Personalizing Medication Management with Pharmacogenetic Testing (PGT) and Urine Drug Testing (UDT) in Mental Health

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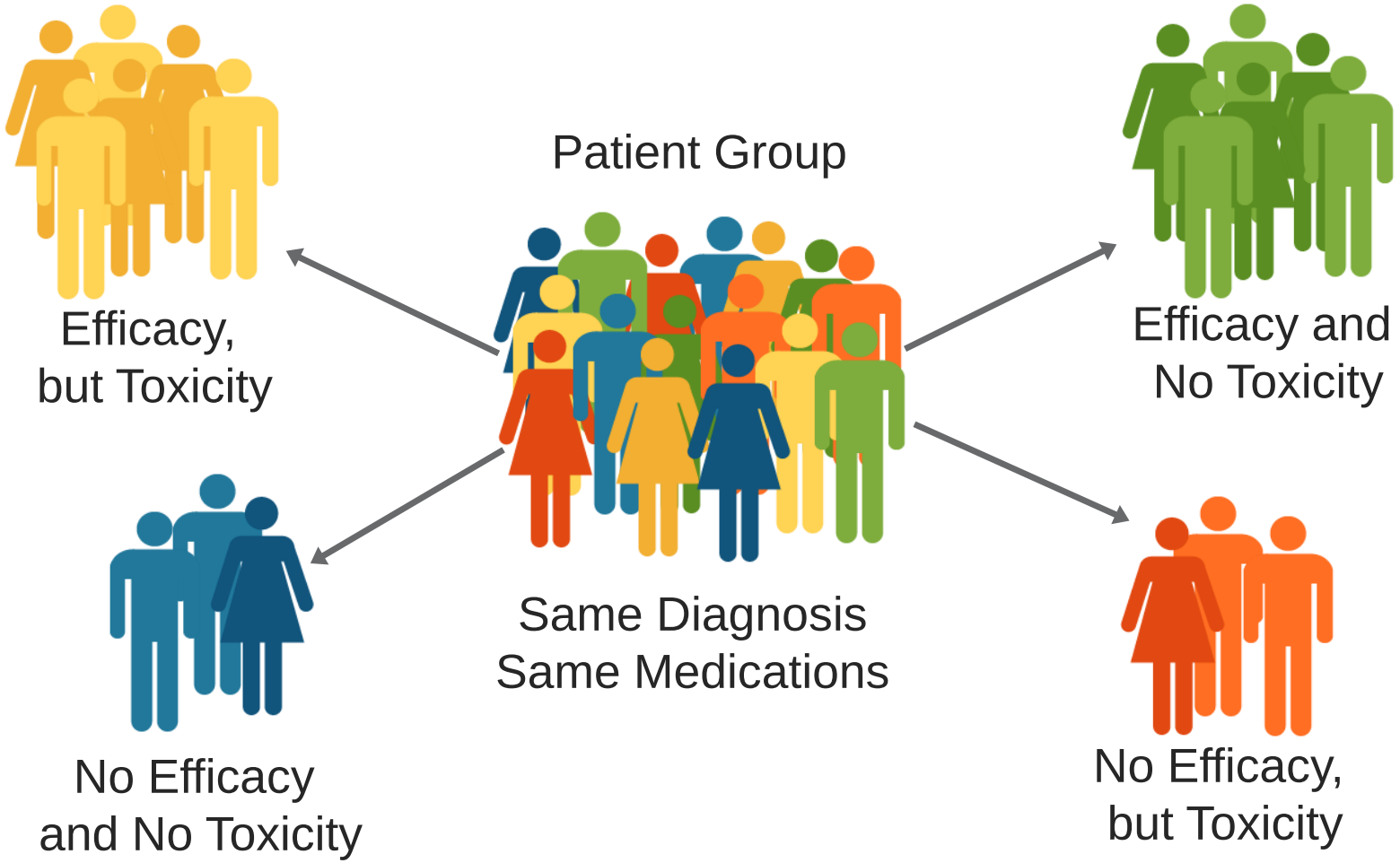
Learning Objectives

Upon completion of this program, you should be able to:

1. Conceptualize how PGT provides information which may be valuable for personalized medication therapy
2. Differentiate the advantages and limitations of the different types of UDTs & interpret results in the context of a patient's clinical presentation
3. Through clinical vignettes, integrate PGT and UDT to understand how they may provide more complete information about medication efficacy and adverse drug reactions

Patient Response Variability



American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

Individual Response to Treatment

How the body alters the drug

How the drug affects the body

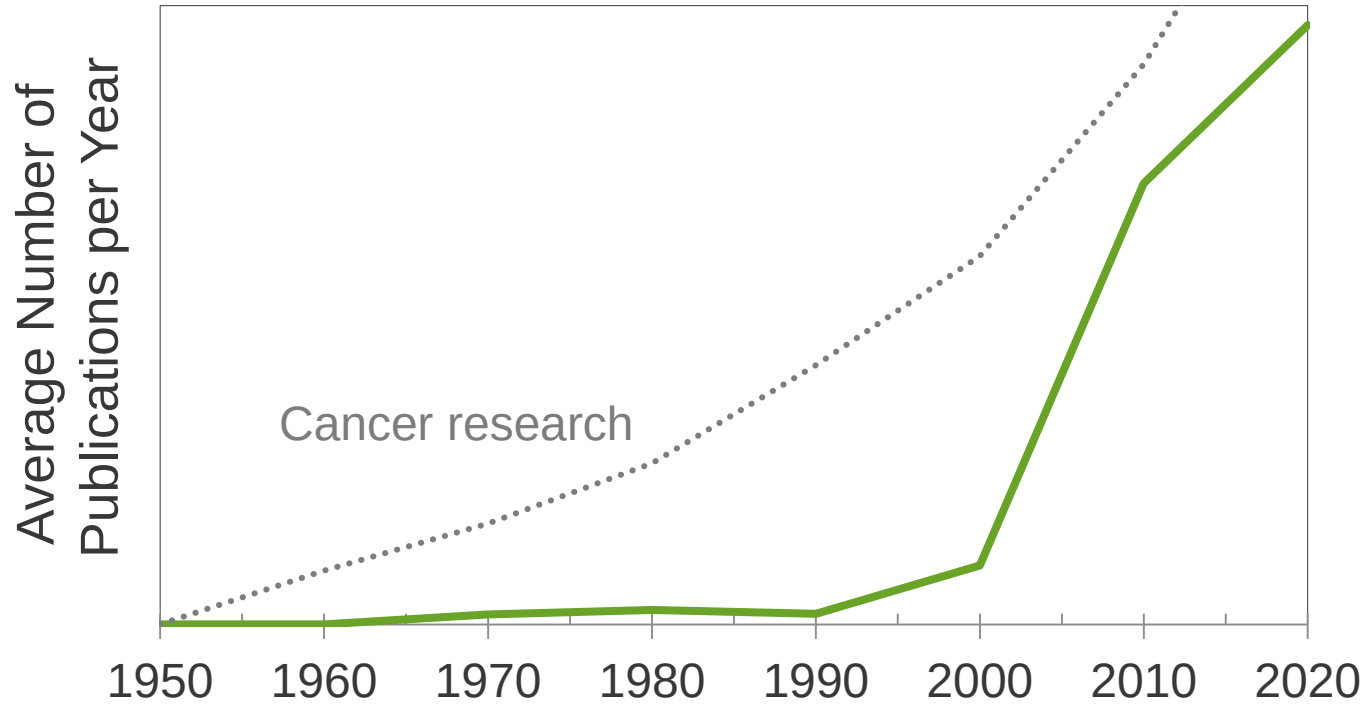
Pharmacogenetics

The science of how genetic variability impacts individual responses to medications

Argoff CE. Clinical implications of opioid pharmacogenetics. *Clin J Pain*. 2010;26(1):S16-S20.
Belle DJ, Singh H. Genetic factors in drug metabolism. *Am Fam Physician*. 2008;77(11):1553-1560.

