Psychiatric Pharmacogenomics: Introduction and Applications

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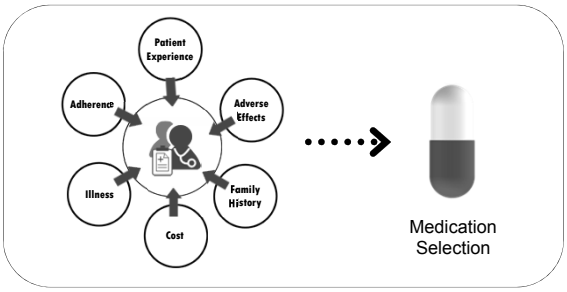
Medical Affairs Manager

Disclosure

- Relevant Financial Relationships:
  - Employed as a Medical Affairs Manager by Assurex Health (a wholly owned subsidiary of Myriad Genetics)
- The DMU CME Director has reviewed the content and determined the presentation is without influence by a commercial interest company.

Current Medication Decision Factors



Challenges in Clinical Practice

LACK OF RESPONSE	~50% of patients with depression do not respond to their first treatment[1]
SIDE EFFECTS	In clinical studies, up to 30% of patients discontinued treatment due to intolerable side effects[2,3]
NONADHERENCE	Up to 70% of patients receiving prescriptions for antidepressant drugs are nonadherent, with side effects being the most common reason[4,5]

•These challenges can lead to symptomatic decline, the need to change medication, and frustration for both the patient and the clinician.

1.Trivedi MH, Rush AJ,Wisniewski SR, et al; for the STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry*. 2006;163:28-40. 2. Rush AJ, Trivedi MH, Wisniewski SR, et al; for the STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354:1231-1242. 3. Rush AJ,Trivedi MH,Wisniewski SR, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905-1917. 4. Khawam EA, Laurencic G, Malone DA Jr. Side effects of antidepressants: an overview. *Cleve Clin J Med*. 2006;73:351-353, 356-361. 5. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care*. 1995;33:67-74.

Current Standard of Care

Current Prescribing Practice is Highly Empiric

"Trial and Error" standard of care prescribing leads to:

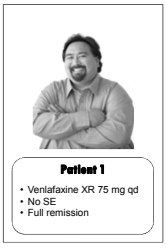
- Repeated drug trials with limited efficacy
- Increasing rates of side effects
- 70% non-compliance
- High rates of polypharmacy

Sequenced Treatment Alternatives to Relieve Depression[1]

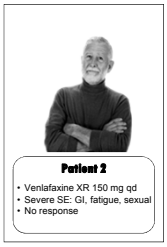
Drug Trial	Treatment Response	Treatment Intolerance
1	49%	16%
2	29%	20%
3	17%	26%
4	16%	34%

Rush J, et al. Acute and longer term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163(11):1905-1917.

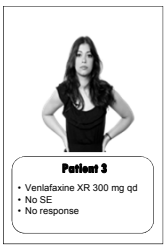
Three Patients



Patient 1
- Venlafaxine XR 75 mg qd
- No SE
- Full remission



Patient 2
- Venlafaxine XR 150 mg qd
- Severe SE: GI, fatigue, sexual
- No response



Patient 3
- Venlafaxine XR 300 mg qd
- No SE
- No response

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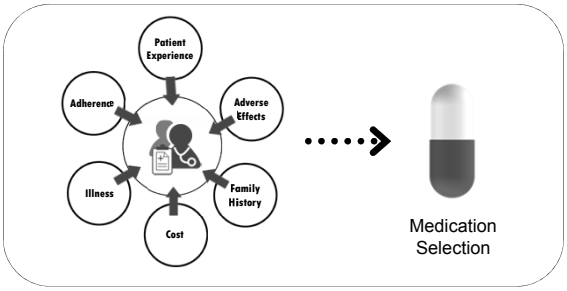
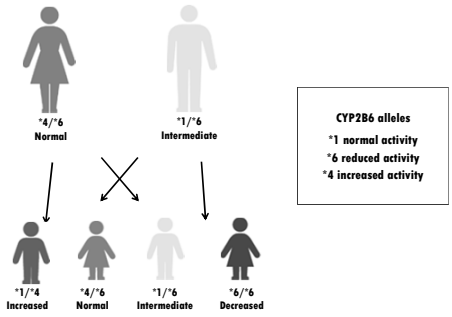
Current Medication Decision Factors



