# Using Pharmacogenomics to Inform Depression Treatment

Holly Johnson, Ph.D.

Unmet Medical Need from Treatment As Usual

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) Trial[1]

# of Medication Treatments	Remission Rate	Intolerance Rate (Side Effects)
1	37%	16%
2	31%	20%
3	14%	26%
4	13%	30%
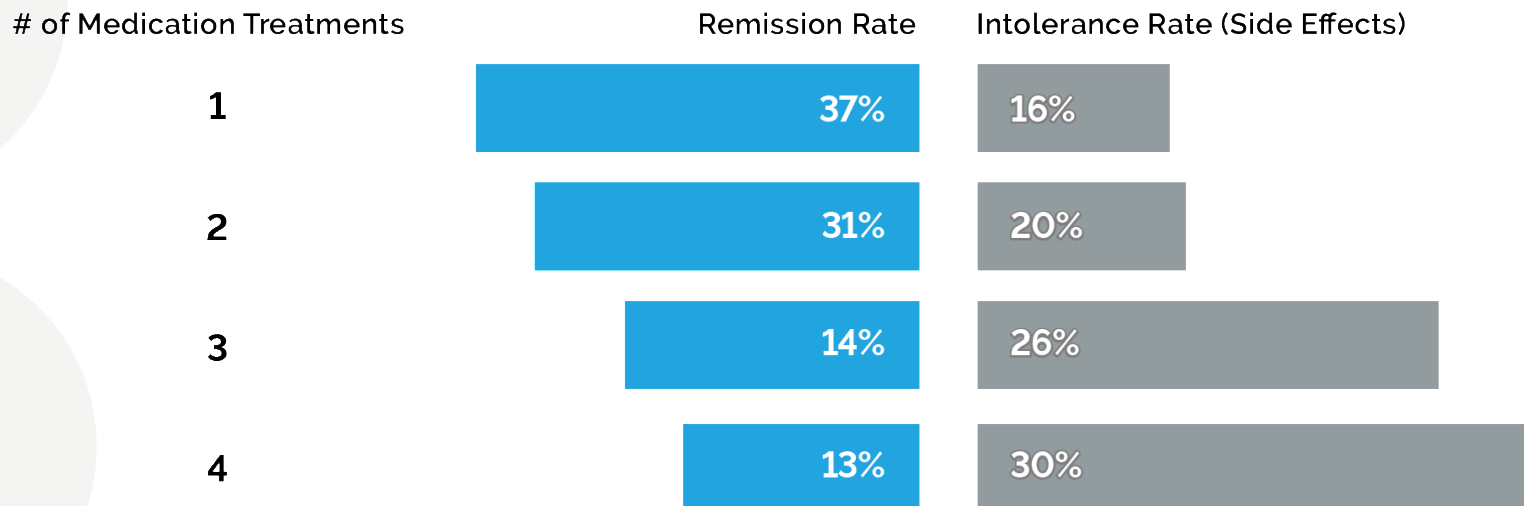
1. Rush AJ, et al. Am J Psychiatry. 2006.

