Personalizing Medication Management with Pharmacogenetic Testing (PGT) in Mental Health and Pain

Disclosure

Adam Rzetelny, PhD

Associate Director, Clinical Affairs

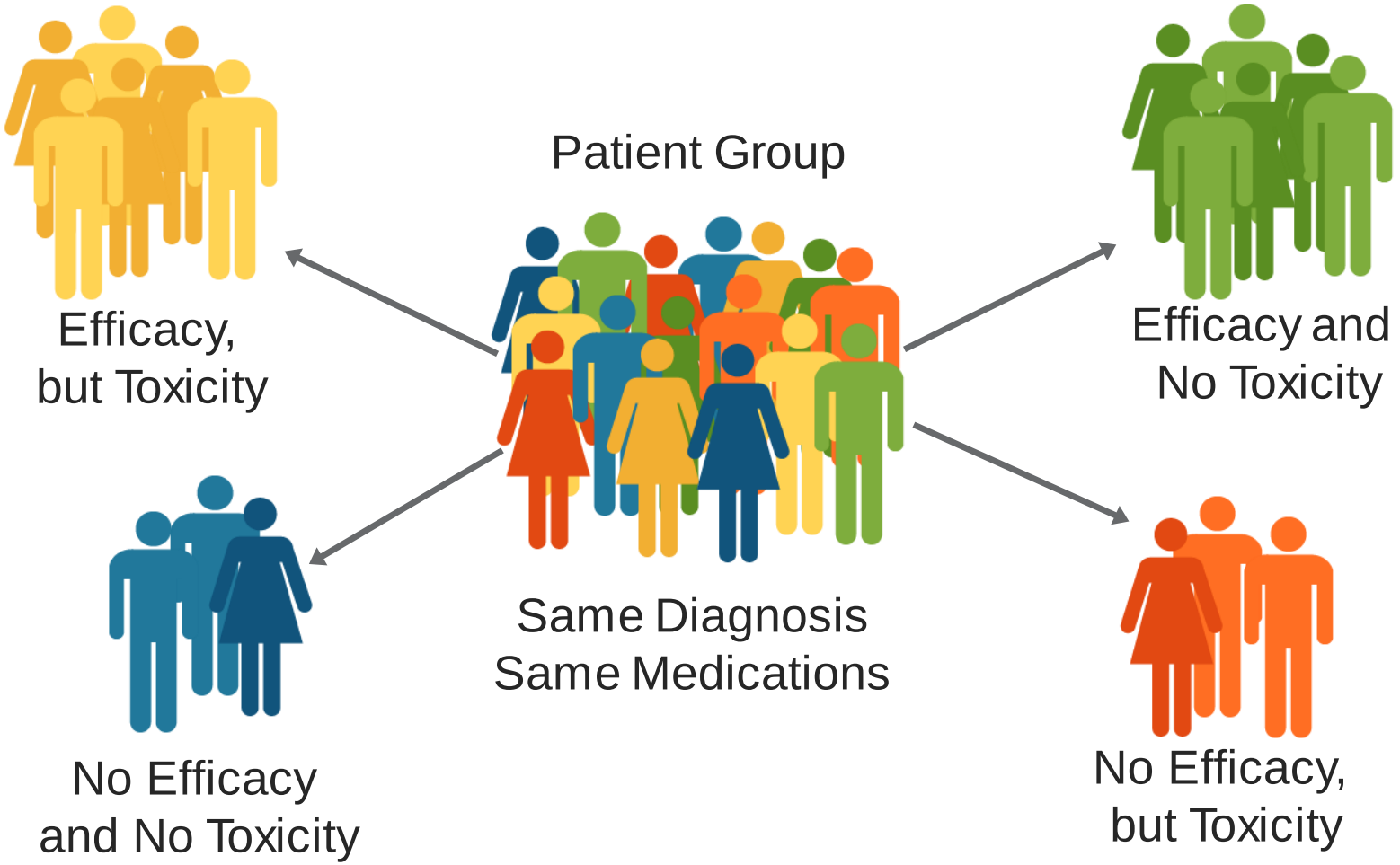
Millennium Health

Learning Objectives

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

1. Genetic variability may influence medication efficacy and toxicity
2. Genetic variations may allow clinicians to more effectively understand medication response
3. PGT may provide valuable data for more personalized therapy

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.

