



How Genetic Testing Can Help with Depression Treatment

Holly Johnson, Ph.D.
Ronni Shapiro



Mental Health America
B4Stage4

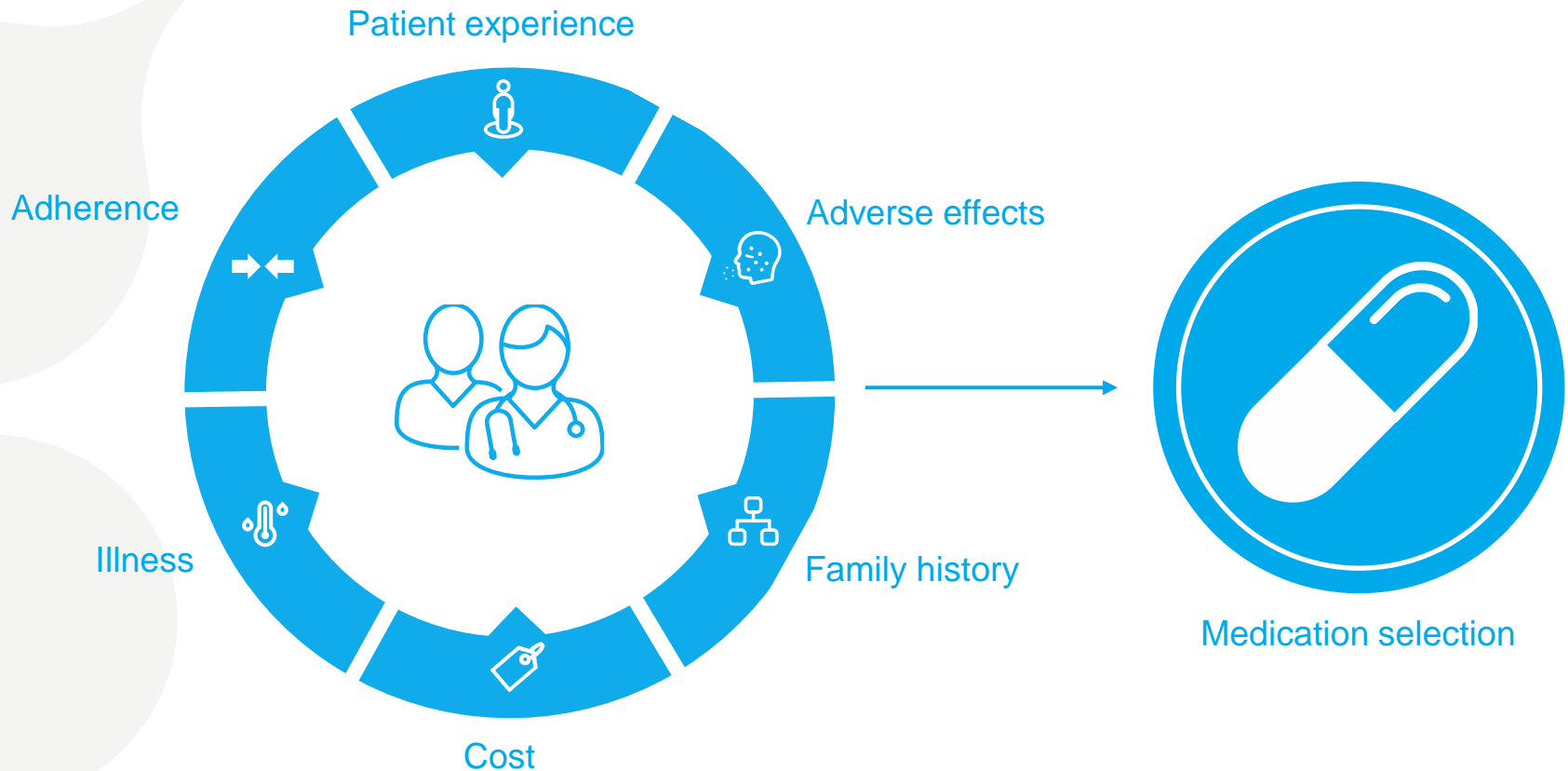


How Genetic Testing Can Help with Depression Treatment



Holly Johnson, Ph.D.
Senior Manager, Medical Information

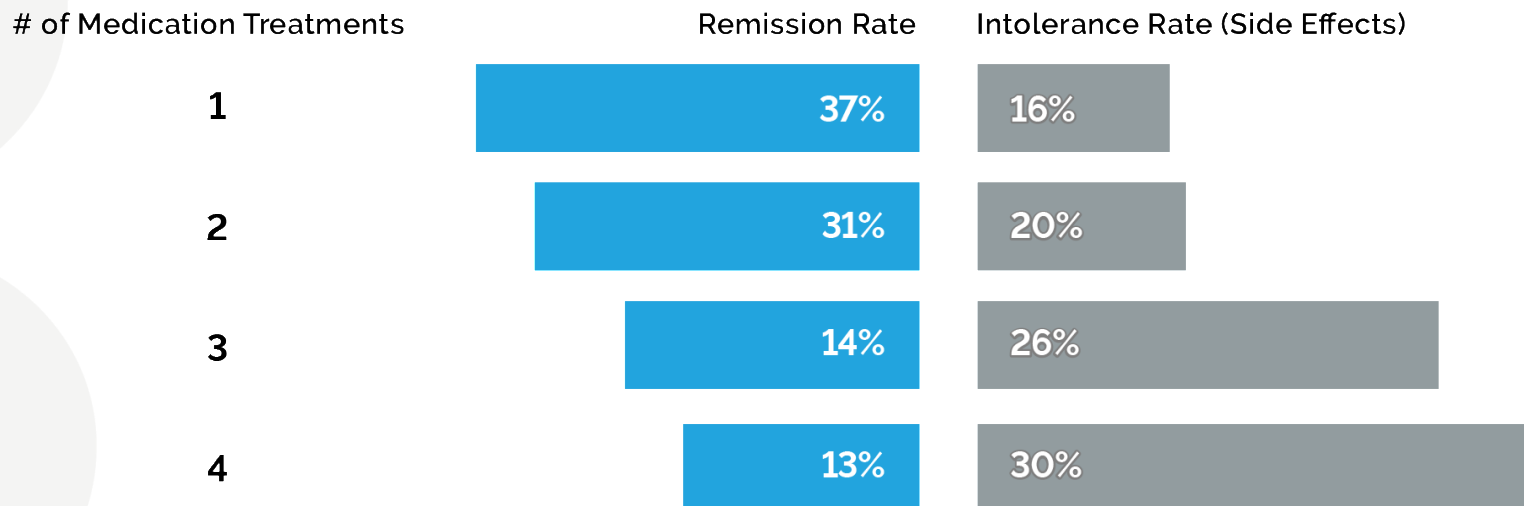
What Your Doctor Considers Before Prescribing Medication Today



This Approach Doesn't Always Work

Less than 40% of patients achieve remission with initial drug treatment. With each additional medication