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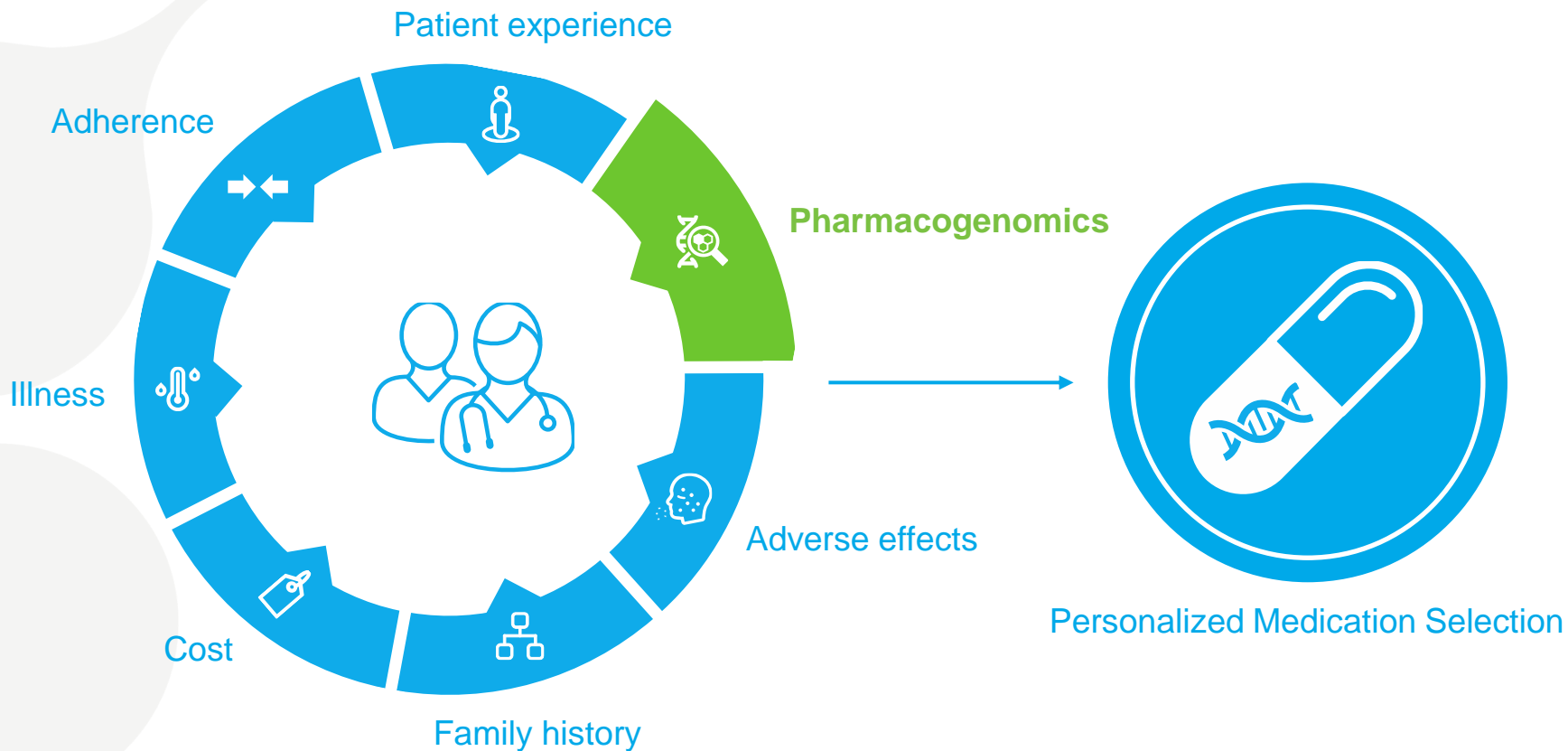genesight

Why Are They Failing?

Why is remission so difficult to achieve?

Here are some of the usual culprits:

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

But have you considered that genetic variability may undermine medication choices and may be a factor in treatment failure?

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Personalized Medication Selection Factors

Patient experience

Adherence

Pharmacogenomics

Illness

Adverse effects

Cost

Family history

Personalized Medication Selection

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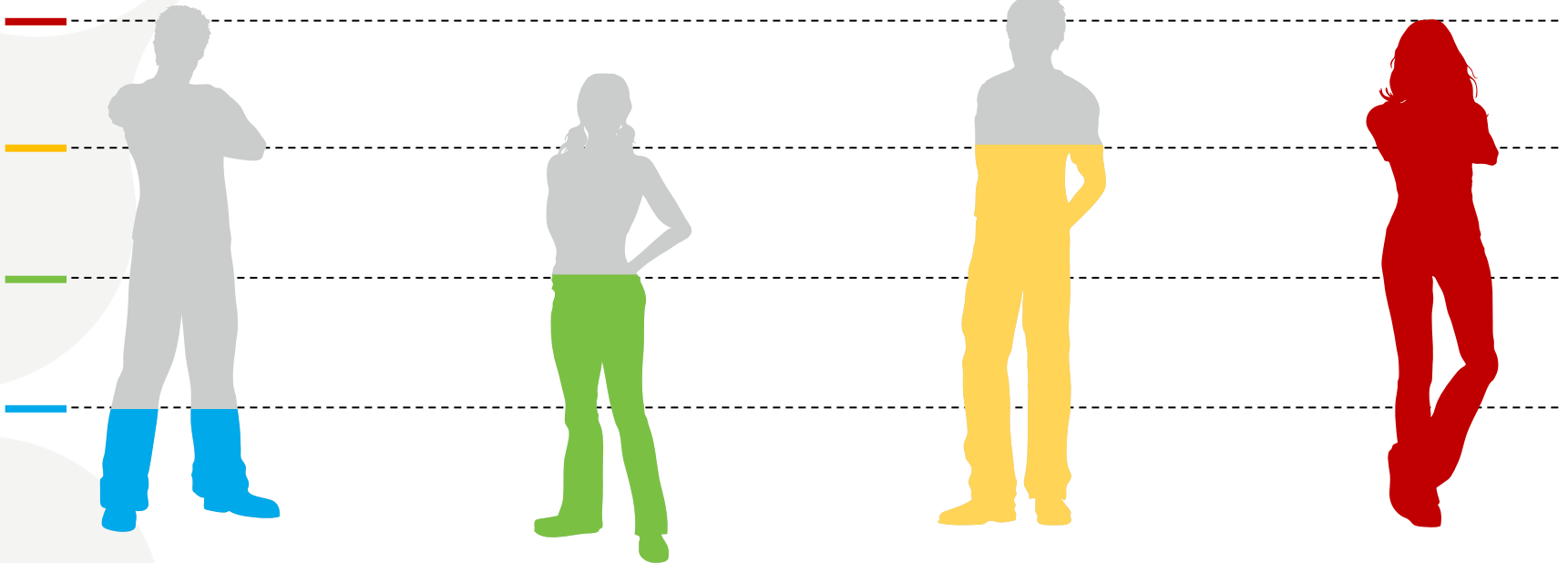
Pharmacodynamics and Pharmacokinetics