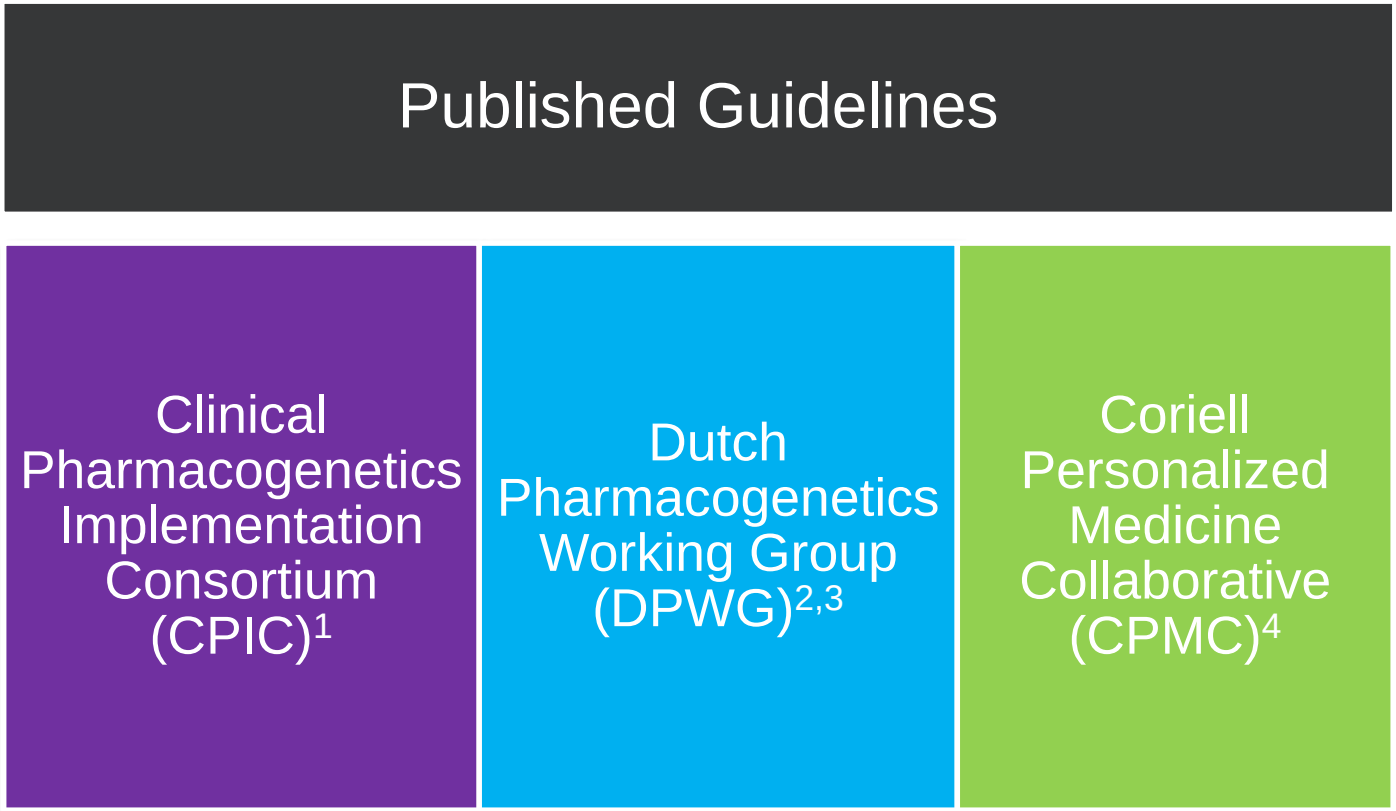
Accelerating Pace of Research

Pharmacogenetic era has been fueled by an explosion of scientific and clinical research that is only accelerating.



PubMed citations (http://www.ncbi.nlm.nih.gov/pubmed) searched using keyword "pharmacogenetics" and "cancer" and filtered by publication date. Accessed September 3, 2013.