trial, the chance of remission decreases, while treatment intolerance increases.

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial¹



1. Rush AJ, et al. Am J Psychiatry. 2006.

Why Don't These Medications Work?

Why is remission so difficult to achieve?

Here are some of the usual culprits:

- ✓ Adherence
- ✓ Environmental Factors
- ✓ Cost / Insurance
- ✓ Adverse Effects

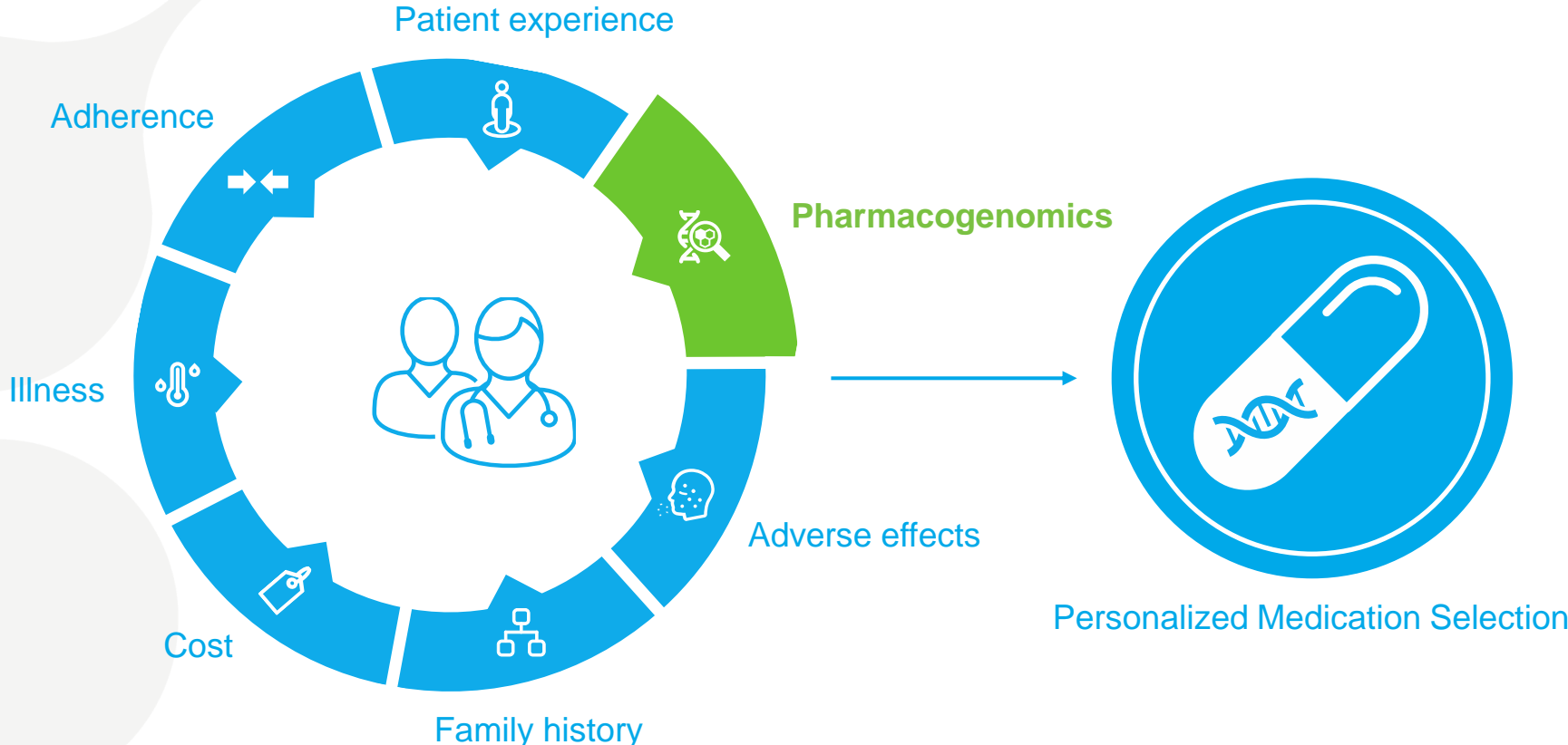
Our unique genetic makeup may undermine medication choices and may be a factor in why medications may not work.