The MINDS™ Assessment Guide to Personalized Care

METABOLISM

INTERACTION OF MEDICATIONS

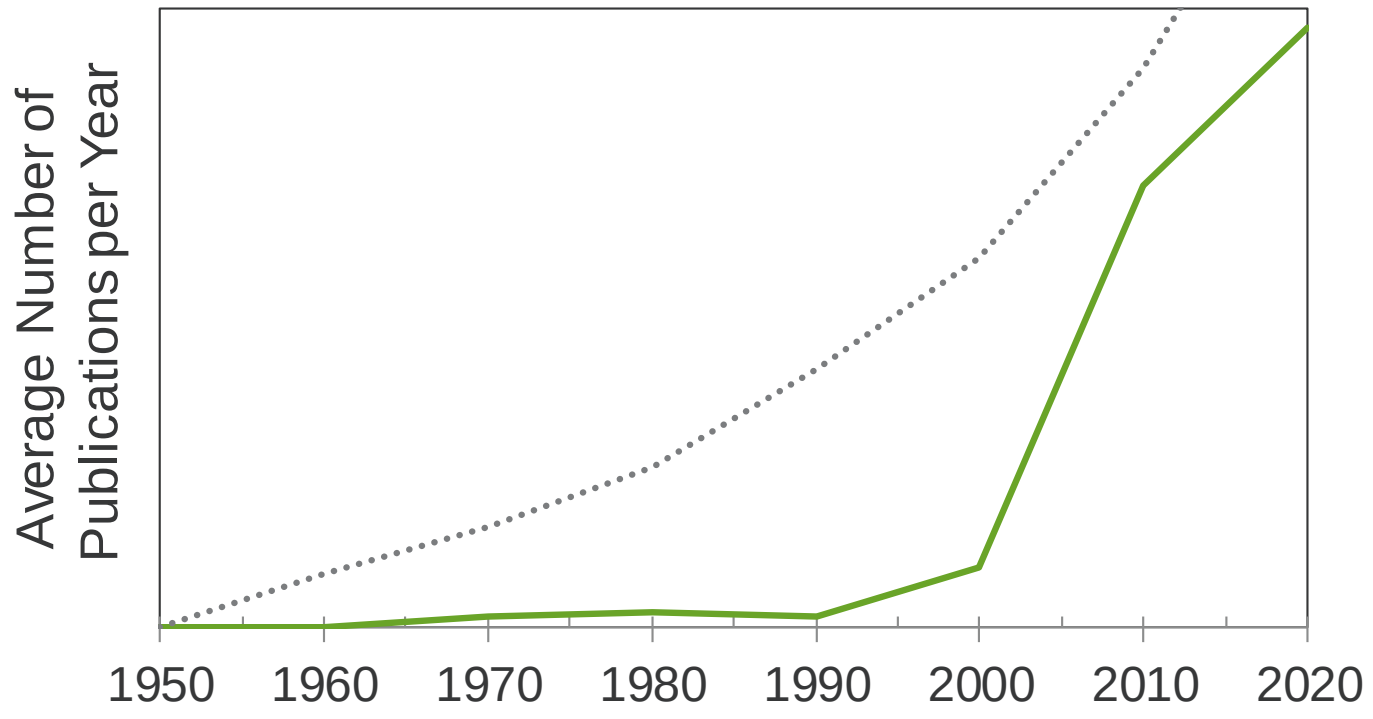
NOT TAKING AS PRESCRIBED

DISEASE STATE

SUBSTANCE ABUSE

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

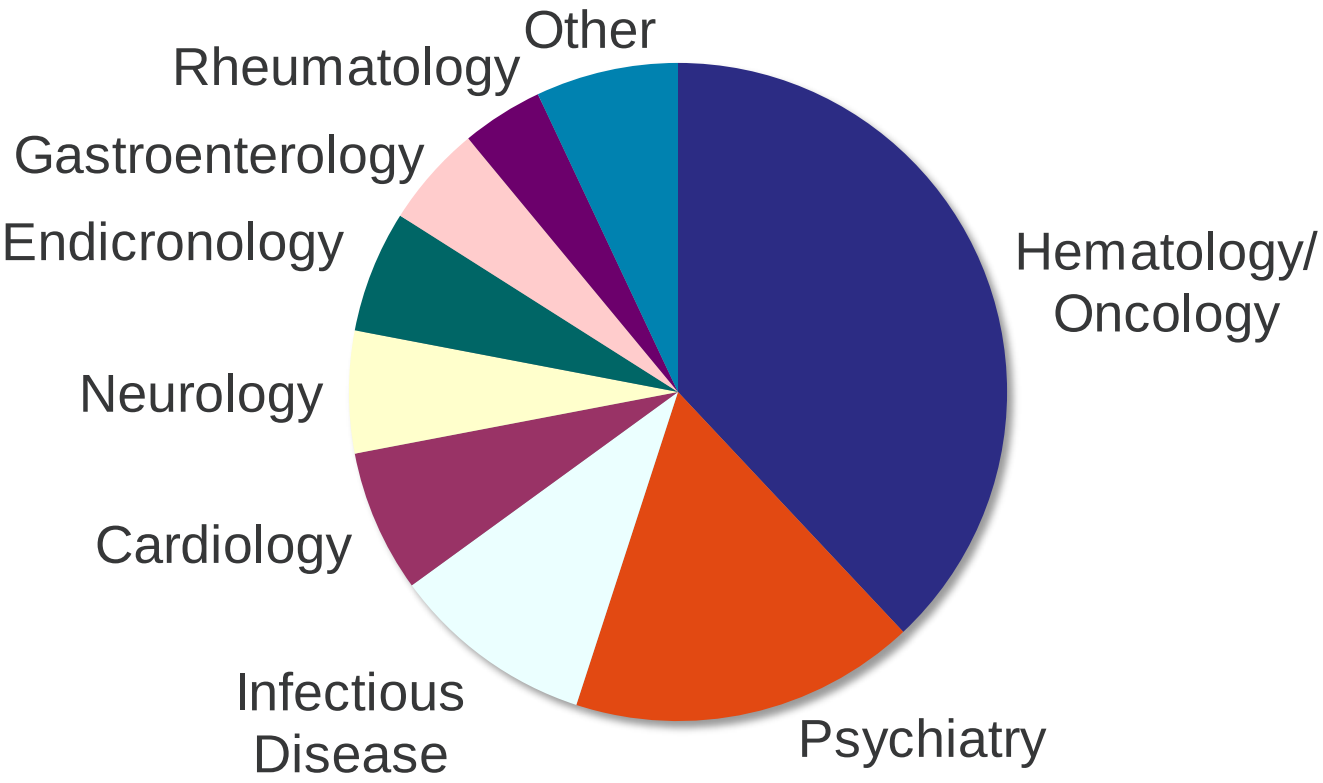
Published Guidelines

- Clinical Pharmacogenetics Implementation Consortium (CPIC)[1]
- Dutch Pharmacogenetics Working Group (DPWG)[2,3]
- Coriell Personalized Medicine Collaborative (CPMC)[4]

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]



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