Pharmacodynamic
variation changes
how the drug
affects the body

Systemic
Circulation
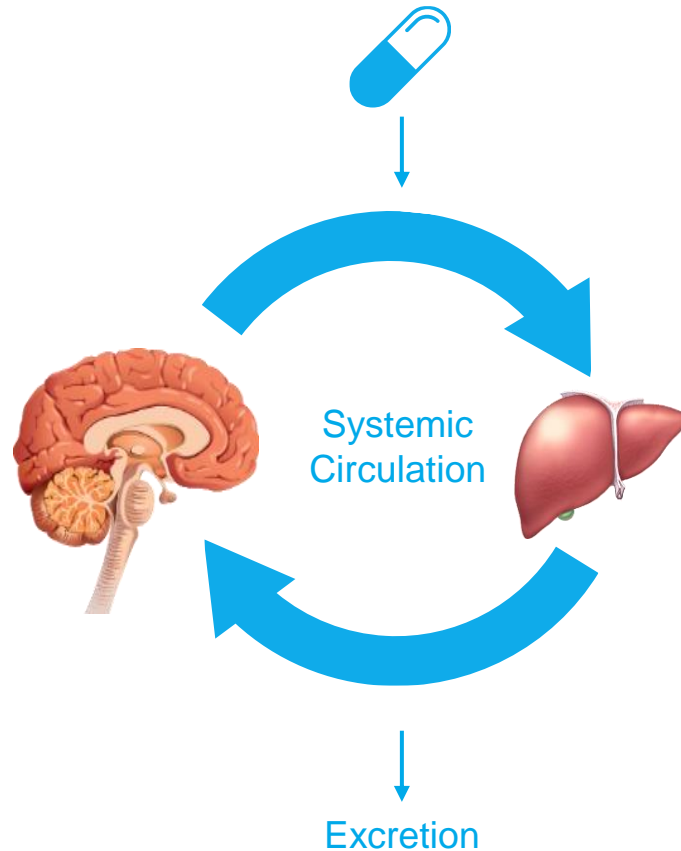
Pharmacokinetic
variation changes
how the body
affects the drug

Excretion

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.

The GeneSight® Psychotropic Report

GeneSight® Psychotropic
Pharmacogenomic Test

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Patient, Sample
Date of Birth: 7/22/1984
Clinician: Sample Clinician

Order Number: 3740219
Report Date: 5/12/2021
Reference: 145CIP

Questions about report interpretation?
Contact our medical information team:
855.891.9415 | medinfo@genesight.com

Antidepressants

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
desvenlafaxine (Pristiq®)	trazodone (Desyrel®)	1	selegiline (Emsam®)	2
levomilnacipran (Fetzima®)	venlafaxine (Effexor®)	1	mirtazapine (Remeron®)	1,6
vilazodone (Viibryd®)	fluoxetine (Prozac®)	1,4	sertraline (Zoloft®)	2,4
	bupropion (Wellbutrin®)	1,6	amitriptyline (Elavil®)	1,6,8
	citalopram (Celexa®)	3,4	clomipramine (Anafranil®)	1,6,8
	escitalopram (Lexapro®)	3,4	desipramine (Norpramin®)	1,6,8
			doxepin (Sinequan®)	1,6,8
			duloxetine (Cymbalta®)	1,6,8
			imipramine (Tofranil®)	1,6,8
			nortriptyline (Pamelor®)	1,6,8
			vortioxetine (Trintellix®)	1,6,8
			fluvoxamine (Luvox®)	1,4,6,8
			paroxetine (Paxil®)	1,4,6,8

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What are the Clinical Considerations?

GeneSight® Psychotropic
Pharmacogenomic Test

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clinical validity and utility of the GeneSight Psychotropic test have been evaluated for patients with major depressive disorder who failed at least one psychotropic medication in multiple clinical studies.