Pharmacogenomics Defined

Pharmacogenomics is a field of research that studies how a person's genes affect how he or she responds to medications.

National Institute of General Medical Sciences

Medication Selection Using Genetic Information



The GeneSight® Psychotropic Report

GeneSight® Psychotropic COMBINATORIAL PHARMACOGENOMIC TEST



Patient, Sample

DOB: 7/22/1984
 Order Number: 219
 Report Date: 8/5/2020
 Clinician: Sample Clinician
 Reference: 1456CIP

Questions about report interpretation?

Contact our Medical Information team

📞 855.891.9415

✉ medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED

desipramine (Norpramin®)
nortriptyline (Pamelor®)
vortioxetine (Trintellix®)

MODERATE GENE-DRUG INTERACTION

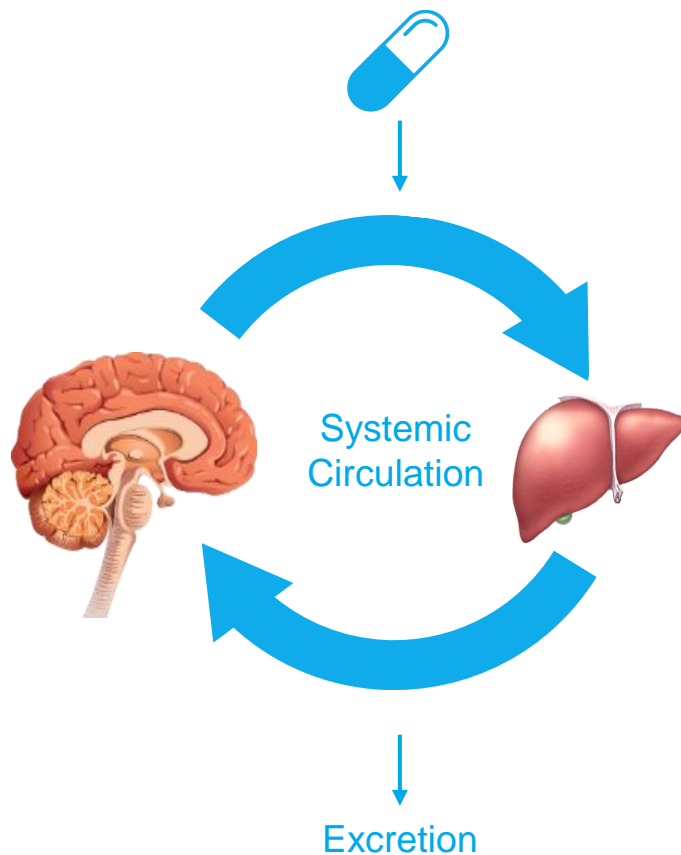
doxepin (Sinequan®) 1
imipramine (Tofranil®) 1,6
desvenlafaxine (Pristiq®) 1,8
trazodone (Desyrel®) 1,8
mirtazapine (Remeron®) 3,7,8

SIGNIFICANT GENE-DRUG INTERACTION

amitriptyline (Elavil®) 1,6
bupropion (Wellbutrin®) 1,6
clomipramine (Anafranil®) 1,6
fluoxetine (Prozac®) 1,6
selegiline (Emsam®) 1,6
duloxetine (Cymbalta®) 2,7
fluvoxamine (Luvox®) 2,7
citalopram (Celexa®) 1,4,6
escitalopram (Lexapro®) 1,4,6
paroxetine (Paxil®) 1,4,6
sertraline (Zoloft®) 1,4,6
levomilnacipran (Fetzima®) 1,6,8
venlafaxine (Effexor®) 1,6,8
vilazodone (Viibryd®) 1,6,8