Potential Benefits to Providers

Explain or predict unexpected medication outcomes

Adverse effects

Inefficacy

Treatment failures

Higher than expected doses needed to achieve response

Identify patients at higher risk for DDI

Reduce the need for multiple medication trials

Support a decision to continue or change Tx

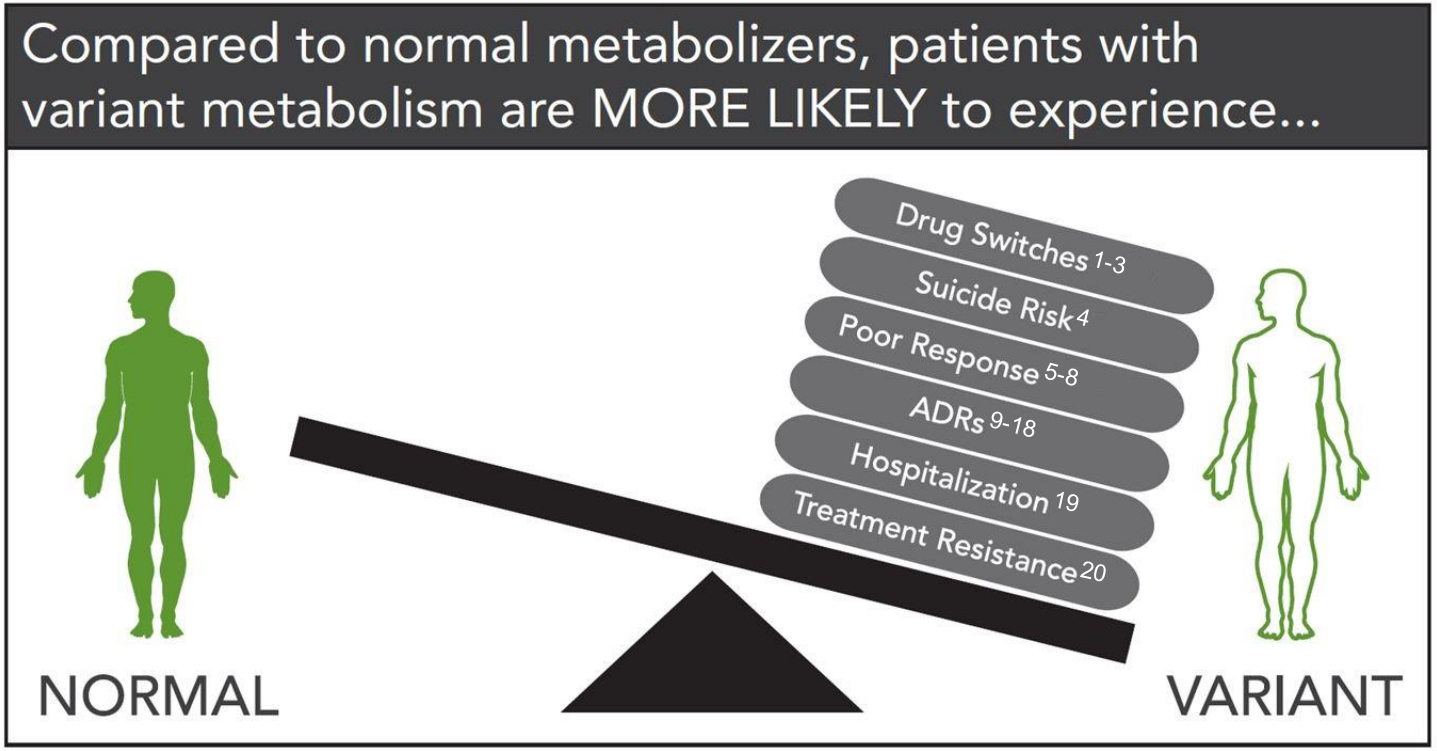
Argoff CE. Clinical implications of opioid pharmacogenetics. Clin J Pain. 2010;26(1):S16-S20.
Jannetto PJ, Bratanow NC. Utilization of pharmacogenomics and therapeutic drug monitoring for opioid pain management. *Pharmacogenomics*. 2009;10(7):1157-1167.