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Patient, Sample
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Clinical Considerations
These state rationale for a medication's classification and offer treatment adjustments if a clinician desires to use this medication.

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.
4: Genotype may impact drug mechanism of action and result in moderately reduced efficacy.
6: Use of this drug may increase the risk of side effects.
8: FDA label identifies a potential gene-drug interaction for this medication.

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 +CES1A1

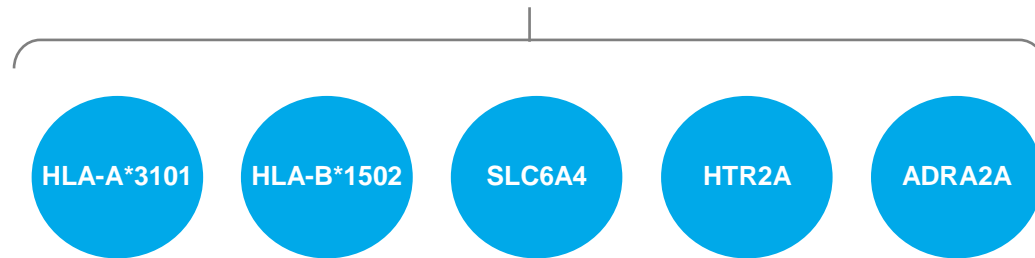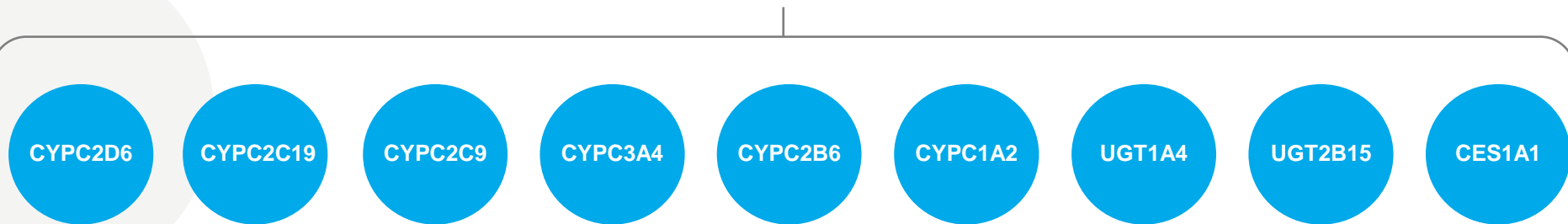| Pharmacodynamic Markers |
| --- |
| ADRA2A |
| HLA-A*3101 |
| HLA-B*1502 |
| HTR2A |
| SLC6A4 |

1,990,656
resultant composite phenotypes based on the 14 genes in the GeneSight® algorithm

Psychotropic Medications Are Processed Through Multiple Genetic Pathways
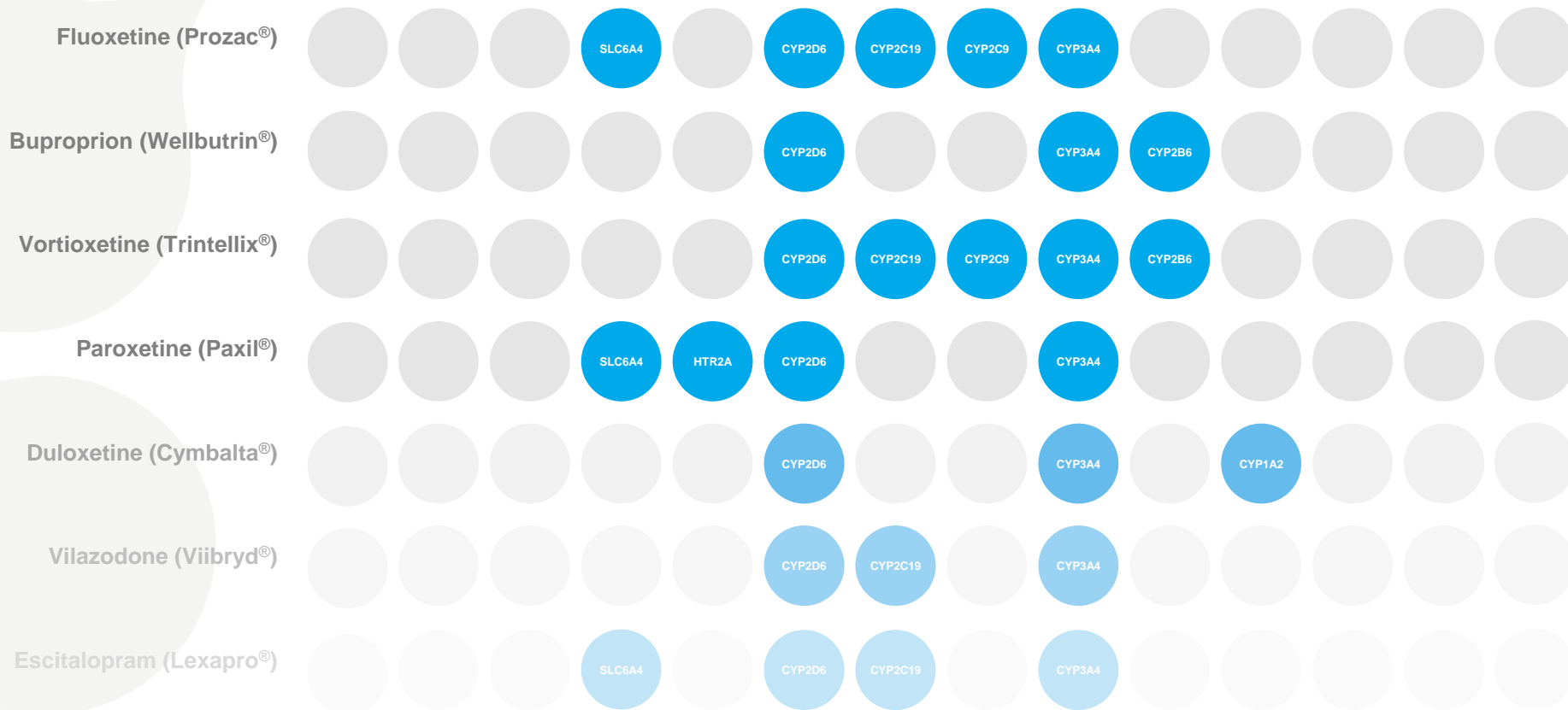
PHARMACODYNAMIC GENES