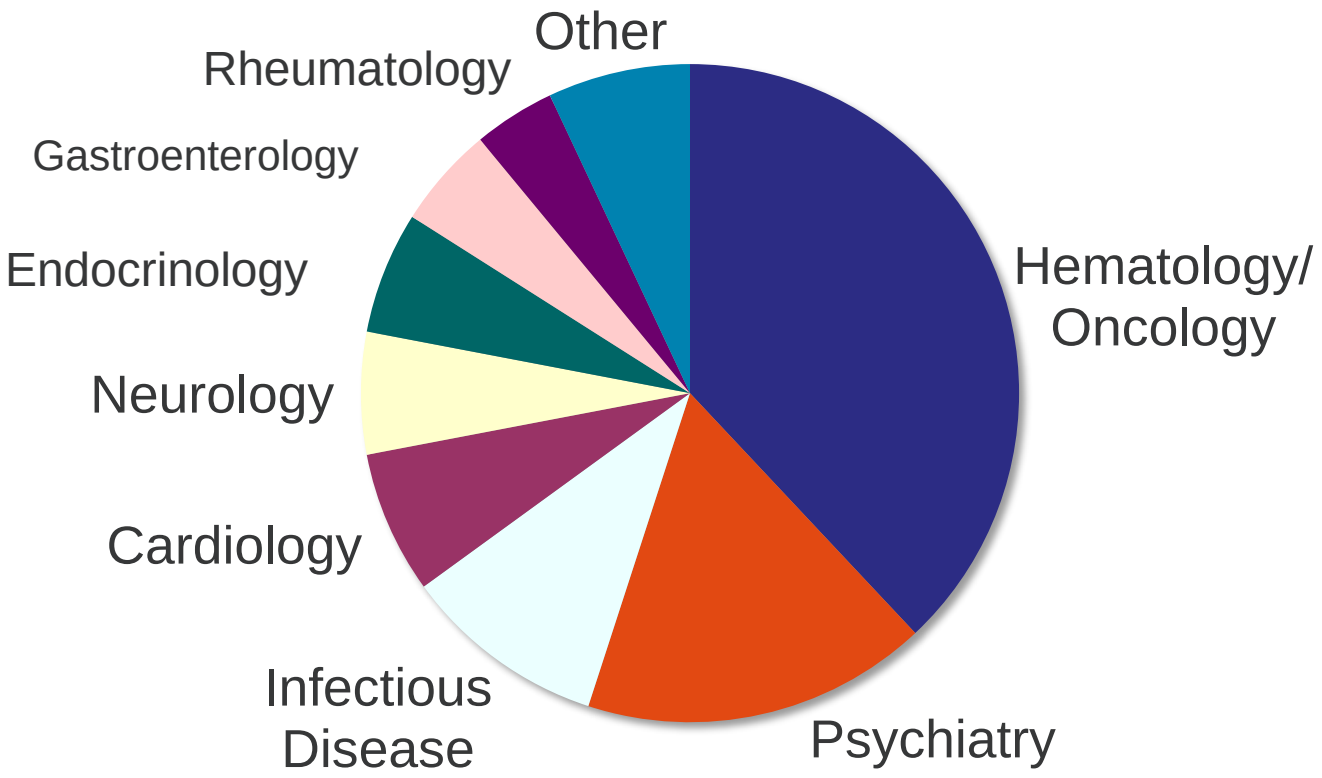
Current Landscape of Evidence



1. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*. 2011 Mar;89(3):464-7.
2. Swen JJ, Wilting I, de Goede AL, et al. Pharmacogenetics: from bench to byte. *Clin Pharmacol Ther*. 2008 May;83(5):781-7.
3. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte--an update of guidelines. *Clin Pharmacol Ther*. 2011 May;89(5):662-73.
4. Gharani N, Keller MA, Stack CB, et al. The Coriell personalized medicine collaborative pharmacogenomics appraisal, evidence scoring and interpretation system. *Genome Med*. 2013 Oct 18;5(10):93.

Pharmacogenetics in FDA Labeling

> 135 medications carry pharmacogenetic information in FDA product label[1]



US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labels. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. Accessed November, 2015

PGT in Mental Health

Gene	Functional Significance	Medications Affected
CYP2D6	Variants can lead to poor, intermediate, or ultrarapid metabolism	Antidepressants[1], Antipsychotics[1]
CYP2C19	Variants can lead to poor, intermediate, or ultrarapid metabolism	Antidepressants[1]
UGT2B15	Variants can lead to poor or intermediate metabolism	Benzodiazepines[2]
MTHFR	Impaired folic acid metabolism	SSRI/SNRIs[3]
DRD2	Altered medication response	Antipsychotics[4]
HTR2C	Variant protective against antipsychotic induced weight gain	2nd Generation Antipsychotics[5]
HLA-B*15:02	Risk of serious skin hypersensitivity reaction	Anticonvulsants[6]

1. Spina et al. *J Neural Transm*. Sept 2014:1-24.
2. Stingl JC, Bartels H, Viviani R, Lehmann ML, Brockmoller J. Relevance of UDP-clucoronosyltransferase polymorphisms for drug dosing: A quantitative systematic review. *Pharmacol Ther*. 2013. doi:10.1016/j.pharmther.203.09.002
3. Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. *Am J Psychiatry*. 2012 Dec;169(12):1267-74.
4. Zhang J et al. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry*. 2010 Jul;167(7):763-72
5. De Luca V et al. Association of the HTR2C gene and antipsychotic induced weight gain: a meta-analysis. *Int J Neuropsychopharmacol*. 2007 Oct;10(5):697-704.
6. Leckband SG et al. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. *Clin Pharmacol Ther*. 2013 Sep;94(3):324-8.

Potential Benefits to Providers

Explain or predict unexpected medication outcomes

- Adverse effects
- Inefficacy
- Treatment failures
- Higher than expected doses needed to achieve response

Argoff CE. Clinical implications of opioid pharmacogenetics. Clin J Pain. 2010;26(1):S16-S20.

Jannetto PJ, Bratanow NC. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics.* 2009;10(7):1157-1167.

Potential Benefits to Providers

- Identify patients at higher risk for certain medication interactions
- Reduce the need for multiple medication trials and contribution to treatment resistance
- Support a decision to continue or change the current medication regimen

Argoff CE. Clinical implications of opioid pharmacogenetics. Clin J Pain. 2010;26(1):S16-S20.
Jannetto PJ, Bratanow NC. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics.* 2009;10(7):1157-1167.

Pharmacogenetics and Antipsychotics

Significant inter-individual variation in response to antipsychotics

- 74% of patients with schizophrenia discontinued antipsychotic use due to ADRs and/or inefficacy[1]
- ~10%–30% of patients have little or no response to antipsychotics, and up to an additional 30% of patients have partial response to treatment[2]

Pharmacogenetic differences may impact patient response and toxicity to antipsychotics

- Majority of antipsychotics metabolized by CYP2D6[3]
- DRD2 and HTR2C may impact antipsychotic response[4,5]

1. Liberman JA, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005 Sep 22;353(12):1209-23.
2. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Schizophrenia Second Edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/schizophrenia.pdf. Published 2010. Accessed January 26, 2015.
3. Ravyn D, Ravyn V, Lowney R, Nasrallah HA. CYP450 Pharmacogenetic treatment strategies for antipsychotics: A review of the evidence. *Schizophr Res*. 2013;149(1-3):1-14.
4. Zhang J et al. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry*. 2010 July ; 167(7): 763–772.
5. De Luca V et al. Association of the HTR2C gene and antipsychotic induced weight gain: a meta-analysis. *Int J Neuropsychopharmacol*. 2007 Oct;10(5):697-704.

Pharmacogenetics and Antidepressants

Clinical responses vary widely among individuals

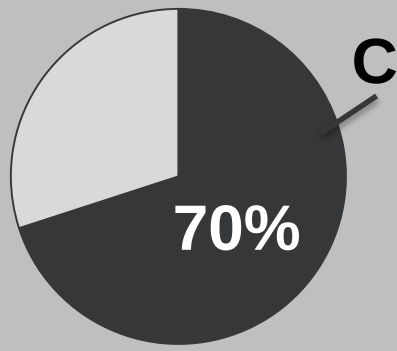
- In STAR-D, after an average of 10 weeks of treatment and 5 visits to their healthcare provider, the remission rate was 27.5%[1]
- After treatment failure with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant[2]

Pharmacogenetic differences may impact patient response to antidepressants

- CYP 450 enzymes commonly involved – CYP2D6 and CYP2C19
- MTHFR differences associated with decreased L-methylfolate levels and depression risk

1. Trivedi M, Rush J et al. 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 J, Trivedi M et al. Buproprion- SR, Sertraline, or Venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med.* 2006; 354:1231-42.

Variability in Medication Response



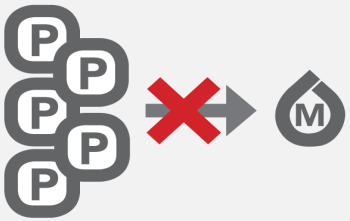
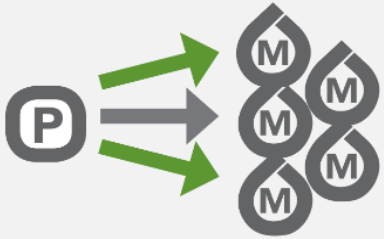
CYP2D6, CYP2C19, CYP2C9, CYP3A4/5

Four CYP450 enzymes metabolize about 70% of medications[1]

CYP450 genetic variability alters response to 1 in 4 medications[2]

1. Zanger UM, Klein K, Thomas M, et al. Genetics, Epigenetics, and Regulation of Drug-Metabolizing Cytochrome P450 Enzymes. *Clinical Pharmacology & Therapeutics*. Advance online publication 22 January 2014.
2. Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. *J Pharm Pract.* 2012 Aug;25(4):417–27.