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. *AmJ 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.

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 ChimActa*. 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 phenotype may 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.

Pharmacogenetics and Antidepressants

Clinical responses vary widely among individuals

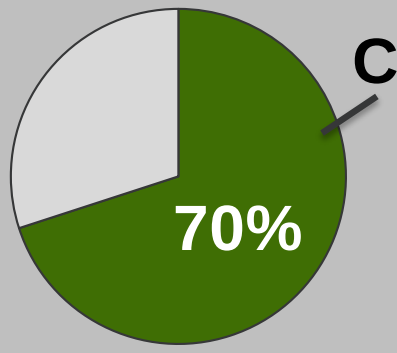
- In STAR-D, after an average of 10 weeks of treatment and 5 visits to their healthcare provider, the remission rate was 27.5%[1]
- After treatment failure with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant[2]

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. *AmJ 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



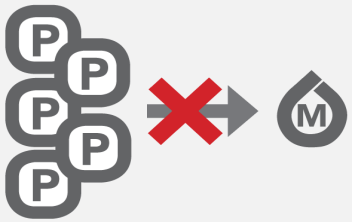
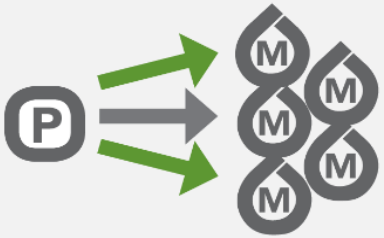
CYP2D6, CYP2C19, CYP2C9, CYP3A4/5

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 PharmPract.* 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.

Not an actual patient

Case: "Jessica"

PGT Example

History

37-year-old woman diagnosed with depression

START

4 wks CELEXA® (20 mg/d)

Reports minimal improvement so dose is doubled

4 wks CELEXA® (40 mg/d)

Mild benefits but symptoms still occur; CELEXA® discontinued

2 wks Start EFFEXOR XR®, titrate

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 several months 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

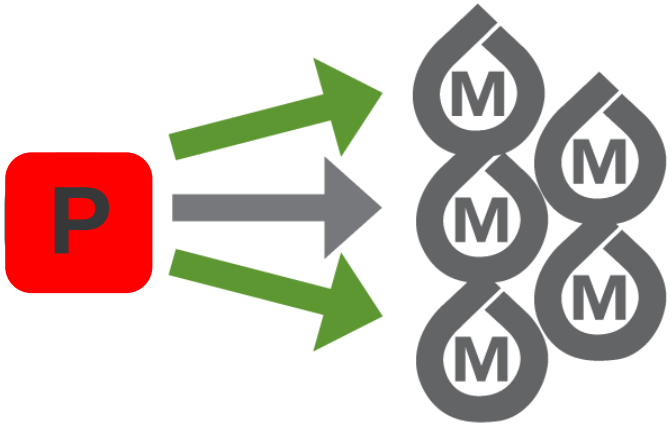
*Pristiq® is not appreciably metabolized by CYP450 enzymes

Not an actual patient

Case: “Jessica”

PGT Interpretation

Citalopram (Celexa®)



CYP2C19

Active parent Less active metabolite

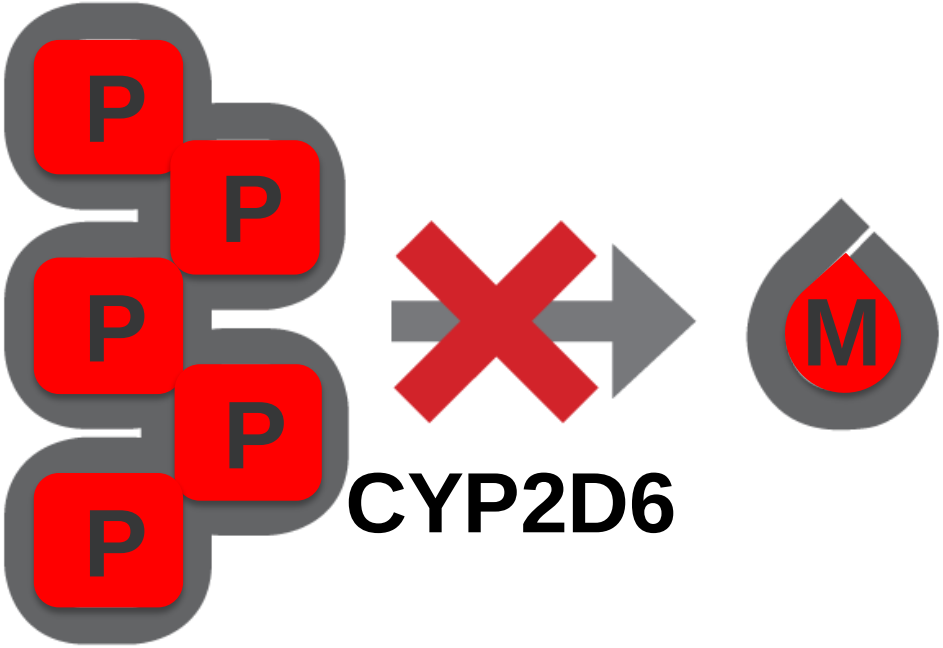
Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients. Clin Pharmacol Ther. Feb 2008;83(2):322-327.
Sangkuhl K, Klein TE, Altman RB. PharmGKB summary: citalopram pharmacokinetics pathway. Pharmacogenetics 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