HLA-A*3101   HLA-B*1502   SLC6A4   HTR2A   ADRA2A

PHARMACOKINETIC GENES

CYPC2D6   CYPC2C19   CYPC2C9   CYPC3A4   CYPC2B6   CYPC1A2   UGT1A4   UGT2B15   CES1A1

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

Fluoxetine (Prozac®)			SLC6A4		CYP2D6	CYP2C19	CYP2C9	CYP3A4				
Buproprion (Wellbutrin®)					CYP2D6			CYP3A4	CYP2B6			
Vortioxetine (Trintellix®)					CYP2D6	CYP2C19	CYP2C9	CYP3A4	CYP2B6			
Paroxetine (Paxil®)			SLC6A4	HTR2A	CYP2D6			CYP3A4				
Duloxetine (Cymbalta®)					CYP2D6			CYP3A4		CYP1A2		
Vilazodone (Viibryd®)					CYP2D6	CYP2C19		CYP3A4				
Escitalopram (Lexapro®)			SLC6A4		CYP2D6	CYP2C19		CYP3A4				

The Significance of Those Genes Varies by Medication
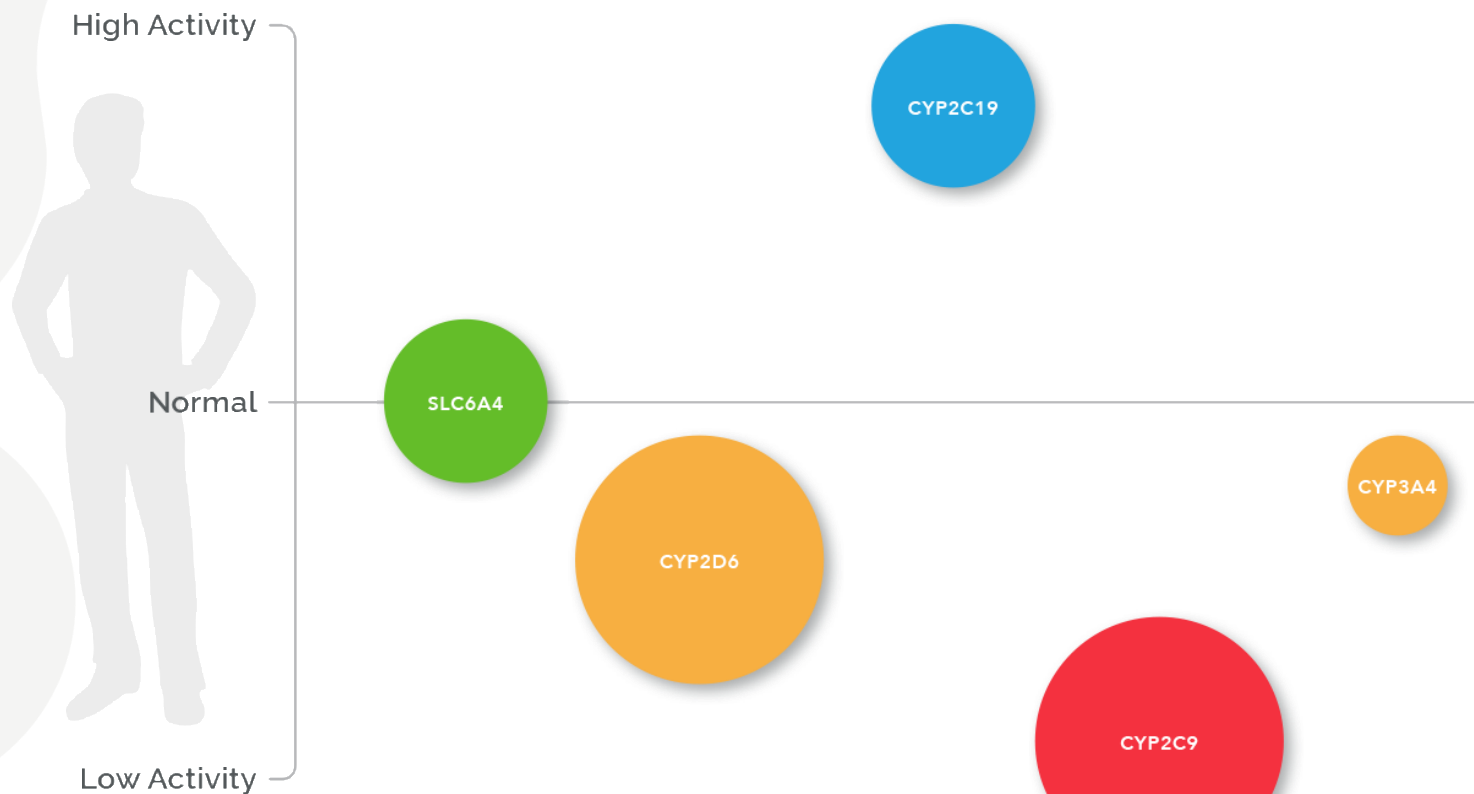

Fluoxetine (Prozac®)

SLC6A4 · CYP2D6 · CYP2C19 · CYP2C9 · CYP3A4