Phenotypes – CYP450

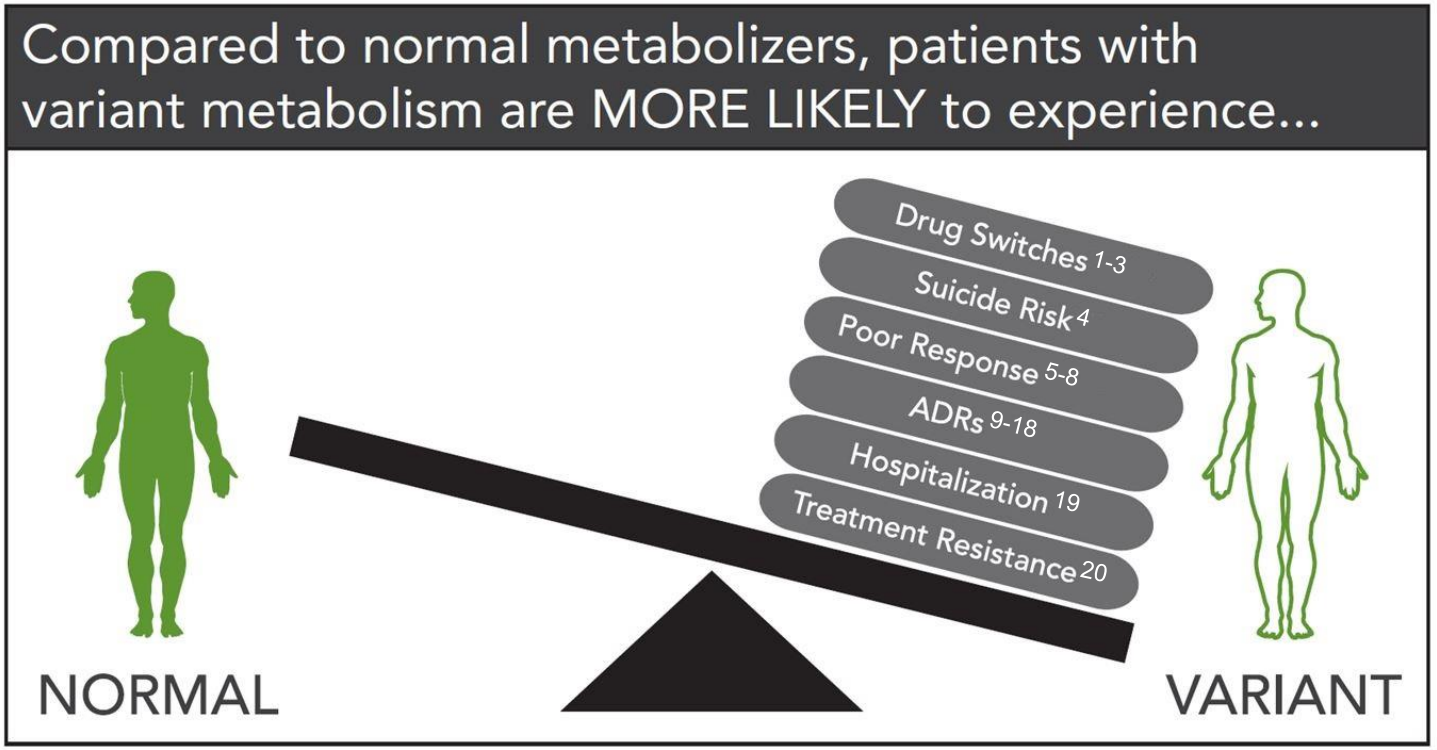
POOR (PM)	INTERMEDIATE (IM)	NORMAL (EXTENSIVE)	ULTRARAPID (UM)
			

CYP2D6: ~8-25% of individuals are UM, PM or IM[1]

CYP2C19: ≥ 25% of individuals are UM, PM, or IM[2]

1. Crews K, Gaedigk A, Dunnenberger H, et al. CPIC Guideline for CYP2D6 Genotype and Codeine Therapy. Nature. 2014: Vol 9(4);376-382.
2. Scott SA, Sangkuhl K, Stein CM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther.* Sep 2013;94(3):317-323.

Impact on Patient Outcomes



1. Mulder H et al. The association between cytochrome P450 2D6 genotype and prescription patterns of antipsychotic and antidepressant drugs in hospitalized psychiatric patients: A retrospective follow-up study. *J Clin Psychopharmacol*. 2005;25(2).
2. Bijl MJ, Visser LE, Hofman A, et al. Influence of the CYP2D6*4 polymorphism on dose, switching and discontinuation of antidepressants. *Br J Clin Pharmacol*. 2008;65(4):558-64.
3. Gregoor JG, van der Weide K, van der Weide J, et al. The association between CYP2D6 genotype and switching antipsychotic medication to clozapine. *Eur J Clin Pharmacol*. 2013;69(11):1927-32.
4. Peñas-Lledó EM, Dorado P, Agüera Z, et al. High risk of lifetime history of suicide attempts among CYP2D6 ultrarapid metabolizers with eating disorders. *Mol Psychiatry*. 2011;16(7):691-2.
5. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet Genomics*. 2013;23(10):535-548.
6. Stauble, ME, Moore, AW, Langman, LJ, et al. Hydrocodone in postoperative personalized pain management: pro-drug or drug? *Clin Chim Acta*. 2014;429:26-9.
7. Rundell JR, Harmandayan M, Staab JP. Pharmacogenomic testing and outcome among depressed patients in a tertiary care outpatient psychiatric consultation practice. *Transl Psychiatry*. 2011;1, e6.
8. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry*. 2012;2:e172.
9. Chen S, Wen-Hwei C, Blouin RA, et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: Screening costs and influence on clinical outcomes in psychiatry. *Clin Pharmacol Ther*. 1996;60:522-34.
10. de Leon J, Susce MT, Pan RM, et al. The CYP2D6 poor metabolizer phenotypemay be associated with risperidone adverse drug reactions and discontinuation. *J Clin Psychiatry*. 2005;66(1):15-27.
11. Jannetto PJ, et al. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics*. 2009;10(7):1157-67.
12. Wuttke H, Rau T, Heide R, et al. Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. *Clin Pharmacol Ther*. 2002;72(4):429-37.
13. Gan SH, Ismail R, Wan Adnan WA, et al. Impact of CYP2D6 genetic polymorphism on tramadol pharmacokinetics and pharmacodynamics. *Mol Diagn Ther*. 2007;11(3):171-81.
14. Scordo MG, Spina E, Romeo P, et al. CYP2D6 genotype and antipsychotic-induced extrapyramidal side effects in schizophrenic patients. *Eur J Clin Pharmacol*. 2000;56(9-10):679-83.
15. Kobylecki CJ, Jakobsen KD, Hansen T, et al. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. *Neuropsychobiology*. 2009;59(4):222-6.
16. Sutter ME, Gaedigk A, Albertson TE, et al. Polymorphisms in CYP2D6 may predict methamphetamine related heart failure. *Clin Toxicol* (Phila). 2013;51(7):540-4.
17. Vandel P, Haffen E, Vandel S, et al. Drug extrapyramidal side effects. CYP2D6 genotypes and phenotypes. *Eur J Clin Pharmacol*. 1999;55(9):659-65.
18. Koski A, Ojanperä I, Sistonen J, et al. A fatal doxepin poisoning associated with a defective CYP2D6 genotype. *Am J Forensic Med Pathol*. 2007;28(3):259-61.
19. de Leon J, Barnhill J, Rogers T, et al. Pilot study of the cytochrome P450-2D6 genotype in a psychiatric state hospital. *Am J Psychiatry*. 1998;155(9):1278-80.
20. Zabrocka M, Woszczek G, Borowiec M, et al. CYP2D6 gene polymorphism in psychiatric patients resistant to standard pharmacotherapy. *Psychiatr Pol*. 1999;33(1):91-100.

