - CYP1A2 => Ultrarapid metabolizer plus smoker

- Knowing these things, what can we do to help Hannah?

Hannah

- Current medication regimen:
  - Duloxetine 60mg daily => ## 1A2 ultrarapid metabolizer so may need higher dose, watch if quits smoking ##
  - Buspirone 10 mg TID ## no change ##
  - Lorazepam 0.5 mg BID PRN severe anxiety ## no change ##
  - Aripiprazole 2 mg daily ## no change ##

Conclusion

- Point #1 : What is the standard of care for PCPs?
- Point #2 : Tons of information on each report, but not all of it is actionable. Only use what you can interpret.
- Point #3 : This is coming so makes sense to have at least some in clinic trained up…. Direct to consumer marketing.

Selected References

- Bousman CA, et al. BMC *Psychiatry*. 2017;17:60.
- Bousman CA, et al. *Pharmacogenomics J*. 2018;18:613-622.
- Bousman CA, et al. *Pharmacogenet Genomics*. 2017;27:387-393.
- Drozda K, Muller DJ, Bishop JR. Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options. Pharmacotherapy. 2014;34:166-184.
- Frigon MP, Blackburn ME, Dubois-Bouchard C et al, Pharmcogenetic testing in primary care practice: opinions of physicians, pharmacists, and patients, 2019; 20:589-598
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