

A stylized illustration of a human head profile in yellow outline, facing right. The brain area is filled with a cluster of blue and white dots, representing a brain scan or genetic data. The background is light green and white with abstract, wavy patterns and several blue and green circular shapes of varying sizes, some resembling DNA helices or molecular structures.

# Genetic Clues to Beating the Blues: Utilizing Pharmacogenomics to Guide Antidepressant and Anxiolytic Therapies

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# Disclosures

The planners and speakers have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

# Objectives

01

Review foundational pharmacogenomics and identify clinically meaningful phenotypes relevant to behavioral health pharmacotherapy.

02

Understand how CYP2D6, CYP2C19, and serotonin transporter genotypes may influence antidepressant and anxiolytic medication response.

03

Utilize evidence-based pharmacogenomic guidelines to optimize antidepressant and anxiolytic medication selection, dosing, and monitoring.

04

Evaluate the clinical utility and limitations of pharmacogenomic testing as an aid in selecting antidepressants and anxiolytics.

# Outline of Presentation



**Review of  
Pharmacogenomics**



**PGx in Behavioral  
Health**



**Guidelines and  
Evidence**



**Clinical  
Considerations**



**PGx in the EHR**



**Future Directions  
and Key Takeaways**

# Abbreviations

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CDS: Clinical decision support

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CPIC: Clinical Pharmacogenetics Implementation Consortium

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CYP: Cytochrome P450 enzyme

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DPWG: Dutch Pharmacogenetics Working Group

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EHR: Electronic Health Record

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GAD: Generalized Anxiety Disorder

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HAM-D: Hamilton Depression Rating Scale

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MAOi: Monoamine oxidase inhibitor

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MDD: Major Depressive Disorder

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PGx: Pharmacogenomics

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PHQ-9: Patient Health Questionnaire – 9 item

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PK: Pharmacokinetics

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QIDS-C: Quick Inventory Depression Symptomatology

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SMS: Serotonin modulator & stimulator

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SNRI: Serotonin & norepinephrine reuptake inhibitor

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SSRI: Selective serotonin reuptake inhibitor

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TDM: Therapeutic drug monitoring

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TCA: Tricyclic antidepressant



# **Antidepressants & Anxiolytics**

# Major Depressive Disorder

- Diagnostic and Statistical Manual of Mental Disorders (DSM-5)  
Criteria for **Major Depressive Disorder (MDD)**:
  - Include 5 or more symptoms present for at least 2 weeks
  - At least one of the symptoms must be decreased mood or loss of pleasure
- 3x more likely in 18–29-year age group vs >60-year age group
- Higher prevalence in females

# Generalized Anxiety Disorder

- DSM-5 Criteria for **Generalized Anxiety Disorder (GAD)**:
  - Excessive worry and thought occurring more days than not for at least 6 months
- Symptoms are severe and interfere with functioning
- Higher prevalence in women

# Antidepressants & Anxiolytics

## Selective Serotonin Reuptake Inhibitors (SSRI)

- Paroxetine, Fluoxetine, Fluvoxamine, Citalopram, Escitalopram, Sertraline

## Serotonin & Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine, Desvenlafaxine, Duloxetine, Milnacipran, Levomilnacipran

## Serotonin Modulator & Stimulators (SMS)

- Vortioxetine, Vilazodone

## Tricyclic Antidepressants (TCAs)

- Amitriptyline, Imipramine, Doxepin, Desipramine

## Monoamine Oxidase Inhibitors (MAOis)

- Selegiline, Isocarboxazid, Tranylcypromine, Phenelzine

## Benzodiazepines

- Lorazepam, Alprazolam, Diazepam, Clonazepam

## Others

- Buspirone, Mirtazapine, Trazodone, Propranolol, Hydroxyzine

# Medication Uses

## Anxiolytics

- Benzodiazepines
- Propranolol
- Hydroxyzine

## Antidepressants

- SSRIs
- SNRIs
- Buspirone
- TCAs
- MAOis
- Mirtazapine
- Trazodone
- Vortioxetine
- Vilazodone

# Pharmacogenomics



# PGx Definitions

## Pharmacogenetics

- The study of how variations in a **single gene** may influence medication response

## Pharmacogenomics (PGx)

- The study of how **multiple genes across the genome** may influence medication response