Implications for Family History

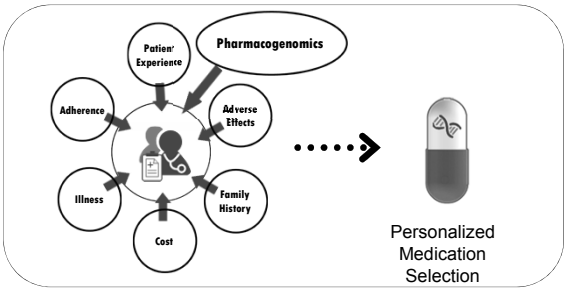


Pharmacogenomics Defined

Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the drugs and drug doses that are likely to work best for that particular person.

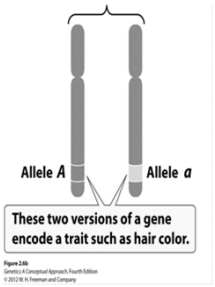
National Institutes of Health
National Human Genome Research Institute

Personalized Medication Selection Factors

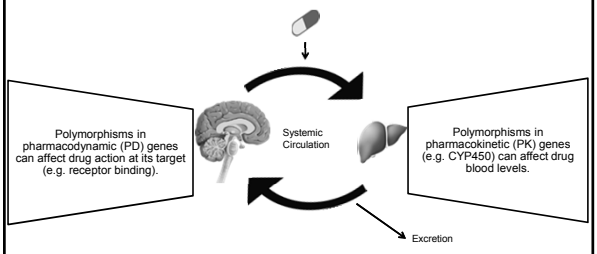


Genes and Alleles

- A gene is a sequence of DNA that codes for a protein.
- An "allele" is the term that refers to the different versions of a gene.
- In most cases, we randomly inherit one copy of each gene from each parent.
- The combination of alleles (genotype) that we receive creates a certain physical presentation (phenotype).

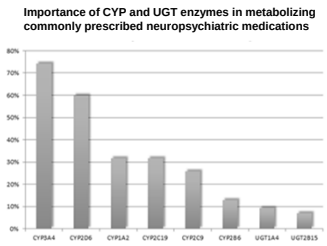


Pharmacodynamics and Pharmacokinetics



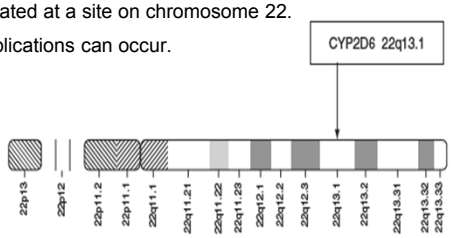
Drug Metabolism

- The CYP450 system is a family of about 57 enzymes responsible for drug metabolism, primarily in the liver.
- The UGT system is made up of 3 known groups of UGT genes – UGT1, UGT2, and UGT3, each of which includes multiple genes
- Multiple enzymes may be involved in the metabolism of a given drug.

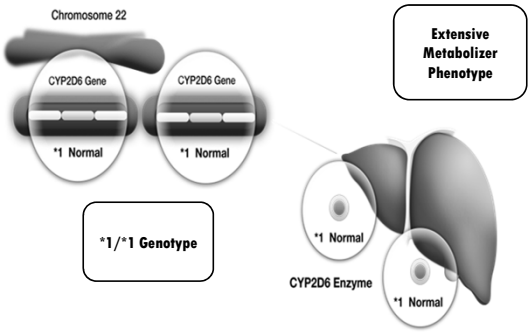


CYP2D6

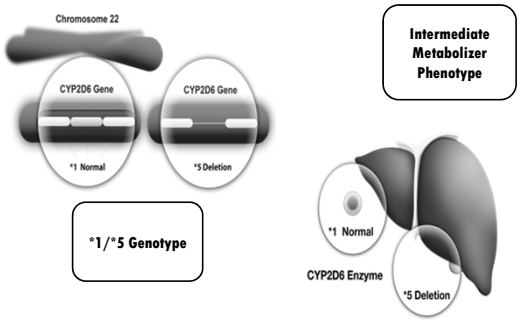
- A highly variable gene with 17 common, clinically relevant polymorphisms.
- Located at a site on chromosome 22.
- Duplications can occur.



