Pharmacogenetics Update

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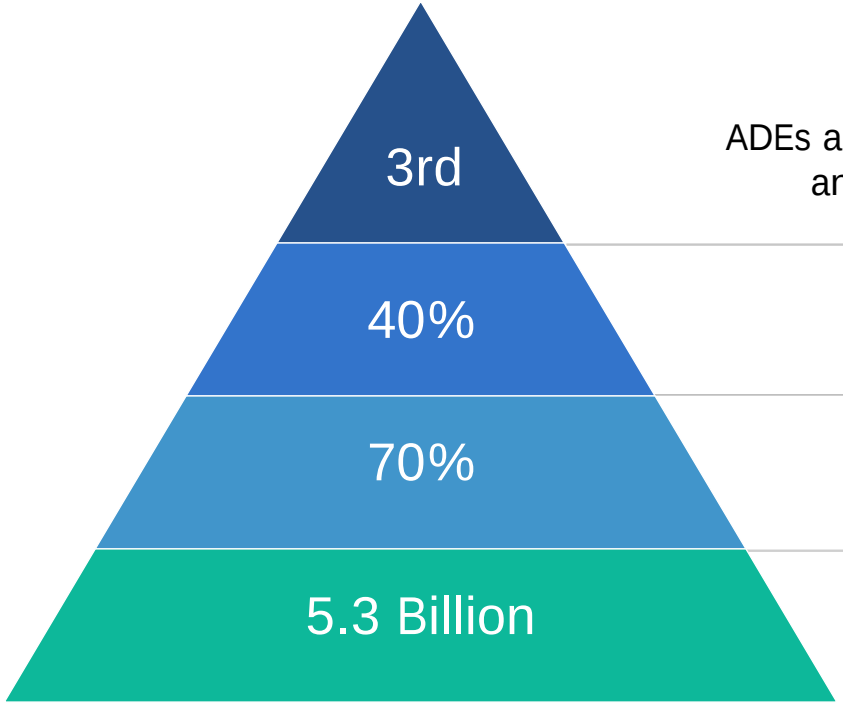
International Foundation
OF EMPLOYEE BENEFIT PLANS

Adverse Drug Events (ADE) Are a Serious Problem



ADEs are now the **3rd** leading cause of death in the U.S. and the 2nd leading cause of hospital readmissions.

40% of hospital and outpatient admissions for ADEs are considered "preventable."

Since 2006, **70%** increase in polypharmacy patients (patients taking 5+ prescription meds).

Treating ADEs add over **$5.3 billion** in additional healthcare costs per year.

Patients With Identical Clinical Presentations Can Respond Differently to Drugs

Patient	Treatment Choices	Outcome
	Drug A	+
	Drug B	- -
	Drug C	-
	Drug A	-
	Drug B	+
	Drug C	+ +