# PGx Definitions

Gene: basic unit of inheritance; codes for proteins

Polymorphism: a naturally occurring variation in a DNA sequence

Allele: a specific version of a gene

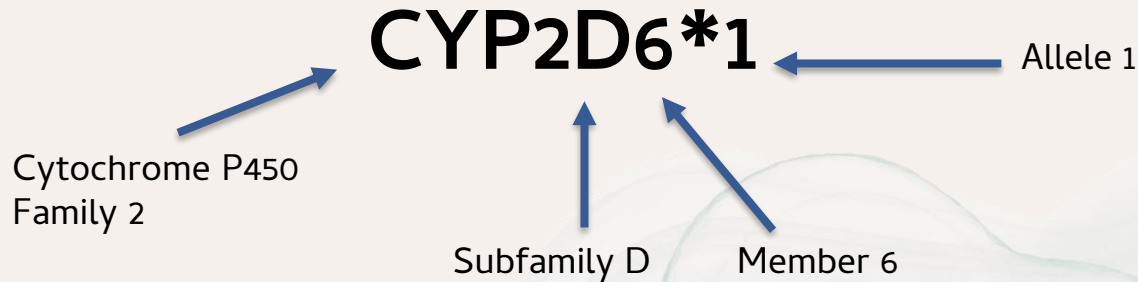
Genotype: the combination of alleles that an individual has for a specific gene

Phenotype: the observable expression or functional outcome of a gene



# Allele Nomenclature

- Pharmacogene Variation Consortium (PharmVar)
  - Used by ClinPGx for allele and haplotype definitions
- Publishes standard definitions regarding the nomenclature of alleles



# Utilizing PGx in Behavioral Health



Pharmacotherapy has inter-individual variability in medication response and the development of side effects



















Personalized medicine, such as PGx, is one tool to optimize medication therapy according to an individual's genetic makeup by targeting genetic variations



Research focuses on genetic polymorphisms and the clinical impacts on medication response

### III. GENE DRUG INTERACTION SUMMARY

CLASS	MEDICATION	PHARMACODYNAMIC ASSOCIATIONS	PHARMACODYNAMIC GENE	DRUG EXPOSURE	PHARMACOKINETIC GENE
<b>ANTIDEPRESSANTS</b>					
SSRIs	 <b>Citalopram</b> (Celexa®)	 Higher odds of remission or response	SLC6A4		2C19, P-gp
	 <b>Escitalopram</b> (Lexapro®)	 Higher odds of remission or response	SLC6A4		2C19, P-gp
	 <b>Fluoxetine</b> (Prozac®)	 Higher odds of remission or response	SLC6A4	↑	2D6, 2C9
	 <b>Fluvoxamine</b> (Luvox®)	 Higher odds of remission or response	SLC6A4	↑	2D6, 1A2, P-gp
	 <b>Paroxetine</b> (Paxil®)	 Higher odds of remission or response	SLC6A4	↑	2D6, P-gp
	 <b>Sertraline</b> (Zoloft®)	 Higher odds of remission or response	SLC6A4	↑	2C19, 2B6, P-gp
SNRIs	<b>Desvenlafaxine</b> (Pristiq®)				
	 <b>Duloxetine</b> (Cymbalta®)			↑	1A2, 2D6
	 <b>Levomilnacipran</b> (Fetzima®)				3A4/5
	 <b>Venlafaxine</b> (Effexor®)			↑	2D6, 2C19, 3A4/5, P-gp
Other	<b>Bupropion</b> [1] (Wellbutrin®)			↑	2B6
	<b>Esketamine</b> (Spravato®)			↑	2B6
	<b>Mirtazapine</b> (Remeron®)			↑	2D6, 3A4/5, 1A2
	<b>Nefazodone</b>				3A4/5
	<b>Trazodone</b> (Desyre®, Olepro®)			↑	3A4/5, 2D6
	<b>Vilazodone</b> (Viibryd®)				3A4/5
	 <b>Vortioxetine</b> (Trintellix®)			↑	2D6, 3A4/5



Alert/Caution



PGx Guided Options



Reduced Drug Exposure  
with 1A2 Inducers



Drug Exposure



[1] See Gene Drug Interaction Summary footnotes for more information

# Types of Metabolizers

Drug Metabolizing Enzyme Status	Functional Definition	Genetic Definition
Ultra-rapid (UM)	Increased enzyme activity compared to rapid metabolizers	Two increased function alleles, or more than two normal function alleles
Rapid (RM)	Increased enzyme activity compared to normal metabolizers but less than ultra-rapid metabolizers	Combinations of normal function and increased function alleles
Normal (NM)	Fully functional enzyme activity	Combinations of normal function and decreased function alleles
Intermediate (IM)	Decreased enzyme activity	Combinations of normal function, decreased function, and/or no function alleles
Poor (PM)	Little to no enzyme activity	Combinations of no function alleles and/or decreased function alleles