Not an actual patient

Case: “Jessica”

PGT Example

History

37-year-old woman diagnosed with depression

START

4 wks CELEXA® (20 mg/d)

4 wks CELEXA® (40 mg/d)

Mild benefits but symptoms still occur; CELEXA® discontinued

2 wks Start EFFEXOR XR®, titrate

Reports minimal improvement so dose is doubled

4 wks EFFEXOR XR® (150 mg/d)

Symptoms improve but has side effects; Clinician orders PGT; Discontinue EFFEXOR XR® and switch to PRISTIQ®

4 wks PRISTIQ® (50 mg/d)

Symptoms improve with minimal side effects

FINISH

Patient improves but only after <u>several months</u> of medication trials

Not an actual patient

Case: “Jessica”

PGT Results & Interpretation

Treatment	Gene Tested	Predicted Phenotype	Possible Clinical Results
CITALOPRAM (CELEXA®)	CYP2C19	Ultrarapid Metabolizer (UM)	Decreased efficacy; guidelines recommend consider alternative medication
VENLAFAXINE XR (EFFEXOR XR®)	CYP2D6	Poor Metabolizer (PM)	Increased efficacy and toxicity; guidelines recommend select alternative medication
DESVENLAFAXINE (PRISTIQ®)	None*	N/A	Efficacy with minimal side effects
N/A	MTHFR	Normal Activity	Expected to have normal folic acid metabolism and folate levels

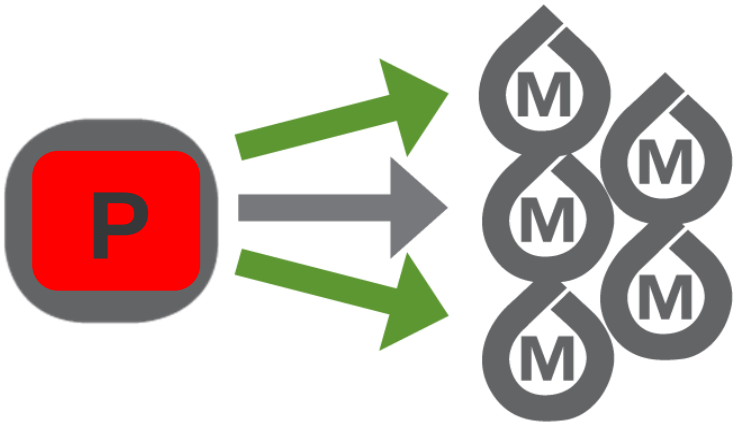
*Pristiq® is not appreciably metabolized by CYP450 enzymes

Not an actual patient

Case: “Jessica”

PGT Interpretation

Citalopram (Celexa®)



CYP2C19

Active parent Less active metabolite

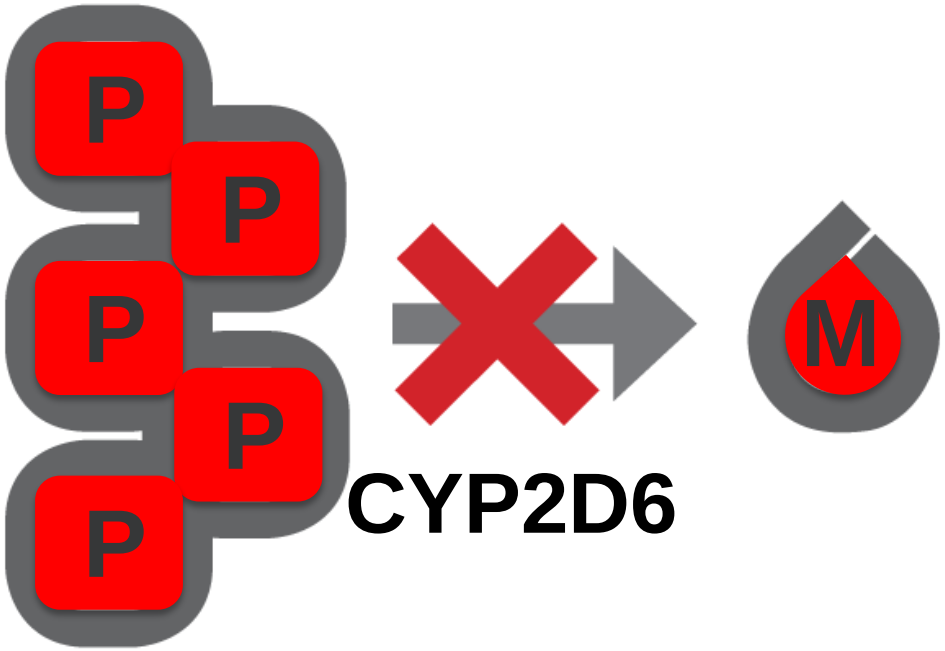
Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther. Feb 2008;83(2):322-327.
Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. Pharmacogenetics and genomics. Nov 2011;21(11):769-772.
Huezo-Diaz P, Perroud N, Spencer EP, et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. Journal of psychopharmacology. Mar 2012;26(3):398-407.
Chang M, Tybring G, Dahl ML, Lindh JD. Impact of cytochrome P450 2C19 polymorphisms on citalopram/escitalopram exposure: a systematic review and meta-analysis. Clin. Pharmacokinet. Sep 2014;53(9):801-811.

Not an actual patient

Case: “Jessica”

PGT Interpretation

Venlafaxine XR (Effexor XR®)



Active parent **Active metabolite**

McAlpine DE, O'Kane DJ, Black JL, Mrazek DA. Cytochrome P450 2D6 genotype variation and venlafaxine dosage. Mayo Clinic proceedings. Mayo Clinic. Sep 2007;82(9):1065-1068.

Whyte EM, Romkes M, Mulsant BH, et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. International journal of geriatric psychiatry. Jun 2006;21(6):542-549.

Not an actual patient

Case: “Jessica”

PGT Interpretation - MTHFR

L-methylfolate
- Biologically active
- Affects NE, DA, 5HT synthesis

MTHFR

Dietary Folate, Folic Acid

Ginsberg L, et al. L-methylfolate plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode. Innov Clin Neurosci. 2011;8(1)19-28.