Pharmacodynamics and Pharmacokinetics

Pharmacodynamic
variation changes
how the drug
affects the body



Pharmacokinetic
variation changes
how the body
affects the drug

Key Pharmacogenomic Genes

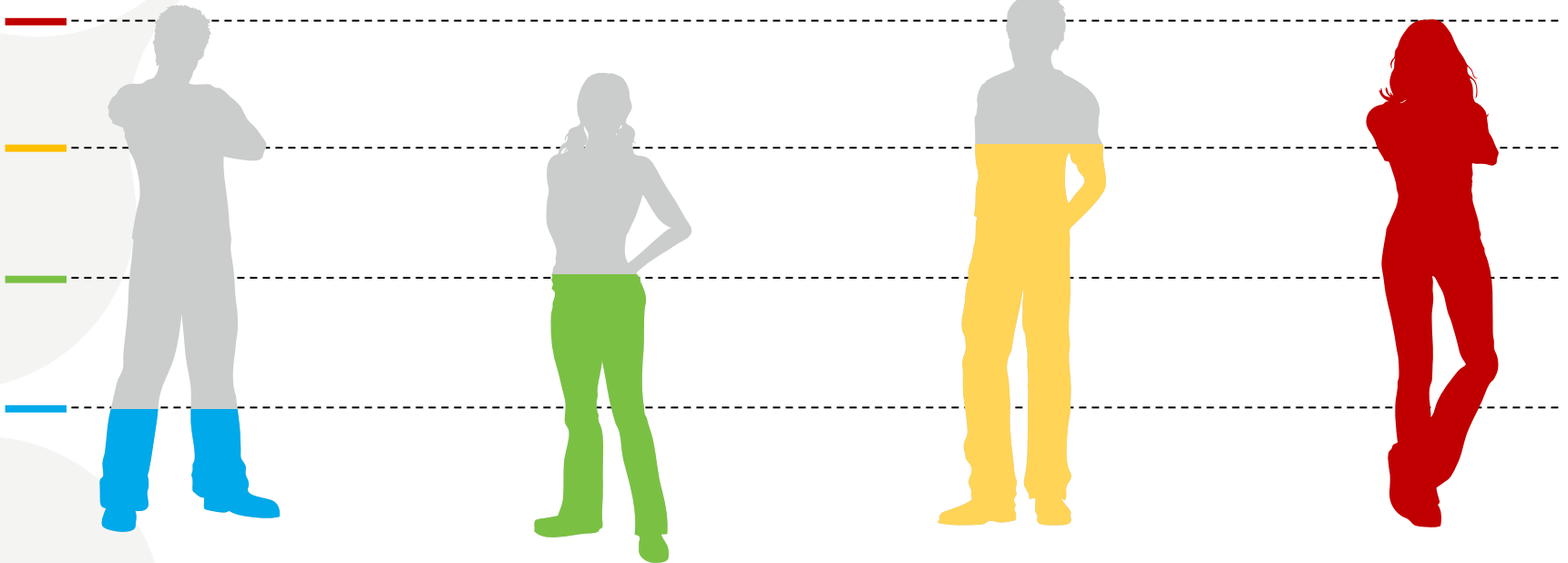
GeneSight® Psychotropic	
Pharmacokinetic (PK)	Pharmacodynamic (PD)
CYP2D6	SLC6A4 (Serotonin Transporter)
CYP2C19	5HTR2A (Serotonin 2A Receptor)
CYP2C9	HLA-B*1502 (Human Leukocyte Antigen)
CYP1A2	HLA-A*3101 (Human Leukocyte Antigen)
CYP2B6	
CYP3A4	
UGT1A4	
UGT2B15	

GeneSight Psychotropic only tests for genes that have a variant that has a significant impact on medication outcomes, as demonstrated in multiple well-designed studies¹, and appears at a high enough frequency to be clinically meaningful.

1. <https://genesight.com/references>

How Genetics Can Affect Medication Blood Levels

Phenotypes



Ultrarapid Metabolizer

Breaks down medications rapidly. May not get enough medication at normal doses.

Extensive (Normal) Metabolizer

Breaks down medications normally. Has normal amounts of medication at normal doses.

Intermediate Metabolizer

Breaks down medications slowly. May have too much medication at normal doses.