# CYP Enzymes of Interest

**CYP2D6**

**CYP2C19**

**CYP2B6**

CYP Enzymes	Antidepressants/Anxiolytics Metabolized
CYP2D6	<ul style="list-style-type: none"><li>• Paroxetine</li><li>• Fluvoxamine</li><li>• Fluoxetine</li><li>• Venlafaxine</li><li>• Vortioxetine</li><li>• Most TCAs</li></ul>
CYP2C19	<ul style="list-style-type: none"><li>• Citalopram</li><li>• Escitalopram</li><li>• Sertraline</li><li>• Amitriptyline</li><li>• Imipramine</li></ul>
CYP2B6	<ul style="list-style-type: none"><li>• Sertraline</li></ul>

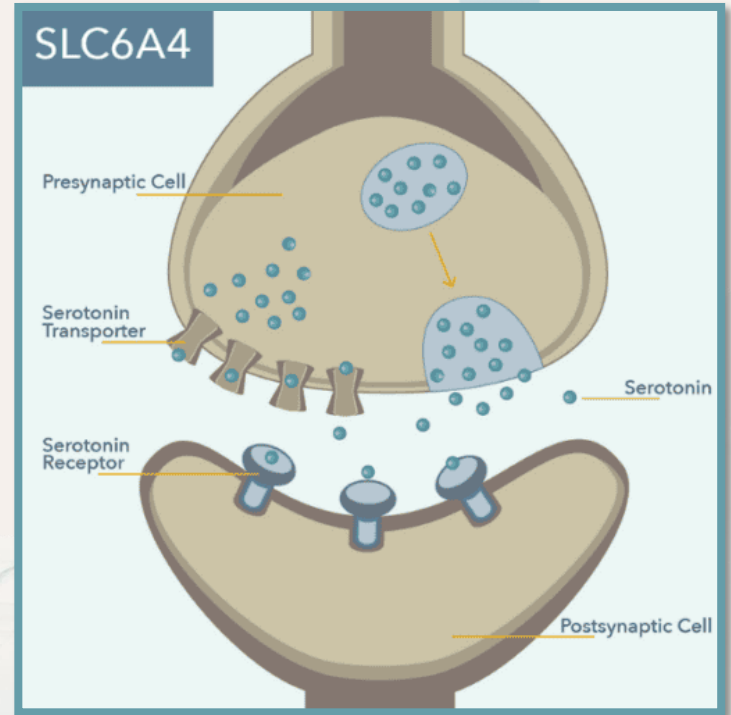


# CYP450 Phenoconversion

- Conversion between CYP450 genotype and how individuals metabolize medication
  - Due to nongenetic factors
  - May be due to concomitant medications, sex, age, nutritional status, hormones, comorbidities, smoking
- Documented with CYP2D6, particularly strong 2D6 inhibitors, but varies with genotype
- Exact mechanism unknown
- Propelling Clinical Pharmacogenomics Into Practice (PROP) Pharmacogenetics Calculator may be used as a resource

# Serotonin Transporter (SERT)

- Serotonin transporter gene (SLC6A4) - terminates reuptake of neurotransmitters from the synaptic space
- Promotor region (HTTLPR) studied and focus on an insertion/deletion mutation polymorphism
  - Long allele single nucleotide polymorphism responsible for greater activity
- Serotonin transporter gene: HTR2A - encodes for postsynaptic serotonin-2A receptor (5-HT<sub>2A</sub>)



# Assessment Question #1

TN is a 41-year-old Asian American female with GAD presenting for pharmacotherapy adjustments. Based on the available PGx results, standard doses of medications metabolized by which enzyme may increase her risk of developing adverse effects?

- A. CYP2D6
- B. CYP2B6
- C. CYP3A4
- D. CYP2C19

Past Medication Trials	Bupropion XL 300 mg daily
Current Medications	Fluoxetine 60 mg daily Lorazepam 0.5 mg BID PRN anxiety
PGx Results	CYP2D6: ultra-rapid CYP3A4: normal CYP2C19: poor CYP1A2: intermediate

# Guidelines



**2023 CPIC Guidelines for CYP2D6, CYP2C19, CYP2B6,  
SLC6A4, and HTR2A Genotypes and SSRIs**

**&**


**CPIC for CYP2D6 and CYP2C19 Genotypes and Dosing  
of Tricyclic Antidepressants: 2016 Update**



# **Dutch Pharmacogenetics Working Group (DPWG) Guidelines**



# SSRIs



Paroxetine  
Fluvoxamine  
Fluoxetine  
Escitalopram  
Citalopram  
Sertraline

# Paroxetine Therapeutic Recommendations

CYP2D6

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	Select alternative drug	Avoid paroxetine
Normal	No change; follow package insert	No recommendations
Intermediate	Consider a lower starting dose and slower titration	
Poor	Consider a 50% reduction in recommended starting dose, slower titration schedule, and a 50% lower maintenance dose	
<b>FDA Package Insert: No recommendation</b>		

Bousman et al, *Clin Pharmacol Ther.* 2023;2023;114(1):51-68.

Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.

Food and Drug Administration. Paxil. 2024.

# Fluvoxamine Therapeutic Recommendations

CYP2D6

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	No recommendation	No change; follow package insert
Normal	No change; follow package insert	
Intermediate		
Poor	Consider a 25-50% lower starting dose and slower titration schedule or select alternative drug	

**FDA Package Insert:** Acknowledges that poor metabolizers have significantly altered PK requiring caution; no recommendation

Bousman et al, *Clin Pharmacol Ther.* 2023.2023;114(1):51-68.

Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.

Food and Drug Administration. Fluvoxamine. 2025.

# Fluoxetine Therapeutic Recommendations

CYP2D6

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	No recommendation	No change; follow package insert
Normal	No change; follow package insert	
Intermediate	No recommendation	
Poor		
<b>FDA Package Insert: No recommendation</b>		

Bousman et al, *Clin Pharmacol Ther.* 2023;2023;114(1):51-68.

Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.

Food and Drug Administration. Fluoxetine. 2025.

# Escitalopram & Citalopram Therapeutic Recommendations

CYP2C19

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	Select alternative drug; or titrate to a higher maintenance dose	<b>Escitalopram:</b> Avoid escitalopram <b>Citalopram:</b> No recommendation
Rapid	No change; titrate to higher maintenance dose if necessary; or select alternative drug	No recommendations
Normal	No change; follow package insert	

# Escitalopram & Citalopram Therapeutic Recommendations

CYP2C19

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Intermediate	No change; consider a slower titration schedule and lower maintenance dose	<b>Escitalopram:</b> Max dose 15 mg/day for adults <65 years old; 7.5 mg/day for adults > 65  <b>Citalopram:</b> Max dose 30 mg/day for adults <65 years old; 22 mg/day for adults > 65
Likely intermediate		No recommendation

# Escitalopram & Citalopram Therapeutic Recommendations

CYP2C19

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Likely poor	Select alternative drug; or consider a lower starting dose, slower titration schedule, and 50% reduction of the standard maintenance	No recommendation
Poor		<b>Escitalopram:</b> Max dose 10 mg/day for adults <65 years old; 5 mg/day for adults >65 <b>Citalopram:</b> Max dose 20 mg/day for adults <65 years old; 10 mg/day for adults >65

**FDA Package Insert:** Max recommended dose of citalopram is 20 mg/day in poor metabolizers; no recommendation for escitalopram

# Sertraline Therapeutic Recommendations

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	No change	No recommendation
Rapid		
Normal		
Intermediate	No change; consider a slower titration schedule and lower maintenance dose	
Likely intermediate		
Likely poor	Consider a lower starting dose, slower titration schedule, and 50% reduction of standard maintenance dose; or select alternative drug	Max dose 75 mg/day; dose based on response to the medication
Poor		
<b>FDA Package Insert: No recommendation</b>		

CYP2C19

CYP2B6

Bousman et al, *Clin Pharmacol Ther.* 2023;114(1):51-68.  
 Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.  
 Food and Drug Administration. Sertaline hydrochloride. 2024.



# SNRIs

Venlafaxine  
Duloxetine



# Venlafaxine Therapeutic Recommendations



Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	No recommendation	No recommendations
Normal	No change; follow package insert	
Intermediate	No recommendation	
Poor	Select alternative drug	
<b>FDA Package Insert: No recommendation</b>		

Bousman et al, *Clin Pharmacol Ther.* 2023;114(1):51-68.  
Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.  
Food and Drug Administration. Venlafaxine. 2023.

# Duloxetine Therapeutic Recommendations



Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	No recommendation	No recommendations
Normal	No change; follow package insert	
Intermediate	No recommendation	
Poor	Select alternative drug	
<b>FDA Package Insert: No recommendation</b>		

Bousman et al, *Clin Pharmacol Ther.* 2023;114(1):51-68.  
Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.  
Food and Drug Administration. Duloxetine. 2022.



# SMS

Vortioxetine



# Vortioxetine Therapeutic Recommendations

CYP2D6

Metabolism Status	CPIC Guidelines	DPWG Guidelines
Ultrarapid	Select alternative drug; if use is warranted, initiate therapy at starting dose and titrate based on efficacy and side effects	No recommendations
Normal	No change; follow package insert	
Intermediate		
Poor	Initiate 50% of starting dose and titrate to the maximum recommended dose of 10 mg; consider an alternative drug	

**FDA Package Insert:** Max recommended dose is 10 mg/day in poor metabolizers

Bousman et al, *Clin Pharmacol Ther.* 2023;114(1):51-68.  
Brouwer et al. *Eur J Hum Genet.* 2022;30(10):1114-1120.  
Food and Drug Administration. Trintellix. 2025.