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.

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The GeneSight® Psychotropic Test Analyzes All 61 Medications on Our Panel Using This Approach

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GeneSight® is Easy to Implement in Practice

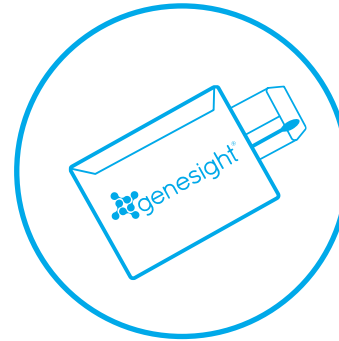**Step 1**
Place your order
on myGeneSight.com.

Step 2
You or a member of your
staff collect the patient's
DNA sample with a simple
cheek swab
OR
your patient collects the
sample at home using our
patient collection kit.

Step 3
Your patient's sample is
sent to our lab for
analysis. After the sample
is received, results are
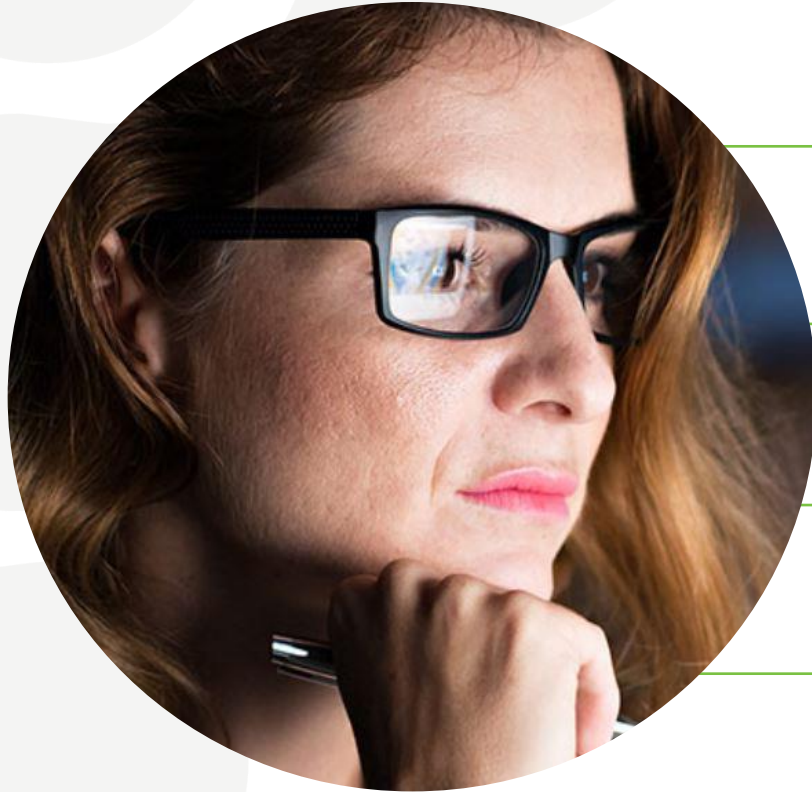typically available in about
2 days.