Poor Metabolizer

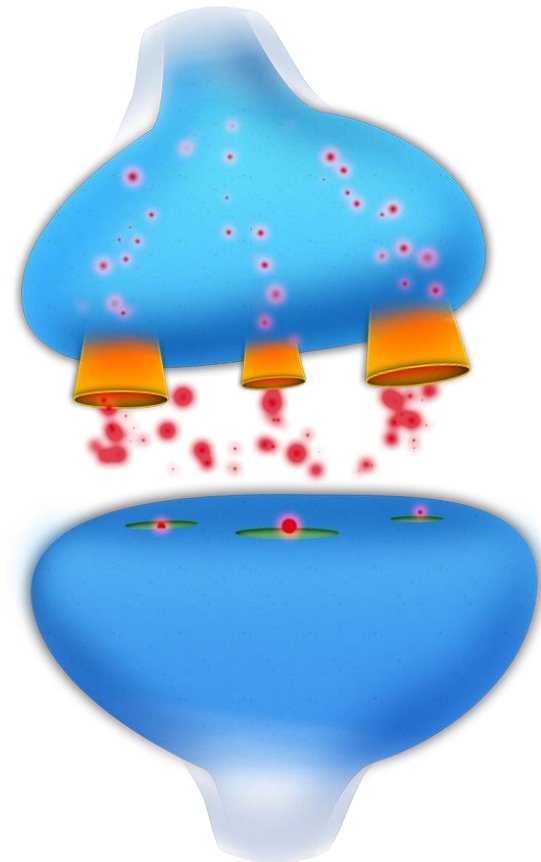
Breaks down medications very slowly. May experience side effects at normal doses.

Pharmacodynamic Pharmacogenomics – SLC6A4

The serotonin transporter is encoded by the SLC6A4 gene.

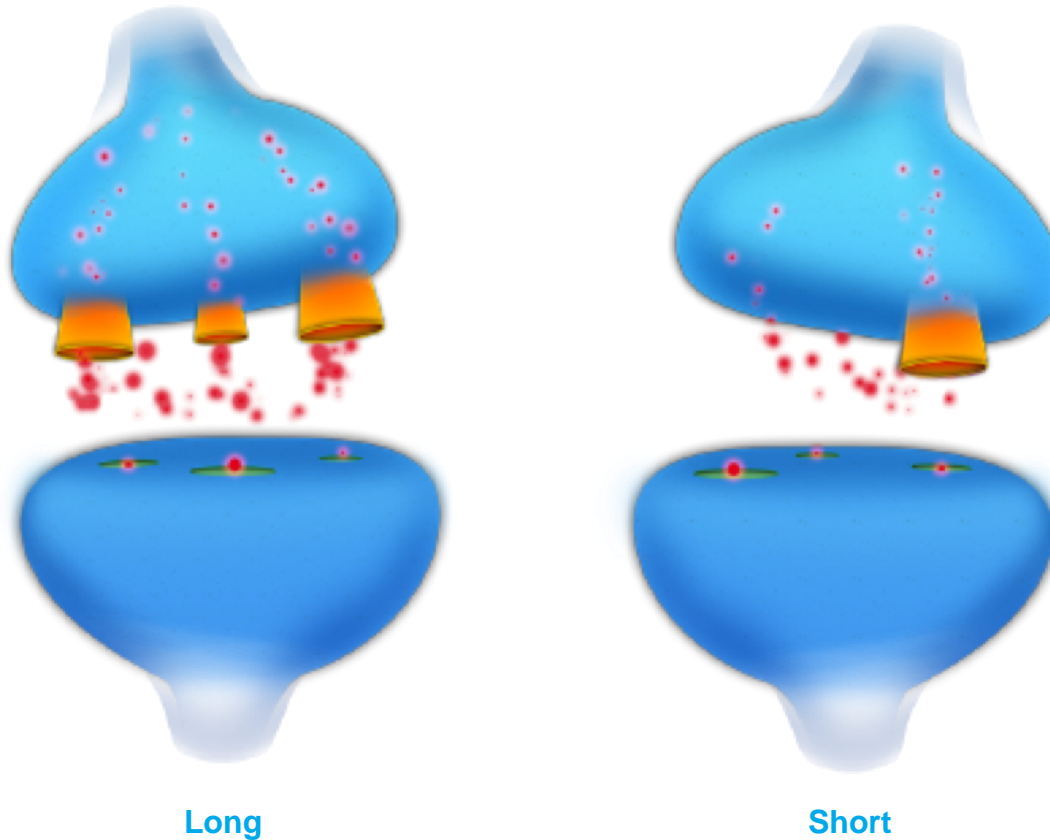
It is responsible for reuptake of serotonin into the presynaptic neuron.

Selective serotonin reuptake inhibitors (SSRIs) inhibit this process, allowing for more serotonin in the synaptic cleft.



The Serotonin Transporter

The SLC6A4 promoter has two main variants: short (S) and long (L)¹.