# Assessment Question #2

CPIC provides antidepressant dosing recommendations for which enzymes? Select all that apply:

- A. CYP2D6
- B. CYP2C19
- C. CYP2B6
- D. CYP3A4



# TCAs




Amitriptyline  
Nortriptyline  
Imipramine  
Desipramine

# TCA Therapeutic Recommendations

Metabolism Status	<b>CYP2D6</b> CPIC Guidelines	<b>CYP2C19</b> CPIC Guidelines	DPWG Guidelines
Ultrarapid	Avoid if possible; select alternative drug; if used, consider ~25% increase in target dose and use TDM	Avoid tertiary amine or switch to secondary amine	No recommendations
Normal	No change; follow package insert	No change; follow package insert	
Intermediate	Reduce dose by ~25%		
Poor	Avoid if possible; select alternative drug; if used, reduce initial dose by ~50% and use TDM	Reduce initial dose by ~50% or choose alternative drug (secondary amine)	
<b>FDA Package Insert: No recommendation</b>			



# Other Anxiolytics



Buspirone  
Mirtazapine  
Trazodone  
Propranolol  
Hydroxyzine  
Benzodiazepines

# Therapeutic Recommendations

Medication	CYP Enzyme	FDA Package Insert Recommendations
Buspirone	CYP3A4	<ul style="list-style-type: none"><li>Use lower doses with CYP3A4 inhibitors</li></ul>
Mirtazapine	CYP2D6, CYP1A2, CYP3A4	<ul style="list-style-type: none"><li>Increase dose if co-administration with CYP3A4 inducer</li><li>Decrease dose if co-administration with CYP3A4 inhibitor</li></ul>
Trazodone	CYP3A4	
Propranolol	CYP2D6, CYP1A2, CYP2C19	<ul style="list-style-type: none"><li>No recommendations</li></ul>
Hydroxyzine	CYP2D6	<ul style="list-style-type: none"><li>No recommendations</li></ul>
Benzodiazepines	CYP3A4, CYP2C19	<ul style="list-style-type: none"><li>Use caution with CYP3A4 inducers and inhibitors</li></ul>

Food and Drug Administration. Buspirone hydrochloride. 2026.

Food and Drug Administration. Mirtazapine. 2025.

Food and Drug Administration. Trazodone hydrochloride. 2025.

Food and Drug Administration. Propranolol hydrochloride. 2025.

Food and Drug Administration. Hydroxyzine hydrochloride. 2024.

Food and Drug Administration. Alprazolam extended release. 2023.



# Serotonin Transporters

# Serotonin Transporters

Gene	Alleles	Select Antidepressants Transported
SLC6A4	<ul style="list-style-type: none"><li>• <b>Rs4795541/5-HTTLPR</b> in promoter region – long (16) and short (14) repeats</li><li>• Long-A (La) or Long-G (Lg)</li></ul>	<ul style="list-style-type: none"><li>• SSRIs</li><li>• SNRIs</li><li>• SMSs</li></ul>
HTR2A	<ul style="list-style-type: none"><li>• Rs6311A&gt;G, rs6313C&gt;T</li><li>• Rs7997012A&gt;G</li></ul>	

# Primary Literature





# **Genomics Used to Improve Depression Decisions (GUIDED) Trial**

# GUIDED Trial

## Study Design & Results

Trial Design	<ul style="list-style-type: none"><li>• TAU group blinded until week 8</li><li>• Both groups unblinded after week 12</li><li>• Collected data through 24 weeks</li></ul>
Primary Outcome	<ul style="list-style-type: none"><li>• <b>27.2% decrease in HAM-D17</b> in guided-care compared to 24.4% decrease in TAU (<math>p = 0.107</math>)</li></ul>
Select Secondary Outcomes	<ul style="list-style-type: none"><li>• Response rate per HAM-D17: <b>26.0%</b> vs 19.9% (<math>p = 0.01</math>)</li><li>• Remission per HAM-D17: <b>15.3%</b> vs 10.1% (<math>p = 0.007</math>)</li></ul>

# GUIDED Trial

Conclusions	
Author's Conclusions	<ul style="list-style-type: none"><li>• Using pharmacogenomic testing to guide treatment increases the response and remission rates over TAU</li><li>• Congruent medication use may lead to fewer side effects and improve patient safety</li></ul>
Strengths	<ul style="list-style-type: none"><li>• Trial design aligns with guidelines for MDD trials</li><li>• Included multiple times of practice settings and providers</li><li>• Active-controlled trial</li></ul>
Limitations	<ul style="list-style-type: none"><li>• Unable to blind the treatment-arm</li><li>• Majority of patients were white</li><li>• Fewer mild depression patients</li><li>• Primary outcome not statistically significant</li></ul>