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

Reduced Activity

- Decreased metabolism of folic acid into L-methylfolate[1]
- Supplementation with L-methylfolate may improve SSRI/SNRI response[2]

Normal Activity

- Normal metabolism of folic acid into L-methylfolate[1]

Reduced Activity: ~51% of individuals[3]

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

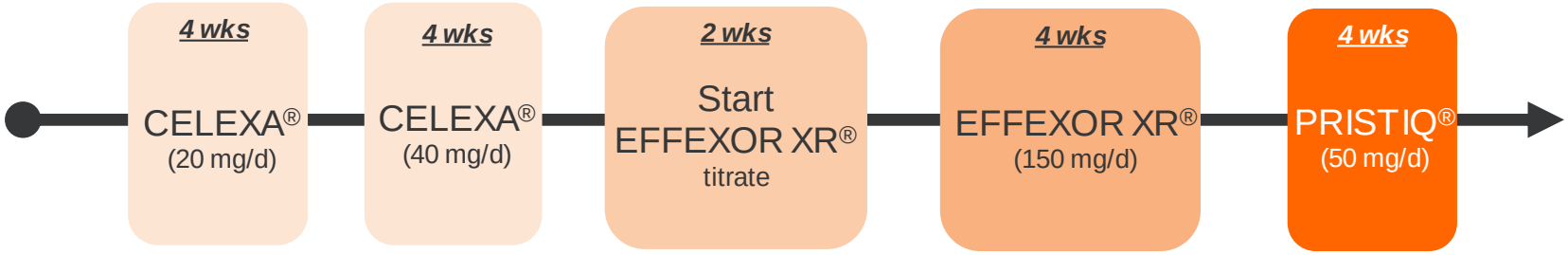
Nazki FH, Sameer AS, Ganaie BA. Folate: Metabolism, genes, polymorphisms and the associated diseases. *Gene.* 2014;533:11-20.
Papakostas GI, Shelton RC, Zajecka JM, et al. L-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials. *AmJ Psychiatry*. 2012;169:1267-1274.
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**



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

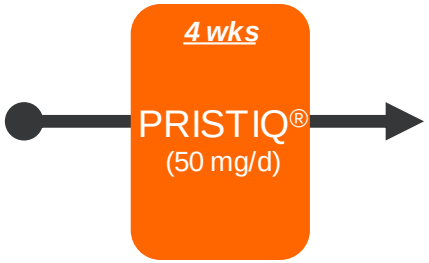
Chen S, et al. The cytochrome P450 2D6 (CYP2D6) enzyme polymorphism: screening costs and influence on clinical outcomes in psychiatry. *Clin Pharmacol Ther*. 1996 Nov;60(5):522-34.
Chou WH, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol*. 2000 Apr;20(2):246-51.
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]**

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

Pharmacogenetics and Opioids

Even among "effective" opioid therapies, there is a non-responder rate of 30% - 40%[1]

Pharmacogenetic differences may impact patient response and toxicity to opioids.

- Genetic variations in OPRM1 associated with increased pain sensitivity and opioid dose requirements[3]
- Genetic variations in CYP450 enzymes impact opioid metabolism and response[2]
- Genetic variations in COMT associated with opioid dose requirements[4]

1. Argoff CE. Clinical Implications of Opioid Pharmacogenetics. *Clin J Pain.* 2010;26(1):S16-20.
2. Vuilleumier PH, Stamer UM, Landau R. Pharmacogenomic considerations in opioid analgesia. *Pharmgenomics Pers Med.* 2012;5:73-87. doi: 10.2147/PGPM.S23422. Epub 2012 Aug 23.
3. Mura E, Govoni S, Racchi M, et al. Consequences of the 118A>G polymorphism in the OPRM1 gene: translation from bench to bedside? *J Pain Res*. 2013;6:331-53
4. Rakvag TT, Klepstad P, Baar C, Kvam TM, Dale O, Kaasa S, Krokan He, Skorpen F. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. *Pain.* 2005 Jul; 116 (1-2):73-8.