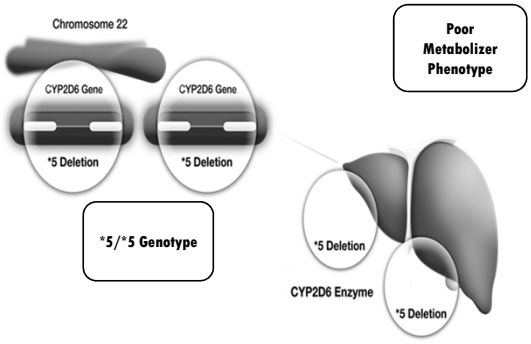
CYP2D6 Expression & Phenotype



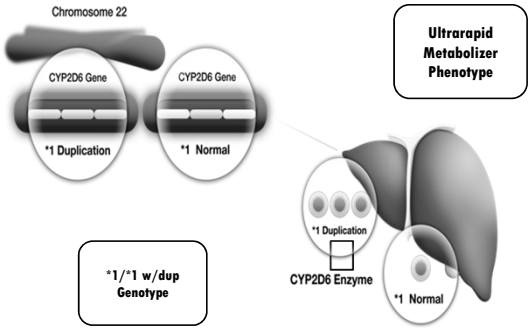
CYP2D6 Expression & Phenotype



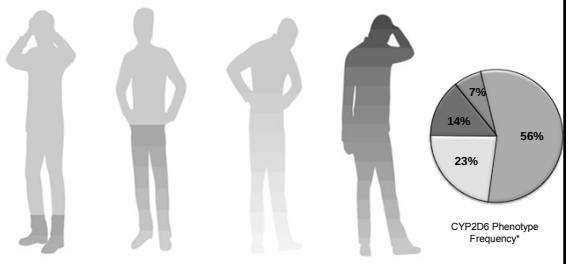
CYP2D6 Expression & Phenotype



CYP2D6 Expression & Phenotype



How Genetics Can Affect Medication Blood Levels

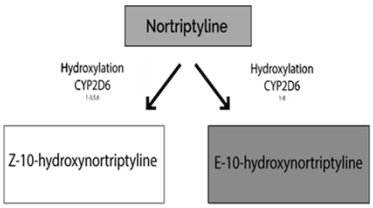


ULTRARAPID METABOLIZER	EXTENSIVE (NORMAL) METABOLIZER	INTERMEDIATE METABOLIZER	POOR METABOLIZER
Breaks down medications rapidly. May not get enough medication at normal doses.	Breaks down medications normally. Has normal amounts of medication at normal doses.	Breaks down medications slowly. May have too much medication at normal doses.	Breaks down medications very slowly. May experience side effects at normal doses.

CYP2D6 Phenotype Frequency*

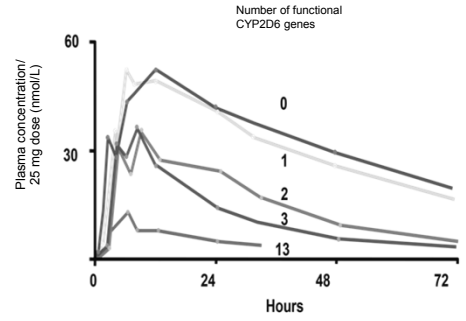
*Phenotype frequency is based on internal Assurex Health data of over 100,000 tested patients.