# **Precision Medicine in Mental Health Care (PRIME Care) Trial**

# PRIME-Care Trial

Study Design & Results	
Trial Design	<ul style="list-style-type: none"><li>• Assess outcomes at 4, 8, 12, 24, 48 weeks</li><li>• Patients assigned to either pharmacogenomic testing group or usual care group</li></ul>
Primary Outcome	<ul style="list-style-type: none"><li>• Treatment initiation:<ul style="list-style-type: none"><li>○ PGx-guided group more likely to receive an antidepressant with a mild drug-gene interaction compared to a moderate interaction (<math>p &lt; 0.001</math>)</li></ul></li><li>• Remission:<ul style="list-style-type: none"><li>○ Remission rates higher in PGx group over 24 weeks (<math>p = 0.02</math>)</li><li>○ At 24 weeks, remission rates not significant (<math>p = 0.45</math>)</li></ul></li></ul>
Select Secondary Outcomes	<ul style="list-style-type: none"><li>• PGx-group had higher treatment response and reduction in symptoms (<math>p = 0.05</math>)</li><li>• Symptom improvement greater at 24 weeks in PGx-group (<math>p = 0.02</math>)</li></ul>

# PRIME-Care Trial

Conclusions	
Author's Conclusions	<ul style="list-style-type: none"><li>• Pharmacogenomic testing had less medications prescribed with gene-drug interactions</li><li>• Positive effects on symptom remission and response early in the trial, but not through week 24</li></ul>
Strengths	<ul style="list-style-type: none"><li>• Expanded on results from the GUIDED trial</li><li>• Higher rates of minority patients</li></ul>
Limitations	<ul style="list-style-type: none"><li>• Clinicians and patients were not blinded</li><li>• Not powered to detect changes in dosing for either group</li><li>• Uses a pharmacogenomic test not commercially available</li></ul>



# 2023 Meta Analysis

# Meta Analysis

- 11 randomized-controlled trials included; compared pharmacogenomic-guided therapy to treatment as usual

Outcome	Effect	Notes
Response rate	Increased in PGx-guided group at week 8 (OR 1.32) and week 12 (OR 1.36)	No significant difference at week 4 or week 24
Remission rate	Increased in PGx-guided group at week 8 (OR 1.58) and week 12 (OR 2.23)	No significant difference at week 4 or week 24
Medication congruency at 30 days	Reduced in PGx-group (OR 2.07)	Assessed in 3/11 studies
Conclusions: pharmacogenomic testing leads to increased response and remission at weeks 8 and 12, but was not significant early in the trials or at week 24. The increased response and remission may be due to a catalyst effect.		
Strengths: multiple sub-group analyses performed, included studies with longer durations Weaknesses: most studies unblinded, used per-protocol analysis		

# Assessment Question #3

A 42-year-old woman presents with a 2-year history of major depressive disorder.

Which of the following best describes the clinical utility and limitations of using PGx results to guide selection of her next antidepressant?

Past Medication Trials	Sertraline 100 mg daily Venlafaxine ER 150 mg daily
Side Effects from Past Medications	Nausea, insomnia
PGx Results	CYP2D6: poor CYP2C19: rapid

- A. Pharmacogenomic testing can reliably predict which antidepressant will be most effective for her and is recommended as a first-line tool for medication selection.
- B. Pharmacogenomic results may help avoid medications metabolized by CYP2D6, but they cannot reliably predict overall treatment response or eliminate the need for clinical monitoring.
- C. Her CYP2D6 poor-metabolizer status means all SSRIs should be avoided because they will be ineffective
- D. Because she is a CYP2C19 rapid metabolizer, she will experience fewer side effects with TCAs and should be started on amitriptyline.