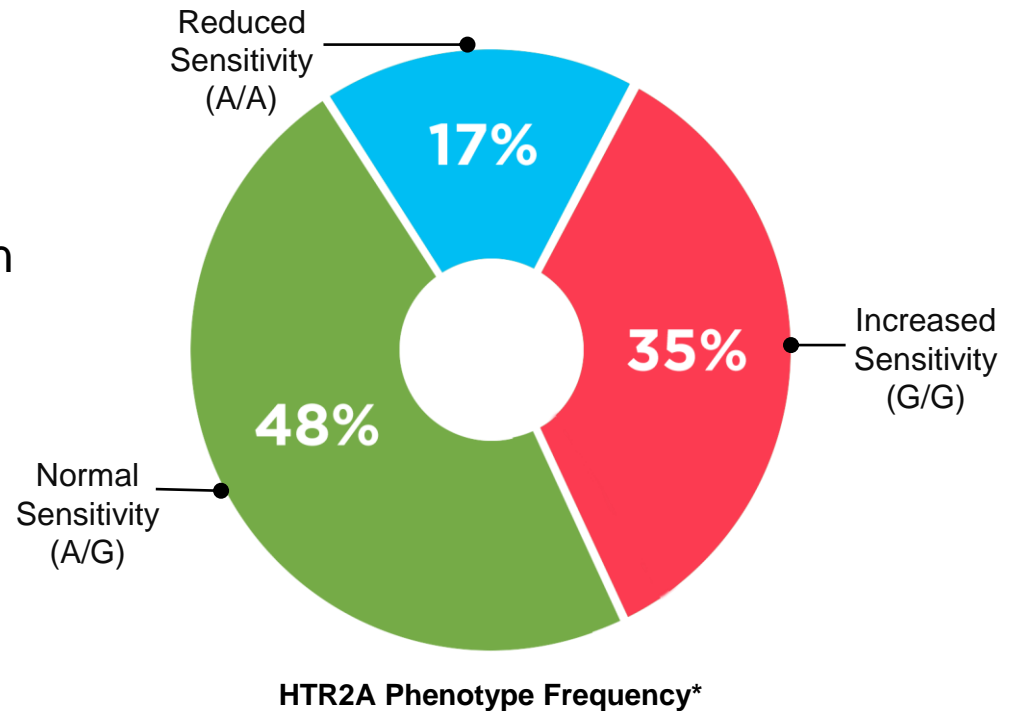


1. Lesch KP, et al. Science. 1996.

HTR2A

HTR2A encodes the serotonin 2A receptor, one of the principal excitatory receptors in the serotonin system.

Studies show increased risk for adverse effects with paroxetine in patients who are homozygous for the G allele.¹⁻³



*Phenotype frequency is based on internal Myriad Neuroscience data of over 700,000 tested patients.

1. Wilkie MJ, et al. *Pharmacogenomics J.* 2009. 2. Kato M, et al. *Neuropsychobiology.* 2006. 3. Murphy GM, et al. *Am J Psychiatry.* 2003.

Human Leukocyte Antigen (HLA)

Carbamazepine, oxcarbazepine, and lamotrigine: three medications most commonly associated with severe skin reactions¹⁻³

Meta-analysis of 20 studies found certain HLA alleles significantly overrepresented in patients showing CBZ-induced severe skin reactions⁴

Drug	HLA-A*3101	HLA-B*1502
Carbamazepine (Tegretol®) ¹	✓	✓
Oxcarbazepine (Trileptal®) ²	-	✓
Lamotrigine (Lamictal®) ³	-	✓

Subcategorized by Severity of Skin Reactions		
	HLA-A*3101 (OR)	HLA-B*1502 (OR)
SJS/TEN	5.65	80.70
Less Severe Skin Reactions	8.58	NS for predictive value

1. Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014. 2. Trileptal [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014. 3. Deng Y, et al. Seizure 2018. 4. Grover S, et al. Pharmacogene Genomics. 2014.