Step 4
Use the genetic insights
from the GeneSight
report to inform your
treatment.

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GeneSight® Supports Improved Outcomes in MDD

Identifies medications with significant gene-drug interactions (GDIs) to inform prescribing

10 clinical utility publications demonstrating improvement in patient outcomes[1-10]

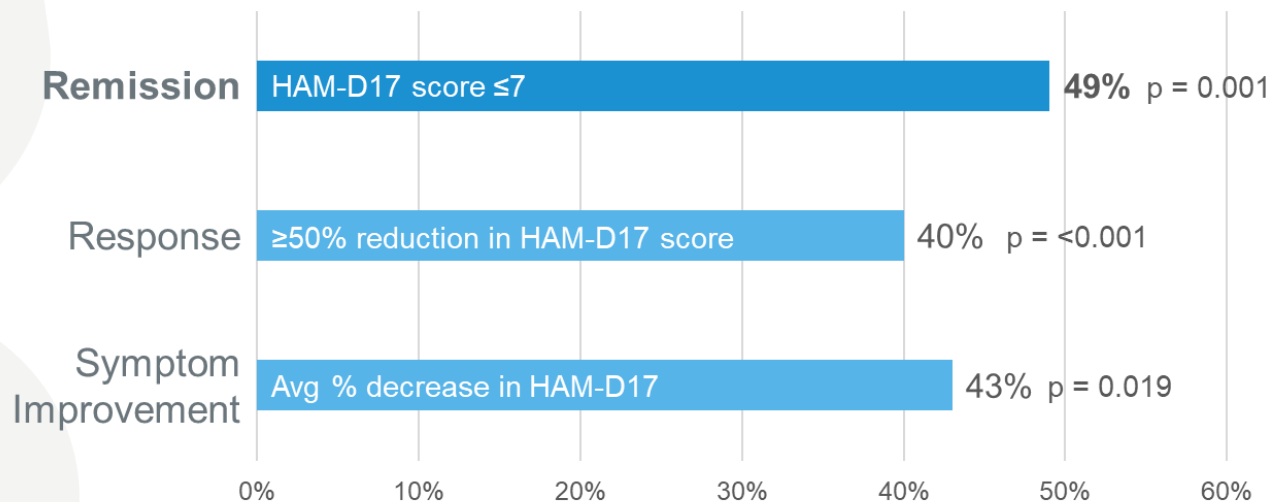Level 1 evidence demonstrating 49% relative improvement in remission[10]

Saved >$1,000 in total annual medication costs compared to treatment as usual[11]

Note: Not all patients who receive the GeneSight test will achieve remission or experience cost savings.

[1]Hall-Flavin DK, et al. Transl Psychiatry 2012; 2:e172 [2]Hall-Flavin DK, et al. Pharmacogenet Genomics 2013; 23(10):535-48. [3]Winner JG, et al. Discov Med 2013; 16(89):219-27. [4]Altar CA, et al. Mol Neuropsychiatry.2015 Oct;1(3):145-155. [5]Tanner JA, et al. Journal of Psychiatric Research 2018; 104:157-62. [6]Greden JF, et al. J Psychiatr Res 2019, 111:59-67. [7]Thase ME, et al. J Clin Psychiatry 2019;80(6). [8]Dunlop BW, et al. BMC Psychiatry 2019; 19:420. [9]Forester BP, et al. Am J Geriatr Psychiatry. 2020 Sep;28(9):933-945. [10]Brown LC, et al. Pharmacogenomics. 2020 Jun;21(8):559-569. [11]Winner J, et al. Curr Med Res Opin. 2015 31(9):1633-43

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GeneSight® Arm Realized a Significant Improvement in All Outcomes

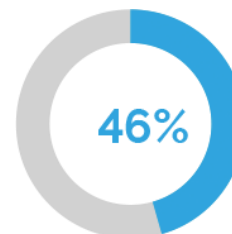*Level 1 evidence*: Relative improvement in patient outcomes compared to TAU

	Remission	Response	Symptom Improvement
Bar	HAM-D17 score ≤7 — 49% p = 0.001	≥50% reduction in HAM-D17 score — 40% p = <0.001	Avg % decrease in HAM-D17 — 43% p = 0.019

Symptom improvement
Decrease in HAM-D17

GeneSight	33.8%
TAU	23.7%
Absolute improvement	**10%**
Relative improvement	**43%**

Note: Not all patients who receive the GeneSight test will experience remission, response, or symptom improvement.
Brown LC, et al. Pharmacogenomics. 2020 Jun;21(8):559-569.