# **Clinical Considerations & Future Directions**

# Ethical Considerations

Over-interpreted pharmacogenomic data

Potential for misuse of informed consent and privacy concerns

Utilizing pharmacogenomics for vulnerable populations

Not widely accepted in certain areas around the world

# Barriers to PGx Testing

Insurance coverage and out-of-pocket costs

- Types of tests

Timing of test results

- Orderable within Encompass vs send-out

Multi-gene testing unavailable in Encompass

Lack of integration in Encompass

Provider unfamiliarity with PGx and clinical implementation

- Provider and patient

# Practical Considerations

Genetic Test	Genes Tested	Insurance & Cost	CPIC Report Standardization
Genesight	15 genes including CYP2D6, 3A4, 2B6, 2C19, 2C9, 1A2, SLC6A4, HLA-A*3101, HLA-B*1502, HTRA2, COMT	Medicare Part C/Medicaid - \$0 Medicare, Commercial, or Self Pay: \$330 or less	Overall report not standardized
Genomind	26 genes including CYP 1A2, 2B6, 2C9, 2C19, 2D6, 3A4/5, COMT, HTRA2, MTHFR, SLC6A4	Medicaid, Medicare Part B, Medicare Part C - \$0 if patients meet criteria Commercial - \$399 Self-Pay - \$599	Overall report not standardized for PD genes
OneOme	27 genes with 100 alleles including CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4, COMT, HR2A, MTHFR, TMPT, SLC6A4	Insurance Coverage Financial Assistance - \$199 Self-Pay - \$349	Aligned with CPIC standardization
Tempus	13 genes with 90 variants	Medicaid, Medicare Part B, VA - \$0 Self-pay including commercial - \$295	Aligned with CPIC standardization

Myriad Genetics, Inc./Assurex Health, Inc. *Genesight*. 2026.

Genomind. *Gene Drug Interaction Summary*. 2025.

OneOme LLC. RightMed test. 2024.

Tempus AI Inc. Neurology & psychiatry. 2024.

# Pharmacogenomics at Atrium Health

- Pharmacogenomics program at Atrium Health started at Carolina's Medical Center in 2014 – looking into CYP2C19 variations in voriconazole
- Built pharmacogenomics clinical support into Encompass & can provide current drug-gene interaction recommendations
- Current consults are orderable for Charlotte market

Contact Information: [Pharmacogenomics@atriumhealth.org](mailto:Pharmacogenomics@atriumhealth.org)

# Encompass Integration

The screenshot displays the 'Results Review' section of a medical software interface. At the top, a navigation bar includes tabs for 'Summary', 'Chart Review', 'Results Review' (highlighted with a red box), 'Notes', 'Allergies', 'Immunizations', 'MAR', 'Medications', and 'Orders'. Below the navigation bar, the 'Results Review' section is titled. On the left, a search box is present, and a filter menu is open, showing 'LABORATORY RESULTS' and 'GENETICS / MOLECULAR' both checked with green checkmarks. The main content area shows a table of results. The table header includes a refresh icon, '3m ago', a 'Time Mark' icon, and a 'Most Recent Column' dropdown menu. The table lists various pharmacogenomics tests and their results.

PHARMACOGENOMICS	
CYP2B6 Genotype	*1/*6
CYP2B6 Phenotype	Intermediate ...
CYP2C19 Genotype	*1/*17
CYP2C19 Phenotype	Rapid metab...
CYP2C9 Gen Activity Score	1.5
CYP2C9 Genotype	*1/*2
CYP2C9 Phenotype	Intermediate ...
CYP2D6 Gen Activity Score	2.00
CYP2D6 Genotype	*1/*1
CYP2D6 Phenotype	Normal meta...
CYP3A5 Genotype	*3/*3
CYP3A5 Phenotype	Poor metabol...

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# Encompass Integration

← Summary Chart Review Results Review Notes Allergies Immunizations MAR Medications Orders Verify Orders Synopsis Enter/Edit Results **Genomic Indicators**

## Genomic Indicators

Add a new indicator [+ Add](#)

Drug

- CYP2B6 Intermediate metabolizer** [Edit](#) [View Results](#) Shared:

The CYP2B6 enzyme contributes to the metabolism of 8-13% of clinically important drugs such as sertraline and efavirenz. There is high inter-individual variation in CYP2B6 expression which may impact drug response and/or toxicity.  
[Efavirenz and CYP2B6 \(PharmGKB\)](#) | [CYP2B6 gene overview \(PharmGKB\)](#) | [Sertraline and CYP2B6/CYP2C19 \(PharmGKB\)](#)


- CYP2C19 Rapid Metabolizer** [Edit](#) [View Results](#) Shared:

The CYP2C19 enzyme contributes to the metabolism of a large number of clinically relevant drugs and drug classes such as antidepressants, benzodiazepines, mephenytoin, proton pump inhibitors (PPIs), and the antiplatelet prodrug clopidogrel.  
[CYP2C19 gene overview \(PharmGKB\)](#) | [Amitriptyline and CYP2C19/CYP2D6 \(PharmGKB\)](#) | [Citalopram/escitalopram and CYP2C19 \(PharmGKB\)](#) | [Clopidogrel and CYP2C19 \(PharmGKB\)](#) | [Voriconazole and CYP2C19 \(PharmGKB\)](#) | [Proton pump inhibitors and CYP2C19](#)

- CYP2C9 Intermediate Metabolizer** [Edit](#) [View Results](#) Shared:

CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds.  
[CYP2C9 gene overview \(PharmGKB\)](#) | [Phenytoin and CYP2C9/HLA-B \(PharmGKB\)](#) | [Warfarin and CYP2C9/CYP4F2/VKORC1 \(PharmGKB\)](#) | [NSAIDs and CYP2C9](#)