Interpreting **Combinatorial** Pharmacogenomic Testing Can Get Complex

Pharmacokinetic Markers

CYP2D6

CYP2D6 + CYP2C19

CYP2D6 + CYP2C19 + CYP1A2

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9
+ CYP3A4

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9
+ CYP3A4+ CYP2B6

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9
+ CYP3A4+ CYP2B6 + UGT1A4

CYP2D6 + CYP2C19 + CYP1A2 + CYP2C9
+ CYP3A4+ CYP2B6 + UGT1A4 + UGT2B15

Pharmacodynamic Markers

SLC6A4

HTR2A

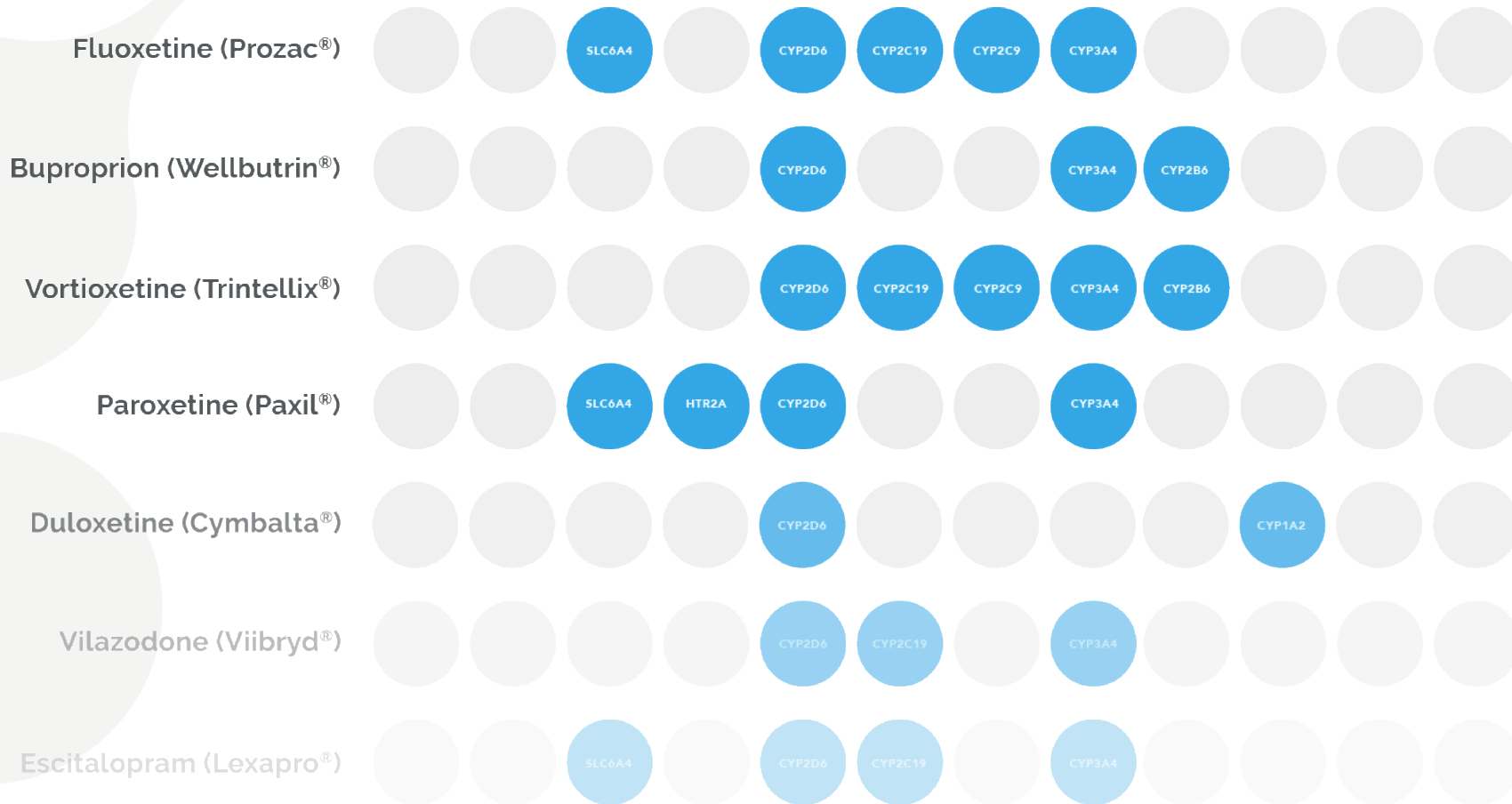
HLA-B*1502

HLA-A*3101

331,776

Resultant Composite Phenotypes

Medications Often Work Through a Unique Combination of These Genetically Controlled Pathways



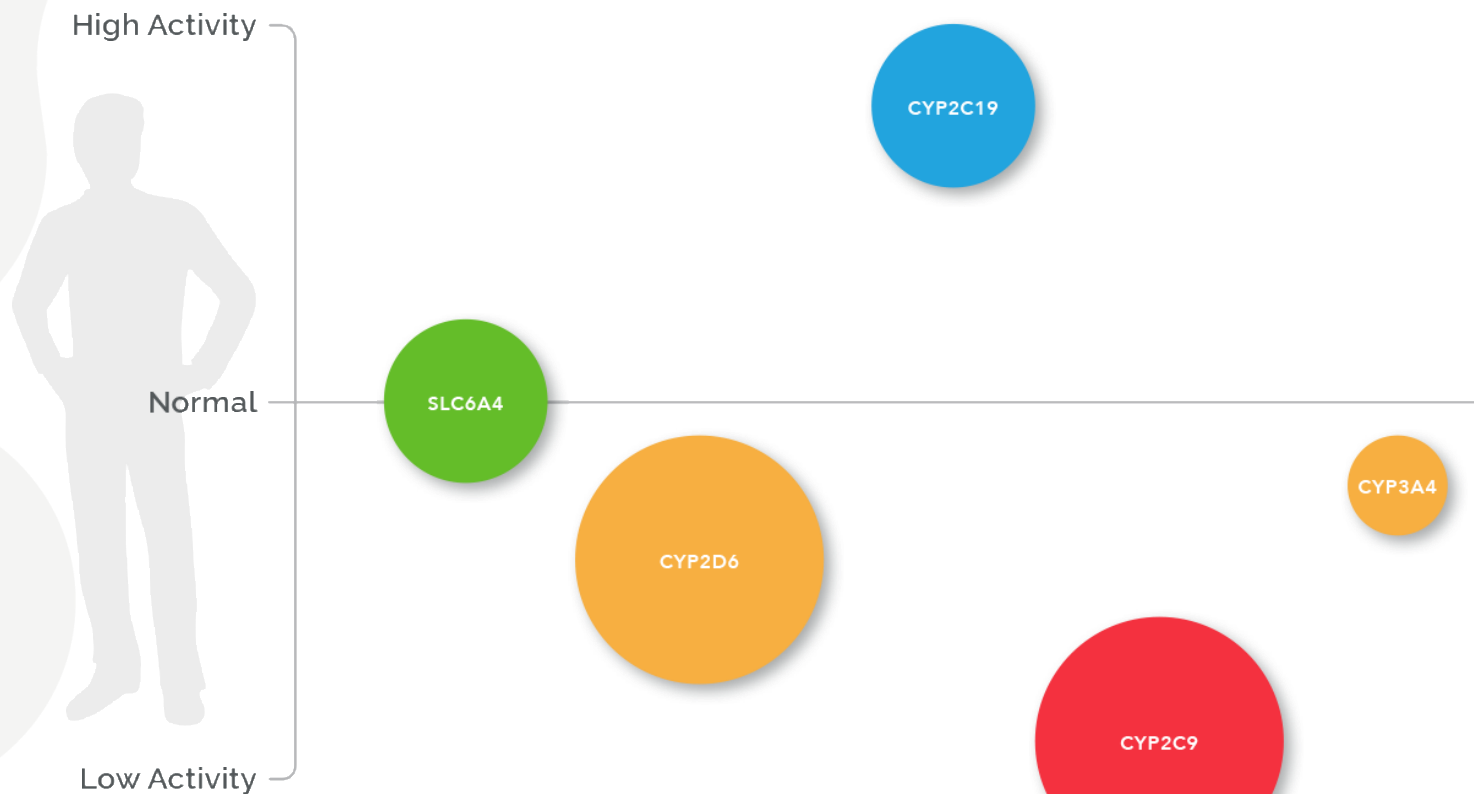
The Significance of Those Genes Varies by Medication