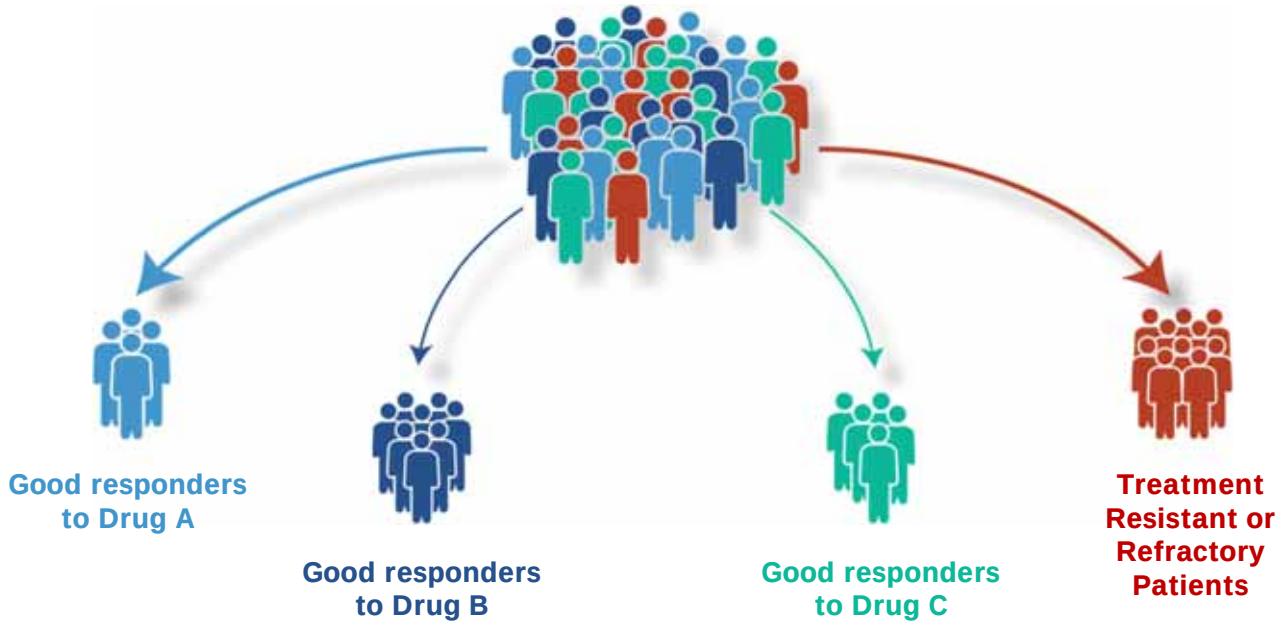
The Lack of Evidence-Based Tools to Guide Therapeutic Decisions Contributes to Poor Treatment Outcomes

What Is Pharmacogenetic Testing?

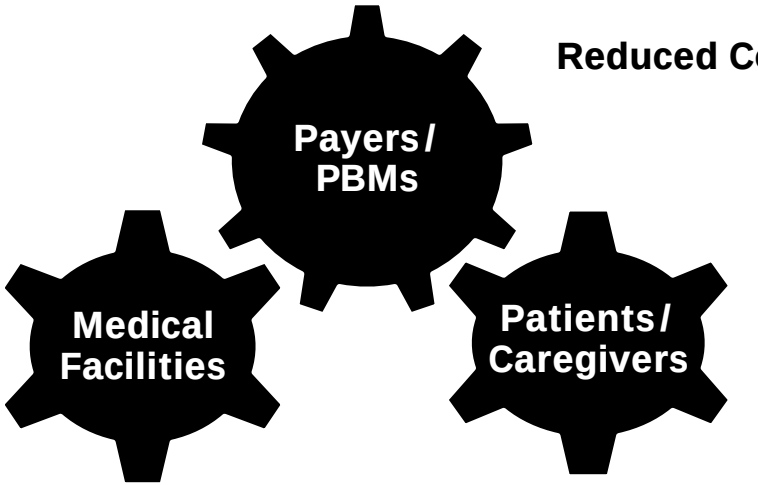
- Pharmacogenetics (PGx) is the science of how a person's individual genetics affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.
- PGx involves analyzing a person's DNA for genetic programming of specific proteins involved in drug response, looking for mutations that impair protein function.
- PGx can identify the specific medications that are best for an individual patient based on their DNA makeup.

Personalized Medicine: One Size Does Not Fit All

- Pharmacogenetics is the basis for personalized medicine. In the example below, you can see how pharmacogenetic testing works within a grouping of people who would all generally be prescribed the same drug.



Personalized Medicine Creates Value Through Alignment of Stakeholder Objectives



Reduced Costs

Better outcomes

Enhanced performance metrics

Reduced hospitalizations

Enhanced disease management

Higher quality of life

Genes and Proteins

- Genes are made of DNA and function as the molecular unit of heredity.
  - Each gene codes for a specific protein.
  - Four nucleotides make up the “alphabet” of the DNA “coding language”
    - Adenine, Thymine, Cytosine and Guanine (A, T, C, and G)

Genes and Proteins

- Proteins are large, complex “action” molecules that impact our physiology.
  - Proteins perform a vast array of biological functions including:
    - Catalyzing metabolic reactions
    - DNA replication
    - Response to stimuli
    - And transporting molecules from one location in the body to another.