- CYP2D6 Normal Metabolizer** [Edit](#) [View Results](#) Shared:

The cytochrome P450 2D6 (CYP2D6) is highly polymorphic and involved in the metabolism of up to 25% of the drugs that are in common use in the clinic.  
[CYP2D6 gene overview \(PharmGKB\)](#) | [Amitriptyline and CYP2C19/CYP2D6 \(PharmGKB\)](#) | [Atomoxetine and CYP2D6 \(PharmGKB\)](#) | [Codeine and CYP2D6 \(PharmGKB\)](#) | [Fluvoxamine and CYP2D6 \(PharmGKB\)](#) | [Nortriptyline and CYP2D6 \(PharmGKB\)](#) | [Ondansetron and CYP2D6 \(PharmGKB\)](#) | [Ondansetron and CYP2D6 \(PharmGKB\)](#) | [Paroxetine and CYP2D6 \(PharmGKB\)](#) | [Tamoxifen and CYP2D6 \(PharmGKB\)](#) | [Tramadol and CYP2D6 \(PharmGKB\)](#) | [Tropisetron and CYP2D6 \(PharmGKB\)](#) | [Hydrocodone and CYP2D6](#)

- CYP3A5 Poor Metabolizer** [Edit](#) [View Results](#) Shared:

CYP3A5 is an important hepatic and extra-hepatic pharmacogene. CYP3A4 and CYP3A5 together account for approximately 30% of hepatic cytochrome P450, and approximately half of medications that are oxidatively metabolized by P450 are CYP3A substrates.  
[CYP3A5 gene overview \(PharmGKB\)](#) | [Tacrolimus and CYP3A5 \(PharmGKB\)](#)

# Encompass Integration

Drug



CYP2B6 Normal Metabolizer [Edit](#)

There is no reason to adjust the initial dose or change prescribing of medications that are affected by CYP2B6 on the basis of this result. Consult CPIC guidelines or a clinical pharmacist for more information.  
[CYP2B6 CPIC Guidelines](#)






 Sertraline



There is no reason to adjust the dose or change prescribing based on CYP2B6 genetic status, however, CYP2C19 genetic status should also be considered as CYP2C19 impacts sertraline metabolism.

See [CPIC Clinical Guidelines](#) or a clinical pharmacist for more information.

# CPIC vs DPWG Guidelines

DRUGS (1)	CPIC (3)	DPWG (2)
<p>escitalopram</p> <p><a href="#">escitalopram</a></p>	<div data-bbox="718 454 1166 596"> <b>CYP2C19</b> 06/25/2024 <span>CPIC</span> Alternate Drug ⓘ Dosing Info ⓘ Pediatric ⓘ</div> <div data-bbox="718 611 1166 703"> <b>SLC6A4</b> 06/25/2024 <span>CPIC</span> <b>No recommendation</b></div> <div data-bbox="718 718 1166 810"> <b>HTR2A</b> 08/12/2024 <span>CPIC</span> <b>No recommendation</b></div>	<div data-bbox="1356 454 1804 596"> <b>CYP2C19</b> 03/18/2024 <span>DPWG</span> Testing Info ⓘ Alternate Drug ⓘ Dosing Info ⓘ</div> <div data-bbox="1356 611 1804 703"> <b>CYP2D6</b> 03/29/2024 <span>DPWG</span> <b>No recommendation</b></div>

# Assessment Question #4

Which of the following is a common barrier to the widespread implementation of pharmacogenomic testing in clinical practice? Select all that apply.

- A. Lack of evidence linking genetic variants to drug response
- B. Limited availability of validated genetic tests
- C. Cost of testing and inconsistent insurance reimbursement
- D. Inconsistent ability to integrate genetic results into the EHR

# Future Directions

## Pharmacoepigenerics

- Investigates how epigenetic mechanisms, which modify gene expression without altering the genetic code, might influence an individual's response to medications

## Increased integration in EHR

## Broader application beyond depression and anxiety

## Improved access, cost-effectiveness, and reimbursement for PGx

# Summary

- The goal of PGx is to provide a tool to optimize medication selection and dosing based on an individual's genetic makeup by targeting genetic variations in pharmacokinetic and pharmacodynamic processes
- CYP2D6, CYP2C19, and CYP2B6 are the primary CYP enzymes along with SLC6A4, and HTR2A that may influence antidepressant and anxiolytic medication response
- The 2023 CPIC and DPWG guidelines provide recommendations on medication dosing based on metabolizer status
- The GUIDED and PRIME Care trials show PGx-guided therapy can improve response to medication treatment
- Future directions include expanded EHR integration, improved access and reimbursement, and pharmacogenetics

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# Thanks!

## Questions?

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