SSRI/SNRI – MTHFR Drug-Gene Pair

Three Possible Clinical Phenotypes

Greatly Reduced Activity	Reduced Activity	Normal Activity
• Greatly reduced metabolism of folic acid into L-methylfolate[1] • Supplementation with L-methylfolate may improve SSRI/SNRI response[2]	• Decreased metabolism of folic acid into L-methylfolate[1] • Supplementation with L-methylfolate may improve SSRI/SNRI response[2]	• Normal metabolism of folic acid into L-methylfolate[1]

Reduced Activity: ~51% of individuals[3]

Greatly Reduced Activity: ~21% of individuals[3]

1. Nazki FH, Sameer AS, Ganaie BA. Folate: Metabolism, genes, polymorphisms and the associated diseases. *Gene*. 2014;533:11-20.
2. Papakostas GI, Shelton RC, Zajecka JM, et al. L-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials. *Am J Psychiatry*. 2012;169:1267-1274.
3. Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate Reductase Gene Variants and Congenital Anomalies: A HuGE Review. *Am J Epidemiol*. 2000;151(9):862-877.

Not an actual patient

Case: “Jessica”

PGT Example

START **FINISH**

4 wks	***4 wks***	***2 wks***	***4 wks***	***4 wks***
CELEXA® (20 mg/d)	CELEXA® (40 mg/d)	Start EFFEXOR XR® titrate	EFFEXOR XR® (150 mg/d)	PRISTIQ® (50 mg/d)

Personalizing treatment with pharmacogenetic testing can decrease healthcare costs and may improve patient outcomes[1-3]

1. Chen S, et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. *Clin Pharmacol Ther*. 1996 Nov;60(5):522-34.
2. Chou WH, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol.* 2000 Apr;20(2):246-51.
3. Hall-Flavin DK, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry*. 2012 Oct 16;2:e172.

Not an actual patient

Case: “Jessica”

PGT Example

START **FINISH**

Personalizing treatment with pharmacogenetic testing can decrease healthcare costs and may improve patient outcomes[1-3]

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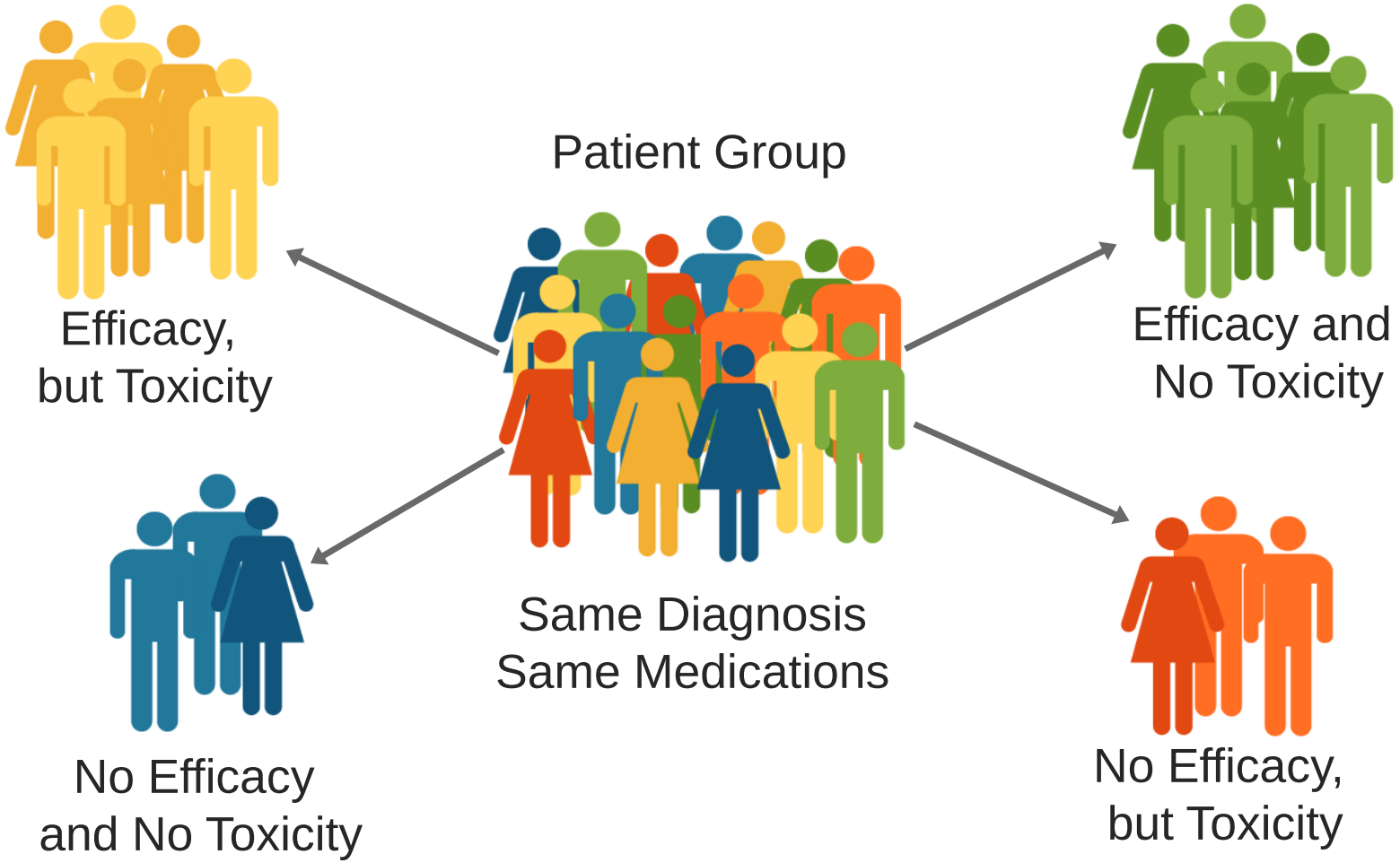
2. Chou WH, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol.* 2000 Apr;20(2):246-51.
3. Hall-Flavin DK, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry*. 2012 Oct 16;2:e172.

“Jessica”: Clinical Documentation

Subjective	Patient is “frustrated.” After minimal symptom improvement with Celexa (discontinued last visit), patient presents with chief complaint of dizziness, drowsiness, and dry mouth after starting Effexor XR. Depressive and anxious symptoms have moderately improved.
Objective	Affect is anxious and congruent with thought content. Speech is soft but otherwise regular rate and rhythm. Motor movements slow and lethargic. Thought process is ruminative. No suicidal or homicidal thoughts or psychotic symptoms. Insight, judgment, and impulse control are fair.
Assessment	Major Depressive Disorder with treatment resistance. Harm threat low.
Plan	Order PGT due to history of citalopram failure and intolerance to venlafaxine XR. Follow-up with patient after receipt of PGT results.

Documenting Clinical Rationale



American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

Clinical Rationale: Toxicity

- ✓ Patient is experiencing intolerable side effects with current medications

Efficacy,
but Toxicity

- ✓ Patient is being considered for treatment with medications that may lead to fewer side effects in individuals with specific genotypes

No Efficacy,
but Toxicity

American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

Clinical Rationale: No Efficacy

- ✓ Patient is being considered for treatment with medications that may lead to improved response in individuals with specific genotypes
- ✓ Patient is experiencing lack of symptom relief with current medication
- ✓ Patient and/or patient's family has a history of medication failures possibly due to undocumented genetic variability

No Efficacy
and No Toxicity

No Efficacy,
but Toxicity

American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

Clinical Rationale: Other Factors

- ✓ Patient is being considered for treatment with medications that require non-standard dosing and/or titration in individuals with specific genotypes
- ✓ Patient is considered for treatment with medications that should be avoided in individuals known to have specific genotypes
- ✓ Patient is on multiple medications increasing the risk for adverse drug reactions or drug-drug interactions

American Medical Association, Arizona Center for Education and Research on Therapeutics, Critical Path Institute. Pharmacogenomics: increasing the safety and effectiveness of drug therapy. Chicago, IL: American Medical Association; 2011. Report 10-0290:5/11:jt. http://www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf. Accessed August 16, 2012.