CYP2D6 and Nortriptyline



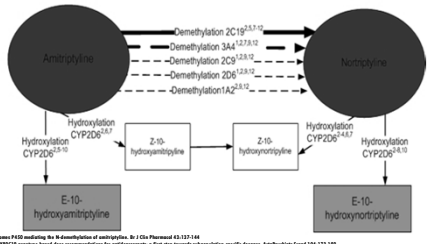
1.Kirchheiner, J., (2001) CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. ActaPsychiatr Scand 104:173-192
2.Olesen, O., et. al (1997) Hydroxylation and Demethylation of the Tricyclic Antidepressant Nortriptyline by cDNA-Expressed Human Cytochrome P-450 Isozymes. Drug Metabolism and Disposition 25(6):740-744
3.Yue, Q., et al. (1998) Pharmacokinetics of nortriptyline and its 10-hydroxy metabolite in Chinese subjects of different CYP2D6 genotypes. Clinic Pharmacology & Therapeutics 64(4):384-390
4.Jiang, Z., et al. (2001) The role of CYP2C19 in amitriptyline N-demethylation in Chinese subjects. Eur J Clin Pharmacol 58:109-113
5.Shimoda, L., et al. (1997) Significance of monitoring plasma levels of amitriptyline, and its hydroxylated and desmethylated metabolites in prediction of the clinical outcome of depressive state. Psychiatry clin neurosci 51(1):35-41
6.Breyer-Pfaff, Ursula (2004) The metabolic fate of amitriptyline, nortriptyline and amitriptylinoxide in man. Drug Metabolism Reviews 36(364):723-746
7.De Vos, A., et al. (2010) Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. The Pharmacogenomics Journal: 1-9
8.Steimer, W., et al. (2004) Allele-specific change of concentration and functional gene dose for the prediction of steady-state serum concentrations of amitriptyline and nortriptyline in CYP2C19 and CYP2D6 extensive and intermediate metabolizers. Clinical Chemistry 50:9: 1623-1633

CYP2D6 and Nortriptyline



Dalén P, Dahl ML, Bernal Ruiz ML, Nordin J, Bertilsson L. Clin Pharmacol Ther. 1998 Apr;63(4):444-52

Metabolic Pathway of Amitriptyline



1. Ghahramani, S., et al.(1997) Cytochromes P450 mediating the N-demethylation of amitriptyline. Br J Clin Pharmacol 43:137-144
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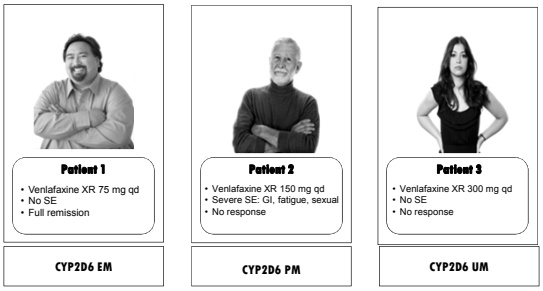
11. Thiems, D., et al. (2000) Correlation of inter-individual variations of amitriptyline metabolism examined in twins with CYP2C19 and CYP2D6 polymorphisms. Int J Legal Med 113:149-155
12. Yoshashikibara, K., et al. (1998) Five distinct human Cytochrome P450s mediate amitriptyline n-demethylation in-vitro. Dominance of CYP2C8 and 2A6. J Clin Pharmacol 38: 113-121

Three Patients



Patient 1	Patient 2	Patient 3
• Venlafaxine XR 75 mg qd • No SE • Full remission	• Venlafaxine XR 150 mg qd • Severe SE: GI, fatigue, sexual • No response	• Venlafaxine XR 300 mg qd • No SE • No response
CYP2D6 EM	CYP2D6 PM	CYP2D6 UM

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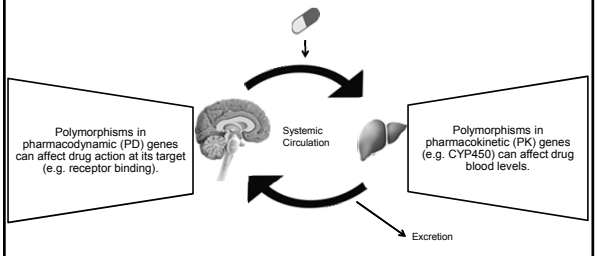
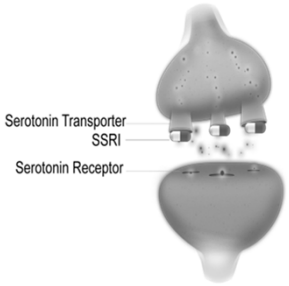
Pharmacodynamics and Pharmacokinetics



Pharmacodynamic Pharmacogenomics – SLC6A4

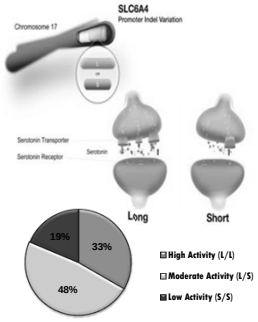
Serotonin Transporter (SLC6A4)

- 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)
- The two variants are differentiated by a 44 base pair insertion/deletion
- The short allele results in lower transcription rates, providing less active sites for SSRIs.
- The short allele is associated with lower rates of remission following SSRI treatment