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Patients in the GeneSight® Arm had Lower Total Annual Medication Costs Compared to TAU*[1]

$1,035
Avg annual savings per patient

p=0.0007

Annual Change in Drug Spend (USD)

- $2,000
- $1,800
- $1,400
- $1,200
- $1,000
- $800
- $600
- $400
- $200
- $0

$1,725

$690

TAU
(n=10,880)
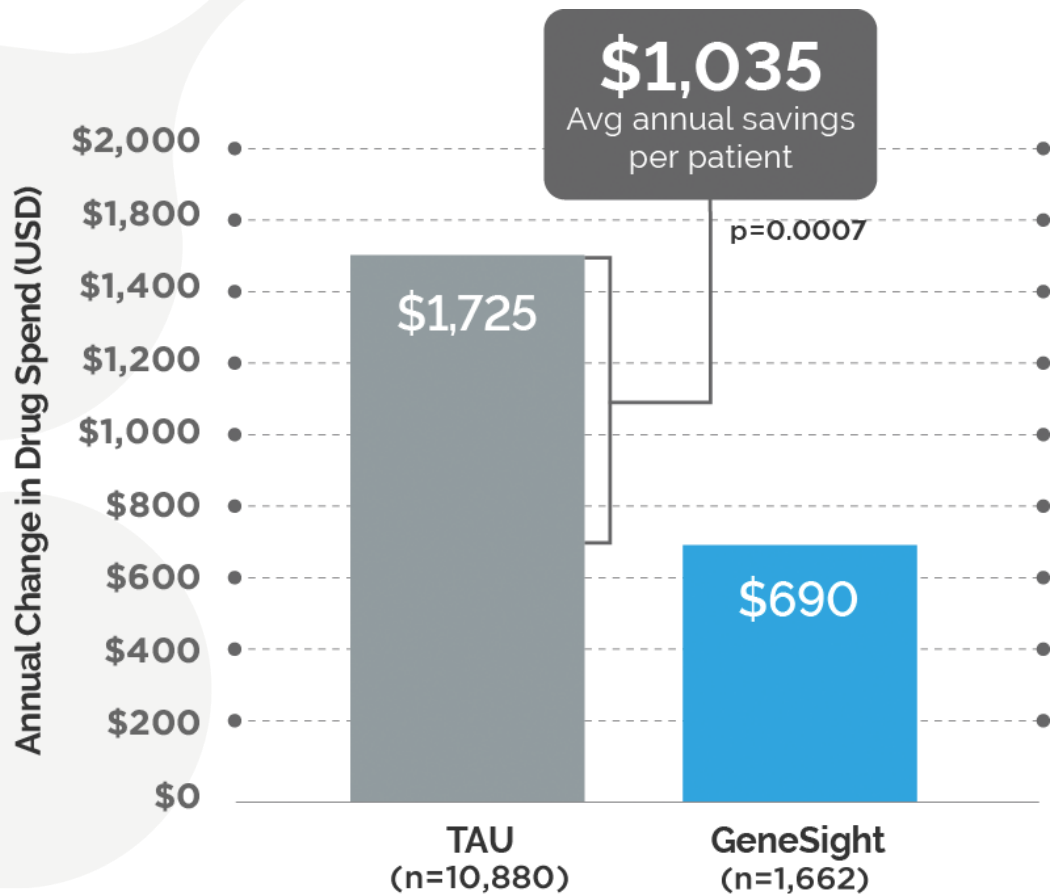
GeneSight
(n=1,662)

GeneSight helped to increase adherence and reduce polypharmacy

46% — Patients in the GeneSight arm stayed on a new medication 46% longer
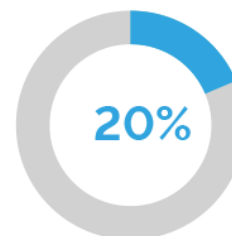
20% — 20% of patients were on fewer medications

* Not all patients who receive the GeneSight Psychotropic test will experience cost savings.
1 Winner et al. Curr Med Research & Opin. (2015)

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Questions? Comments?
Feedback on this presentation?

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