Clinical Rationale for PGT

BEFORE:
One size fits all approach

AFTER:
Personalized medicine

Full response

Partial response

No response

Toxicity

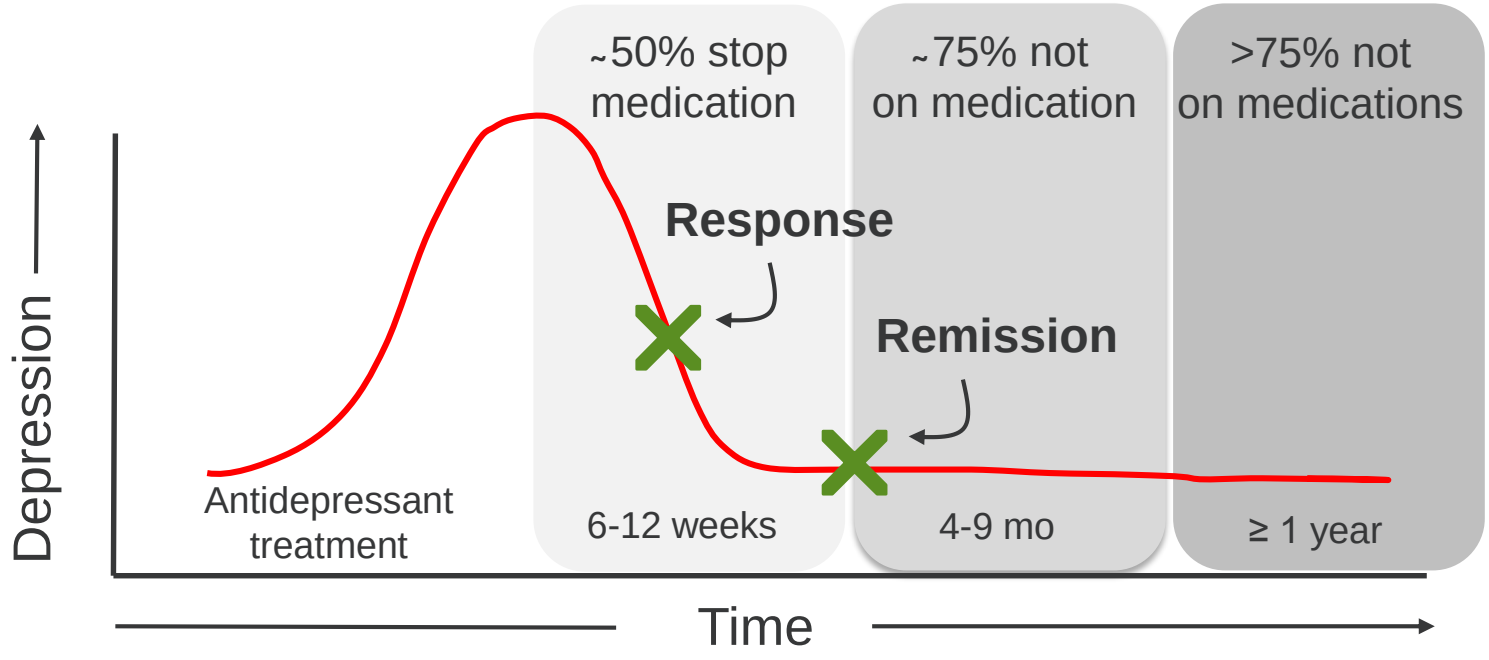
Rationale for Urine Drug Testing (UDT) in Mental Health

- High rates of treatment discontinuation[1]
  - Most patients do not inform their clinician
- Up to half of people living with mental illness also have substance abuse issues[2]
- Provides objective information to help assess medication use, as well as use of non-prescribed or illicit substances

1. Mitchel AJ and Selmes T. Why don't patients take their medicine? Reasons and solutions in psychiatry. *Adv Psych Treatment.* 2007;13:336-346.
2. Dual Diagnosis. National Alliance on Mental Illness Web site. https://www.nami.org/Learn-More/Mental-Health-Conditions/Related-Conditions/Dual-Diagnosis. Accessed July 17, 2015

Medication Adherence

Let's take a look at how medication monitoring may provide clinical value to treatment.



Adapted from Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry*. 1991:52(suppl):23-34.

Not an actual patient

Case: “Jessica” Revisited

UDT Interpretation

Test	Gene Tested	Comments
Citalopram (Celexa®)	Negative	Visit 2: The sample tested negative for citalopram and positive for N-desmethylcitalopram, consistent with the patient having taken Celexa. Absence of the parent drug citalopram is atypical and may be due to various factors, including timing of ingestion, drug-drug interactions, or genetic variation in metabolism. A pharmacogenetic test for CYP2C19 may provide additional information regarding a genetic variation.
N-desmethyl-citalopram	Positive	

Types of Testing

Presumptive Immunoassay Screen	Definitive Mass Spectrometry
In-office Point-of-Care (POC), or Laboratory Qualitative	Laboratory Quantitative (GC-MS or LC-MS/MS)
Minutes (POC) or days (Lab)	Hours to days
Drug classes and some select meds/substances	Specific medications, substances, and metabolites
Guidance for preliminary treatment decisions	Definitive quantitative results
Higher cutoff levels and cross-reactivity common; more false positives and false negatives	Lower cutoff levels. False positive and false negative results are rare

The clinician must choose testing method based on the needs dictated by the patient's history, presentation, community factors and treatment plan goals. The clinician's rationale for test and the analytes ordered must be documented in the patient's medical record.

False Negative vs. False Positive

Most Common with Presumptive/Immunoassay-based Tests

False Negative: *The test fails to detect the presence of the drug or metabolites*[1]	**False Positive**: *The test incorrectly detects the presence of the drug when none is present*[1]
Primary Reasons Include: • Higher cutoffs compared to mass spec. • IAs unable to effectively identify some substances (e.g., lorazepam)	Primary Reason: • Cross-reactivity
Potential Adverse Impact on Patient: • Undetected illicit use • Accused of drug diversion • Not receive ongoing meds • Drug interactions	Potential Adverse Impact on Patient: • Discharged from practice • Not having access to care • Legal decisions – lose family, return to jail

Center for Substance Abuse Treatment. (2012).Clinical drug testing in primary care. Technical Assistance Publication (TAP) Series, 32. DHHS Publication No. (SMA) 12-4668. Rockville, MD: Substance Abuse and Mental Health Services Administration. Available: http://www.kap.samhsa.gov/products/manuals/pdfs/TAP32.pdf