Pharmacodynamic Pharmacogenomics - HLA

Human Leukocyte Antigen (HLA)

- Helps regulate the immune system and recognize foreign substances such as viral and bacterial peptides[1]

Genetics

- Located on chromosome 6; highly polymorphic[1]
- HLA-A*3101 and HLA-B*1502 alleles have been associated with severe cutaneous adverse drug reactions (cADRs), including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Oxcarbazepine and carbamazepine are two medications most commonly associated with cADRs[2,3]

Drug	HLA-A*3101	HLA-B*1502
Oxcarbazepine (Trileptal®)[3]	-	√
Carbamazepine (Tegretol®)[2]	√	√

1. Genver S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet Genomics. 2014;24(2):104-112. doi:10.1097/FPC.0000000000000021.
2. Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.
3. Trileptal [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

HLA Genes and Cutaneous Adverse Drug Reactions (cADRs)

Meta-analysis of 20 studies found certain HLA alleles significantly overrepresented in patients showing CBZ-induced cADRs[1]

- HLA-A*3101 (OR 7.75)
- HLA-B*1502 (OR 19.33)

Subcategorized by severity of cADRs		
	HLA-A*3101 (OR)	HLA-B*1502 (OR)
SJS/TEN	5.65	80.70
Less severe cADRs	8.58	NS for predictive value

1. Genver S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. Pharmacogenet Genomics. 2014;24(2):94-112. doi:10.1097/FPC.0000000000000021.

Prevalence of HLA-A*3101 and HLA-B*1502

HLA-A*3101	Prevalence	HLA-B*1502
Japanese, Native American	> 15%	Hong Kong, Thailand, Malaysia, parts of Philippines
Han Chinese, Korean, European, Latin America	~10%	Taiwan
African American, Indian, Thai, Taiwanese, Chinese (Hong Kong)	~4%	North China
	2%-4%	South Asia, including India
	<1%	Japan, Korea
	Largely Absent	Individuals not of Asian origin (Caucasians, African Americans, Hispanics, Native Americans)

Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

The FDA and the HLA genes

HLA-B*1502

FDA has added a black box warning to the carbamazepine package insert, stating that carbamazepine should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks[1]

The FDA-approved package insert for oxcarbazepine also warns against the use of oxcarbazepine in patients positive for HLA-B*1502[2]

HLA-A*3101

The carbamazepine package insert discourages the use of carbamazepine in HLA-A*3101 positive patients[1]

1. Tegretol [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.
2. Trileptal [package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2014.

The FDA and Pharmacogenomics

The Food and Drug Administration (FDA) includes pharmacogenomic language in the package inserts of many commonly prescribed psychiatric medications:

Aripiprazole	"The aripiprazole dose in PM patients should initially be reduced to one-half (50%) of the usual dose."	CYP2D6 PM
Citalopram	"The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers."	CYP2C19 PM
Thioridazine	"The use of thioridazine in patients known to have reduced activity of P450 2D6 are contraindicated."	CYP2D6 IM or PM
Vortioxetine	"The maximum recommended dose of BRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers."	CYP2D6 PM
Carbamazepine	"Patients testing positive for the HLA-B*1502 allele should not be treated with Tegretol unless the benefit clearly outweighs the risk."	HLA-B*1502 Allele

The contents of this page have not been endorsed by the FDA

Psychiatric Pharmacogenomics: Clinical Studies

Psychiatric Pharmacogenomic Testing Companies

- Access Genetics
- AGI
- Al Bio Tech
- AltheaDx
- Assurex Health
- CompanionDx
- DNA Stat
- ENSr Medical
- Genelex
- GENETWORx
- Genomas
- Genomind
- Genotox
- Infiniti Labs
- Iverson Genetics
- Millennium Labs
- MonogramBio
- Natural Molecular
- NeuroPharmagen
- OneOme
- Pathway Genomics
- ProoveBiosciences
- Vantari Genetics

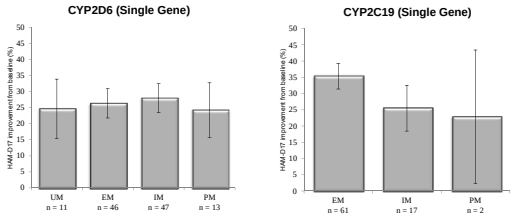
Evaluation of a Pharmacogenomic Test

Clinical Validity	• Is the test predictive of patient outcome?
Clinical Utility	• Does the test help guide a healthcare provider toward a more effective and/or tolerable medication?
Economic Utility	• Does the test reduce healthcare expenditures?