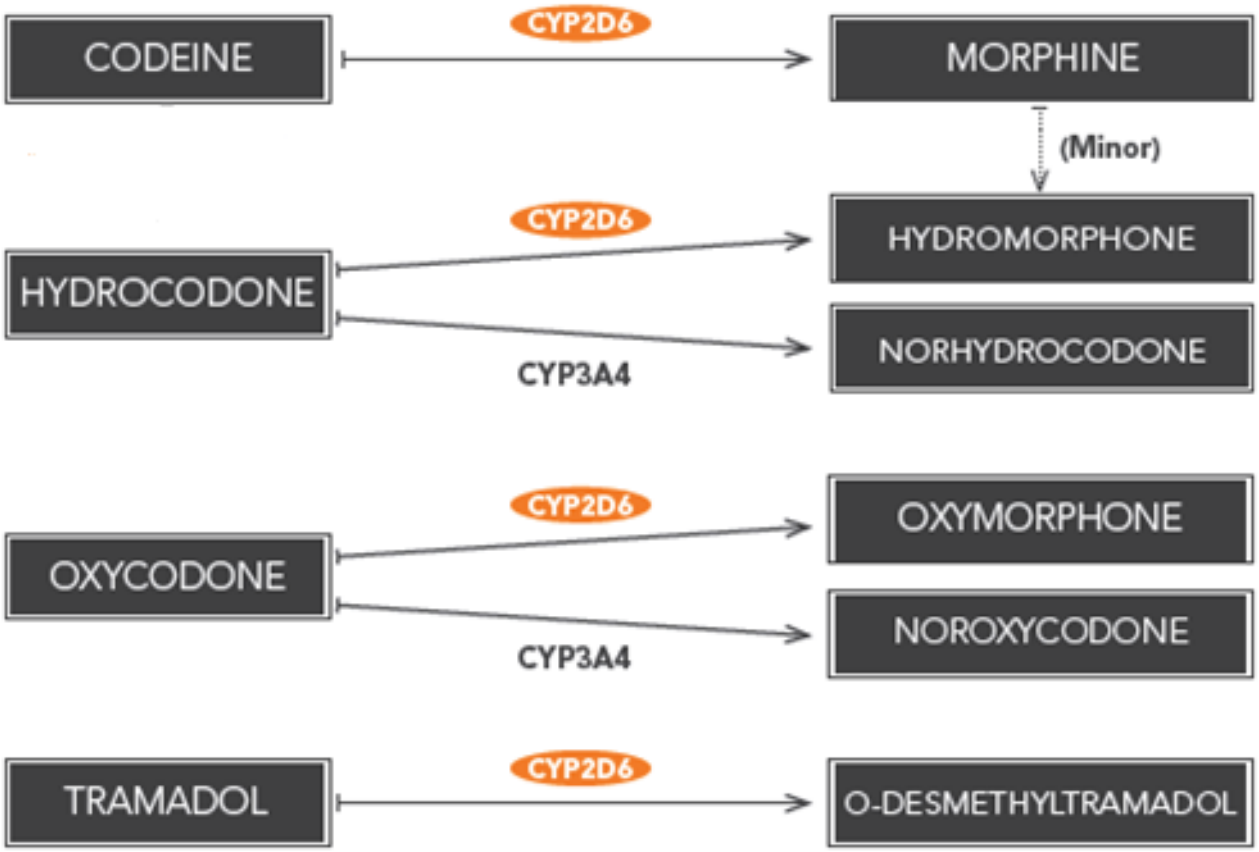
Pharmacogenetics and Pain

Genetic variations have clinical implications for analgesic therapy[1]

- Many opioids metabolized by CYP2D6[2]
  - Codeine CPIC guideline recommends using alternative analgesics in CYP2D6 poor or ultrarapid metabolizers due to risk of therapeutic failure or severe to life threatening side effects[2]
- Fentanyl metabolized by CYP3A4/5[1]
- Medications such as carisoprodol, diazepam metabolized by CYP2C19; celecoxib metabolized by CYP2C9
  - Prescribing information contains PGT guidance[1]

1. US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labels. http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. Revised August 18, 2014. Accessed August 28, 2014.
2. Crews KR, Gaedigk A, Dunnenberger HM, et al; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. *Clin Pharmacol Ther*. 2014 Apr;95(4):376-82.

Opioid Metabolism CYP450



Not an actual patient

Case: "Tammy"

Patient Characteristics:

- 55-year-old woman
- Persistent low back pain s/p spinal fusion with radiculopathy
- History of occasional alcohol use, max 5 drinks/week
- No history of drug abuse/misuse or psychiatric illness
- PMH: hypercholesterolemia, Type II DM

Current Medication Regimen:

- Oxycodone ER 40mg PO Q12h
- Oxycodone IR 10mg PO Q6h PRN
- Gabapentin 800 mg PO TID
- Metformin 500 mg PO BID
- Simvastatin 40 mg PO daily

Brennan MJ. The clinical implications of cytochrome p450 interactions with opioids and strategies for pain management. *J Pain Symptom Manage.* 2012;44(6suppl):S15-22

Not an actual patient

Case: “Tammy”

Presentation and Assessment:

- Husband noticed she had increasing sedation, presented to office for follow up
- Patient recently started weight loss program, including an over-the-counter “weight loss” supplement
- Ruled out other disease states or conditions that may impact response to treatment by history, exam, and labs

Urine drug testing and pharmacogenetic testing may be useful in determining potentially needed changes to Tammy’s therapy.