Fluoxetine (Prozac®)



A Patient's Unique Genetics Impact the Activity Level of Those Pathways

Fluoxetine (Prozac®)



The GeneSight® Psychotropic Report Categorizes Medications and Provides Clinical Considerations Based on a Combined Assessment of the Drug's Pharmacology and the Relevant Genetic Pathways

Significant Gene-Drug Interaction

Fluoxetine (Prozac®)

1,6

Clinical Considerations

1: Serum level may be too high, lower doses may be required.

6: Use of this drug may increase risk of side effects.

The GeneSight® Psychotropic Test Analyzes All 57 Medications on Our Panel Using This Approach

GeneSight® Psychotropic COMBINATORIAL PHARMACOGENOMIC TEST



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citalopram (Celexa®)	1,4,6
escitalopram (Lexapro®)	1,4,6
paroxetine (Paxil®)	1,4,6
sertraline (Zoloft®)	1,4,6
levomilnacipran (Fetzima®)	1,6,8
venlafaxine (Effexor®)	1,6,8
vilazodone (Viibryd®)	1,6,8



Any Prescribing Clinician Can Order the GeneSight® Test

- ✔ Talk to your own doctor about ordering the GeneSight test.
- ✔ Use our Discussion Guide to help with the conversation.
- ✔ Use our Find a Provider Portal to see who may be using the GeneSight test in your area.

Tips for Talking to Your Doctor about the GeneSight® Test



Be Prepared

Take along any information the doctor or staff may need to see, like names and contact information of your past/other clinicians, records showing past medications or current medications for other conditions, or dietary supplements.



Be Open and Confident

Don't be afraid to share how your current depression treatment is working for you and where it may be falling short.



Bring a Friend

The support of a friend or family member can help facilitate the conversation with your doctor and help act as a co-advocate for your care at your next appointment.



Discuss Ordering the Test

If you are interested in the GeneSight test, discuss whether you might be a good candidate with your doctor.

Not Able to See Your Doctor in Person? No Problem.

The GeneSight® test can be ordered by your healthcare provider and sent directly to you.



If you need help finding a healthcare provider, you can use the GeneSight Find a Provider tool on our website.

Five Things to Know about the GeneSight® Test

- ✓ The results of the test can inform your doctor about genes that may impact how you metabolize or respond to certain medications.
- ✓ The GeneSight test is intended to supplement other information considered by a doctor within the context of a comprehensive medical assessment.
- ✓ After we receive your sample, your doctor will typically get the test results within 2 days.
- ✓ More than one million people have taken the GeneSight test.
- ✓ Many healthcare plans, including Medicare, cover the GeneSight Psychotropic test. There is no cost to the provider to administer the test, and we offer the GeneSight Promise for patients.

We Take Privacy Very Seriously

- ✓ We analyze all GeneSight® Psychotropic and GeneSight MTHFR tests at our own accredited lab, so we can ensure the quality and security of your test.
- ✓ Your genetic information is private and protected through various federal laws including HIPAA (Health Insurance Portability and Accountability Act) and GINA (Genetic Information Nondiscrimination Act) that ensure the security of your personal and genetic information.
- ✓ All samples are destroyed within 60 days of processing.



Questions? Comments?
Feedback on this presentation?

Contact Medical Information at:

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(855) 891-9415