Psychiatric Pharmacogenomic Clinical Studies

Clinical Validity	Clinical Utility	Economic Utility
Altar, et al. 2014	Singh 2015	Fagerness, et al 2014.
	Brennan, et al. 2014	Winner, et al. 2013
	Winner, et al. 2013	Winner, et al. 2015
	Hall-Flavin, et al. 2012	
	Hall-Flavin, et al. 2013	

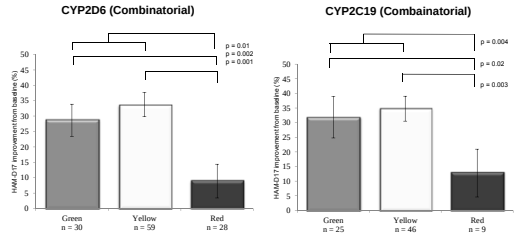
Clinical Validity: Individual Gene Phenotyping



Traditional gene phenotyping fails to identify patients with differential response to medications.

Altar, C. A., Carhart, J. M., Allen, J. D., Hall-Flavin, D. K., Dechairo, B. M., & Winner, J. G. (2015). Clinical validity : Combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes, (August 2014), 1–9. doi:10.1038/tpj.2014.85

Clinical Validity: CPGx Composite Phenotyping



Combinatorial Pharmacogenomics identifies patients who are least likely to respond to their treatment regimen, allowing clinicians to prescribe more suitable medications.

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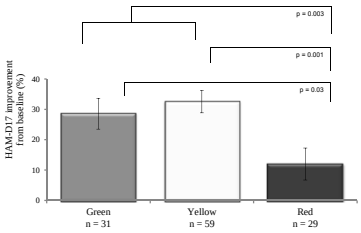
Clinical Validity: Meta Analysis



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Altar, C. A., Carhart, J. M., Allen, J. D., Hall-Flavin, D. K., Dechairo, B. M., & Winner, J. G. (2015). Clinical validity : Combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. (August 2014), 1–9. doi:10.1038/tpj.2014.85

Clinical Utility – A.B. Singh(2015)

- 12 Week , prospective double blind randomized trial comparing outcomes of genetically guided versus unguided treatment.
- Genetically guided group was 2.52 times more likely to remit from depression than unguided group.
- Unguided group was 1.13 times more likely to have medication tolerability problems requiring either dose reduction or cessation.

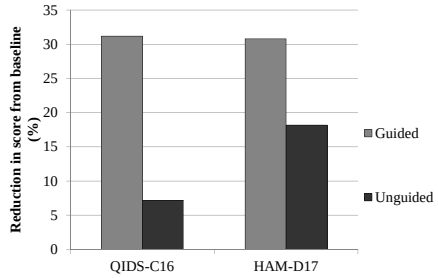
Singh, A. B. Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report. *Clin. Psychopharmacol. Neurosci.* **13**, 150–6 (2015).

Clinical Utility - Brennan, et al. (2015)

- Naturalistic, unblinded, prospective analysis of psychiatric patients and clinicians who utilized the pharmacogenomic report
- 87% showed improvement
- Patients reported significant decreases in depression, anxiety, and medication side effects, and increases in quality of life

Brennan XF, et al. A naturalistic study of the effectiveness of pharmacogenetic testing to guide treatment in psychiatric patients with mood and anxiety disorders. *Prim Care Companion CNS Disord. 2015; 17 (2).*

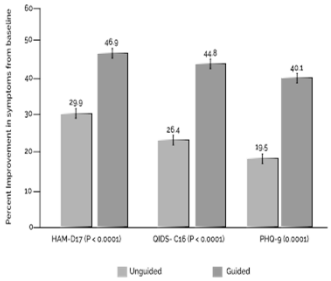
Clinical Utility – Hall-Flavin, et al. (2012)



*Treatment guided by the pharmacogenomic report resulted in up to a **four fold** greater improvement in symptoms*

Hall-Flavin DK, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. Transl Psychiatry. 2012 Oct 16;2:e172.