Not an actual patient

Case: "Tammy"

Urine Drug Test (UDT) Results

Previous Visit

Medication	Form	Outcome	Result
Oxycodone	**Parent**	**Positive**	**11440**
Oxymorphone	Metabolite	Positive	**865**
Noroxycodone	Metabolite	Positive	**6430**
Gabapentin	**Parent**	**Positive**	**97585**

Current Visit

Medication	Form	Outcome	Result
Oxycodone	**Parent**	**Positive**	**20854**
Oxymorphone	Metabolite	Positive	981
Noroxycodone	Metabolite	Positive	1284
Gabapentin	**Parent**	**Positive**	**98000**

Not an actual patient

Case: “Tammy”

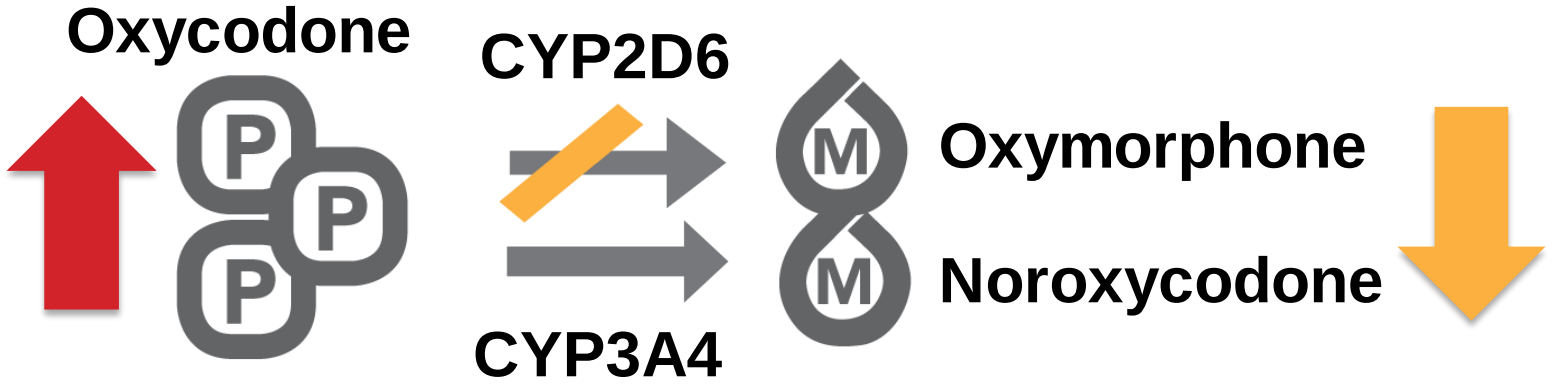
PGT Results

Gene Tested	Predicted Phenotype
CYP2D6	Intermediate Metabolizer (IM)

Not an actual patient

Case: "Tammy"

Interpretation 2D6 Intermediate Metabolizer

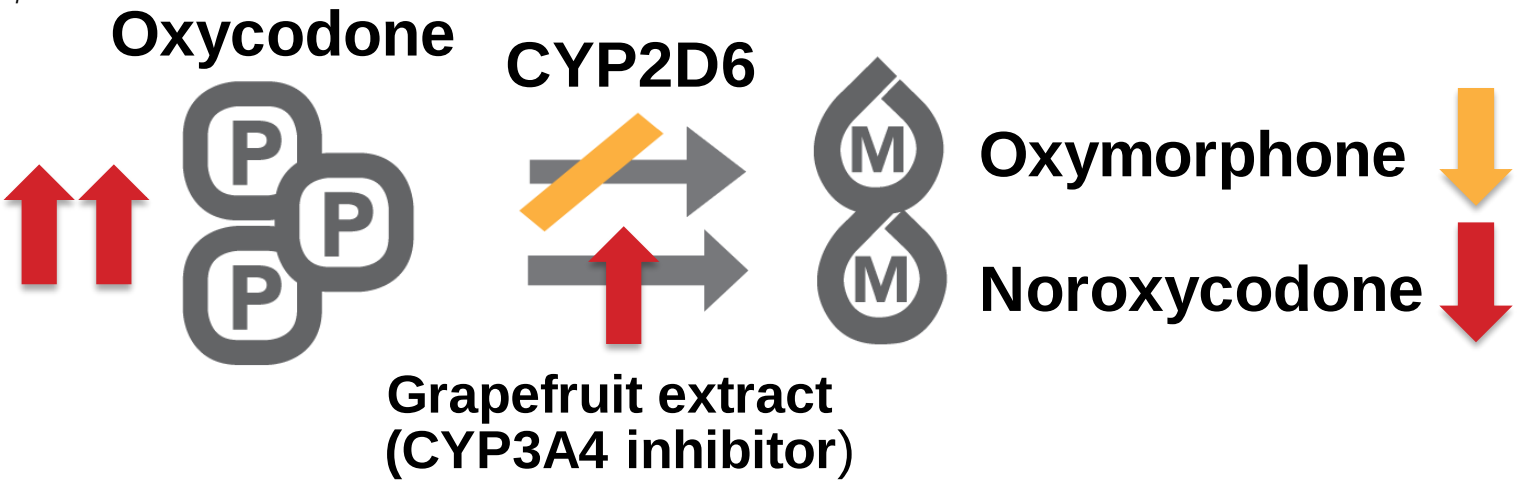


- Intermediate metabolism results in reduced formation of the more potent oxymorphone metabolite[1]
- Decreased analgesia or unexpected toxicity is possible[1-3]
- CYP2D6 phenotype may increase risk for drug-drug interactions via CYP2D6 and CYP3A4[4]

1. Zwisler ST et al. The hypoalgesic effect of oxycodone in human experimental pain models in relation to the CYP2D6 oxidation polymorphism. *Basic Clin Pharmacol Toxicol*. 2009;104(4):335-44.
2. Janetto PJ et al. Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. *J Anal Toxicol*. 2002;26(7):438-47.
3. Samer Cf et al. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol*. 2010;160(4):919-30.
4. Samer CF et al. The effects of CYP2D6 and CYP3A activities on the pharmacokinetics of immediate release oxycodone. *Br J Pharmacol*. 2010;160(4):907-18.