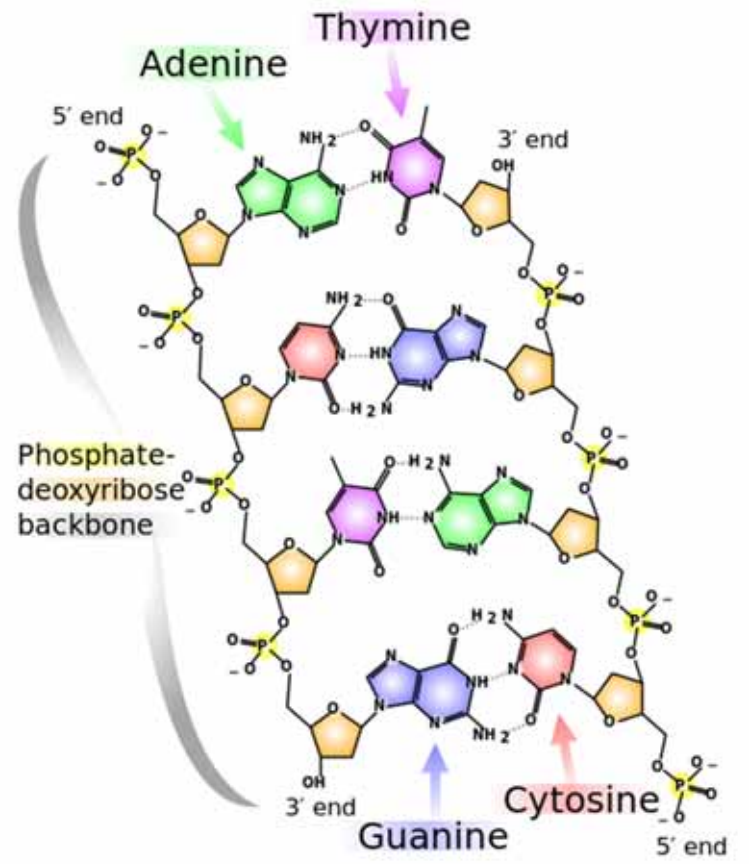
Genes and Proteins

- Some gene variants result in changes to the protein, for which it codes, that impact the protein's function, how much of the protein you produce, or whether you produce the protein at all.
- These inherited changes in protein function can have a dramatic impact on biological function, and in the case of pharmacogenetics, how we respond to medicines.