Sources of False Positive Results

Presumptive/Immunoassay Testing

Test Strip	Drug or Drug Class	Drugs Targeted by an Immunoassay	Substances Known to Cause a False Positive Test Result
AMP	Amphetamine	Amphetamine (i.e. Adderall®) Note: Amphetamine is a metabolic product of Benzphetamine, Selegiline and Famprofazone.	Phenylpropanolamine, Ephedrine, Pseudoephedrine, Ranitidine, Phentermine, Brompheniramine, Bupropion, Trazodone, Chlorpromazine, Promethazine, Dimethylamylamine. (Vicks® Nasal Inhaler metabolizes to Amphetamine in the body.)
BAR	Barbiturates	Butalbital, Phenobarbital, Secobarbital, Amobarbital and other Barbiturates	Ibuprofen, Naproxen
BUP	Buprenorphine	Buprenex®, Butrans®, Suboxone®, Subutex®, Zubsolv®	Tramadol, Morphine, Codeine, Methadone, Dihydrocodeine, Hydroxychloroquine, Chloroquine, Plaquenil®
BZO	Benzodiazepines	Oxazepam, Nordiazepam, Temazepam, Alprazolam and other Benzodiazepines to varying degrees	Oxaprozin, Sertraline
COC	Cocaine	Cocaine	Unknown/Infrequent
MTD	Methadone	Methadone	Verapamil, Quetiapine, Diphenhydramine, Doxylamine, Chlorpromazine
MET	Methamphetamine	Methamphetamine Note: Methamphetamine is a metabolic product of Benzphetamine, Selegiline and Famprofazone.	Adderall®, Phenylpropanolamine, Ephedrine, Pseudoephedrine, Ranitidine, Phentermine, Brompheniramine, Bupropion, Trazodone, Chlorpromazine, Promethazine. (Vicks® Nasal Inhaler (l-isomer), illicit (d-isomer) metabolizes to Amphetamine in the body.)
MDMA	Methylenedioxy-methamphetamine	Methylenedioxymethamphetamine	Phenylpropanolamine, Ephedrine, Pseudoephedrine, Ranitidine, Phentermine
OPI / MOP	Opiates	Codeine, Morphine, Hydrocodone, Hydromorphone	Oxycodone (at high concentrations) and poppy seeds (which contain morphine), certain quinolones
OXY	Oxycodone	Oxycodone, Oxymorphone	Codeine, Morphine, Hydrocodone, Hydromorphone
PCP	Phencyclidine	Phencyclidine	Venlafaxine, Dextromethorphan, Diphenhydramine, Ibuprofen, Tramadol
THC	THC (Marijuana)	Marijuana, Marinol, Dronabinol	Prilosec®, Protonix®, Efavirenz, Nsaids
TCA	Tricyclic Antidepressants	Amitriptyline, Nortriptyline, Imipramine, Desipramine, Doxepin and other Tricyclics to varying degrees	Cyclobenzaprine, Carbamazepine, Diphenhydramine, Quetiapine

Unexpected UDT Results
Possible Reasons

Numerous factors may contribute to unexpected UDT results:

- Patient medication use
- Time of last dose
- Undiscovered/unknown over-the-counter or prescription medication use
- Type of testing
- Pharmacogenetics
- Drug-drug interactions

Christo PJ, Manchikanti L, Ruan X, Bottros M, et al. Urine Drug Testing in Chronic Pain. *Pain Physician*. 2011; 14: 123-143.
Reisfield GM,Goldberger, BA, Bertholf RL. False-positive and false-negative test results in clinical urine drug testing. *Bioanalysis.* 2009. 1(5): 937-52.

Guideline-supported Testing

SAMHSA recommends to consider drug testing when assessing a patient presenting with mood or behavior changes to:[1]

- Aid in diagnosis
- Help determine whether the psychiatric symptoms are substance use or withdrawal related
- Help identify a co-occurring SUD
- Monitor for recent use of controlled medications

1. Substance Abuse and Mental Health Services Administration. (2012). *Clinical drug testing in primary care. T*echnical Assistance Publication (TAP) 32. HHS Publication No. SMA 12-4668. Rockville, MD: Substance Abuse and Mental Health Services Administration.

ASAM White Paper on Drug Testing

"It is appropriate to consider periodic random drug testing for all psychiatric patients, and especially young patients and those with a history of substance use disorders, particularly when they have been prescribed psychostimulants and benzodiazepines."[1]

1. American Society of Addiction Medicine. Drug Testing: A White Paper of the American Society of Addiction Medicine (ASAM). http://www.asam.org/docs/default-source/publicy-policy-statements/drug-testing-a-white-paper-by-asam.pdf?sfvrsn=2; page 66. Published October 26, 2013. Accessed January 27, 2016.

Not an actual patient

Case: “Lois”

Lois is a 54-year-old female with depression, anxiety, and chronic neck pain.

- Current Medications**:**
  - Venlafaxine XR (Effexor XR®)
  - Lorazepam (Ativan®)
  - Morphine ER (MS Contin®)
- PMH: Otherwise negative
- Per published guidelines, her HCP orders a UDT to monitor her use of medications and substances

Not an actual patient

Case: “Lois”

Immunoassay Results

Current Meds:

- Venlafaxine XR
- Lorazepam
- Morphine ER

In-Office Immunoassay Result	
Medication/Substance	**Result**
Benzodiazepines	Positive
Opiate	Positive
PCP	Positive

What are possible reasons for Lois’s immunoassay results?

Not an actual patient

Case: “Lois”

LC-MS/MS Results

LC-MS/MS RESULT		
Medication/Substance	**Test Outcome**	**Creatinine Normalized Results***
Lorazepam	**Negative**	**-**
Alpha-hydroxyalprazolam	**Positive**	**667**
Morphine	**Negative**	**-**
Hydrocodone	**Positive**	**1128**
Norhydrocodone	**Positive**	**1187**
Hydromorphone	**Positive**	**234**
PCP	**Negative**	**-**
Venlafaxine	**Positive**	**7834**
Desmethylvenlafaxine	**Positive**	**14042**

* Measured in ug/g (microgram of analyte per gram of creatinine)

“Lois”: Clinical Documentation

Subjective	Patient seen in routine and ongoing follow up for depression and anxiety with comorbid chronic neck pain. No new physical or psychiatric complaints. Mood and anxiety are reportedly stable.
Objective	In office immunoassay presumptive screen appeared as expected for prescribed medications; positive for PCP, which patient denied using. Definitive testing negative for PCP. However, results indicate the use of non-prescribed opioids and benzodiazepines.
Assessment	Aberrant drug taking behaviors, poor coping with stress and potential for self harm and loss of control.
Plan	Counsel patient on consequences of unauthorized use of non-prescribed substances. Continue medications with limited quantity. Follow up with patient in one week to reassess.

Medical Necessity

Criteria to establish medical necessity must be based on patient-specific elements identified during the clinical assessment and documented in the patient's medical record by the provider.

Documenting Medical Necessity

- Orders must be individualized
- Tests ordered and reasons for testing must be documented in the patient's medical record
- Risk assessment and stage of treatment should match testing frequency

Documenting How the Test Results Were Used

- Review of results and use in the treatment plan

Summary

- Genetic variability can influence medication efficacy and toxicity
- PGT may provide valuable information for individualized medication therapy
- UDT is one objective monitoring tool which requires understanding of testing technology and a patient's clinical picture for interpretation
- Integrating PGT and UDT may provide more complete information about medication efficacy and adverse drug reactions