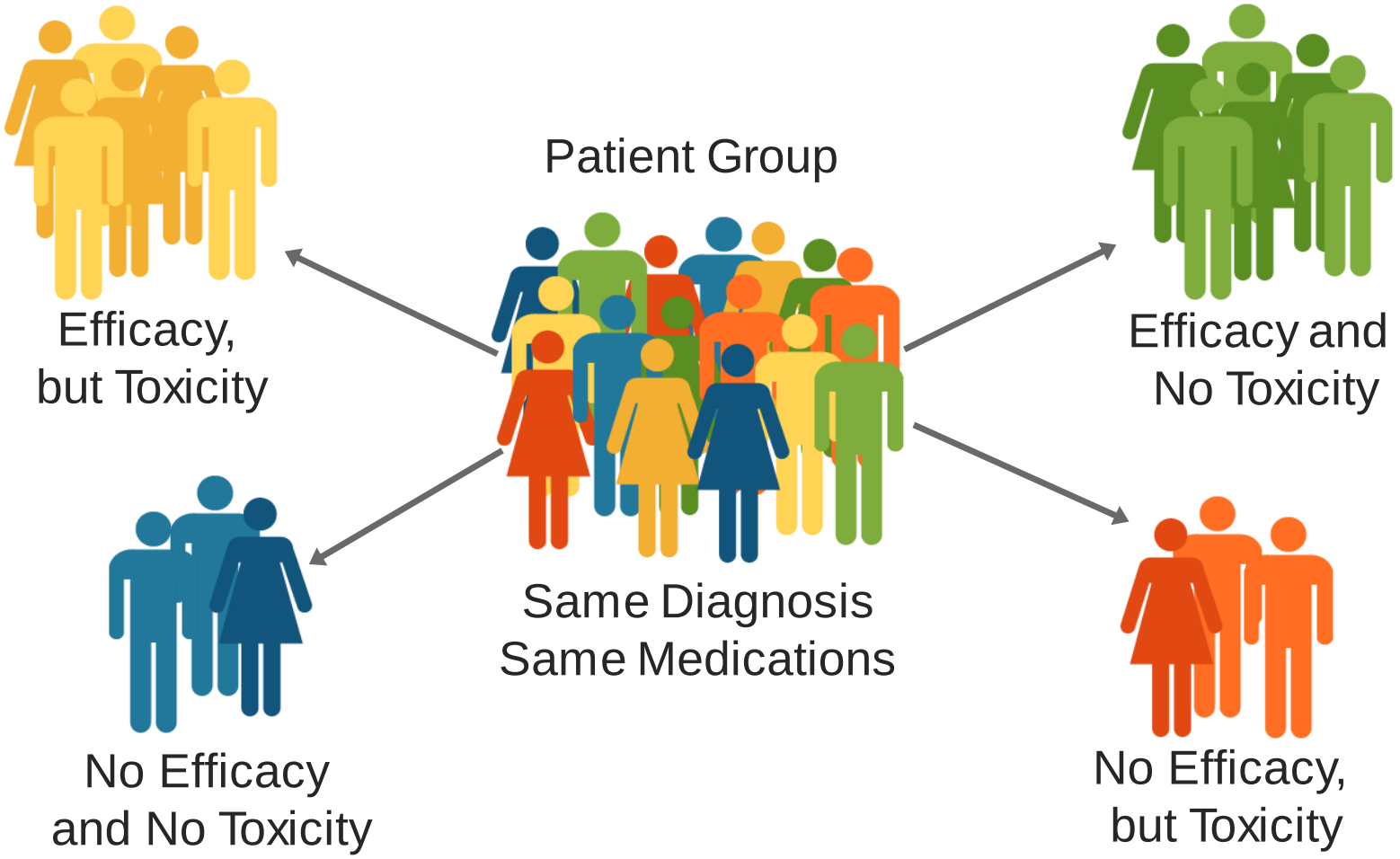
Not an actual patient

Case: "Tammy"



- The addition of the "weight loss" supplement containing grapefruit extract (a potent CYP3A4 inhibitor) resulted in both clearance pathways inhibited
- Inhibitors of CYP2D6 & CYP3A4 may increase the potential for side effects/toxicity due to accumulation of oxycodone
- Tammy's CYP2D6 IM status put her at an increased risk for medication interactions and accumulation of oxycodone

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.

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

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

Thank you

Adam Rzetelny, PhD

Associate Director, Clinical Affairs

Millennium Health

Adam.Rzetelny@millenniumhealth.com