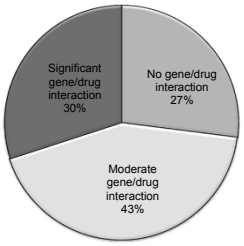
Clinical Utility – Hall-Flavin, et al. (2013)



Treatment guided by the pharmacogenomic report resulted in up to ***two fold*** greater improvement in symptoms

Hall-Flavin DK, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. **Pharmacogenetics & Genomics. 2013 Oct;**23(10):535-548.

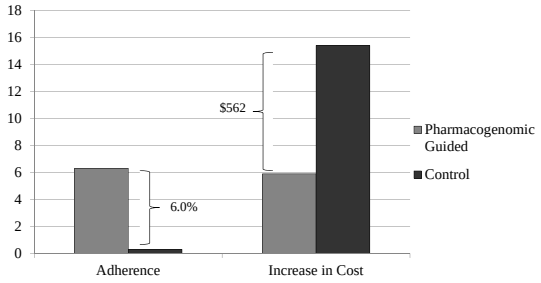
Prevalence of Patients Taking Medications that are Not Genetically Optimal



Thirty percent of the patients in a typical psychiatric practice are taking medications that are not genetically optimal, unbeknownst to their treating clinician.

Winner, J. G., Carhart, J. M., Altar, C. A., Allen, J. D., & Dechairo, B. M. (2013). A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discovery Medicine*, *16*(89), 219–27. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/24229738

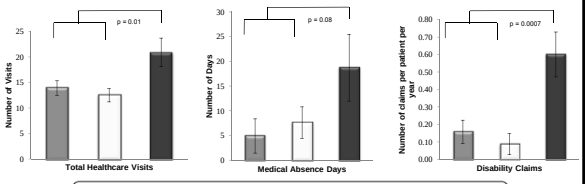
Economic Utility – Fagerness, et al. (2014)



Fagerness, J., Fonseca, E., Hess, G. P., Scott, R., Gardner, K. R., Koffler, M., … Lombard, J. (2014). Pharmacogenetic-guided psychiatric intervention associated with increased adherence and cost savings. *American Journal of Managed Care*, *20*(5), 146–156.

Economic Utility – Winner, et al. (2013)

This was a retrospective chart review of 96 adults diagnosed with a depressive or anxiety disorder. All subjects were treated with one or more psychotropic medications from CPGx panel. Medical records were analyzed for healthcare utilization during a one year period from April 2010 to April 2011.

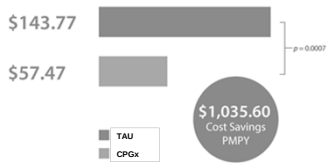


Increased healthcare utilization among subjects taking "red category" resulted in more than $5,100 greater spending than green or yellow category subjects.

Winner JG, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. Transl Psychiatry 2013; 3:e242. doi:10.1038/tp.2013.2

Economic Utility: Winner, et al. (2015)

This was a prospective case-control study of pharmacy data from 2,168 CPGx-guided patients vs. 10,880 propensity matched controls. The study enrolled patients who failed at least one CPGx panel medication and were currently taking another CPGx panel medication. Six months of pre-test data was compared to 12 months of post-test data.

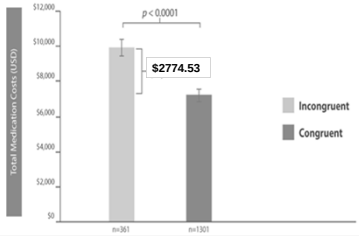


In addition to cost savings, patients treated using CPGx test experienced <u>significant increases in adherence</u> and <u>significant reductions in polypharmacy</u>.

1. Winner, J. G. et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a one year prospective evaluation. *Curr. Med. Res. Opin.* 1–30 (2015). doi:10.1185/03007995.2015.1063483

Economic Utility: Winner, et al. (2015)

Clinicians' medication decisions were evaluated for congruence with CPGx recommendations.



Total medication cost of patients on congruent medication was <u>$ 2,774 lower</u> than for patients whose clinicians did not follow report recommendations..

Winner, J. G. et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a one year prospective evaluation. *Curr. Med. Res. Opin.* 1–30 (2015). doi:10.1185/03007995.2015.1063483