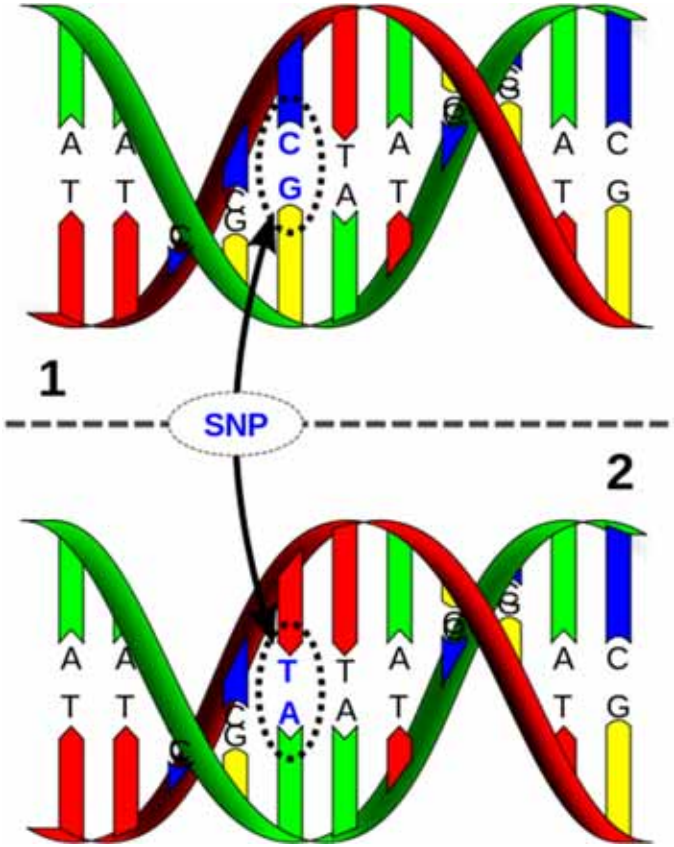
Basic Genetic Concepts

- **Alleles**—Alternative forms of the same gene.
- **Genotype**—Set of alleles that determines the expression of a particular characteristic or trait.
- **Phenotype**—Composite of an organism's observable characteristics resulting from the expression of an organism's genes as well as the influence of environmental factors and the interactions between the two.
- **Single nucleotide polymorphism (SNP)**—A DNA sequence variation occurring when a single nucleotide—A, T, C or G—in a gene (or other shared sequence) differs between members of a biological species or paired chromosomes in a human.

Structure of DNA



Single Nucleotide Polymorphism (SNP)



What Pharmacogenomic Tools Are Currently Available to Healthcare Professionals?

- Response Markers—Genetic markers that **indicate an innate propensity** to a response related to the drug's mechanism of action or distribution.
- Metabolic Markers—Genetic markers that **indicate an alteration in the innate ability to metabolize** particular drugs via particular metabolic enzymes resulting in altered pharmacokinetics

Pharmacogenetic Response Markers

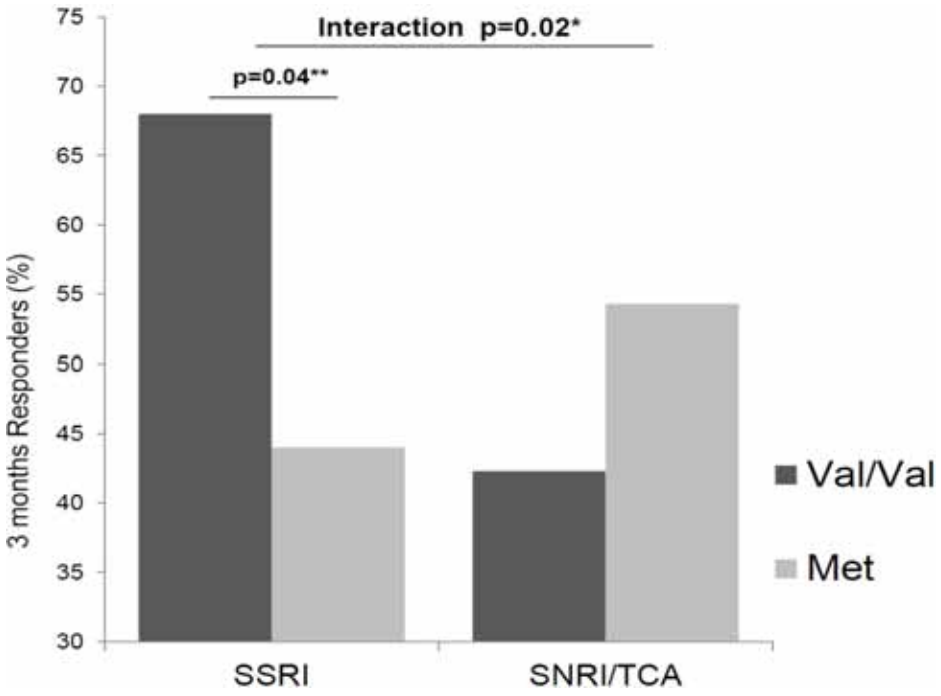
- OPRM1—Determines effectiveness of opiate analgesics.
- SLC6A4—Differential antidepressant response.
- BDNF—Differential antidepressant response.
- MTHFR—Affects the ability to convert dietary folate into its active form, methyl-folate.

Pharmacogenetic Response Markers

- SULT4A1—Affects the safety and efficacy of olanzapine.
- VKORC1—Affects sensitivity to warfarin.
- SLCO1B1—Affects the safety and efficacy of statins.

The BDNF Val66met Polymorphism Predicts Differential Response to SSRIs Versus SNRIs/TCAs

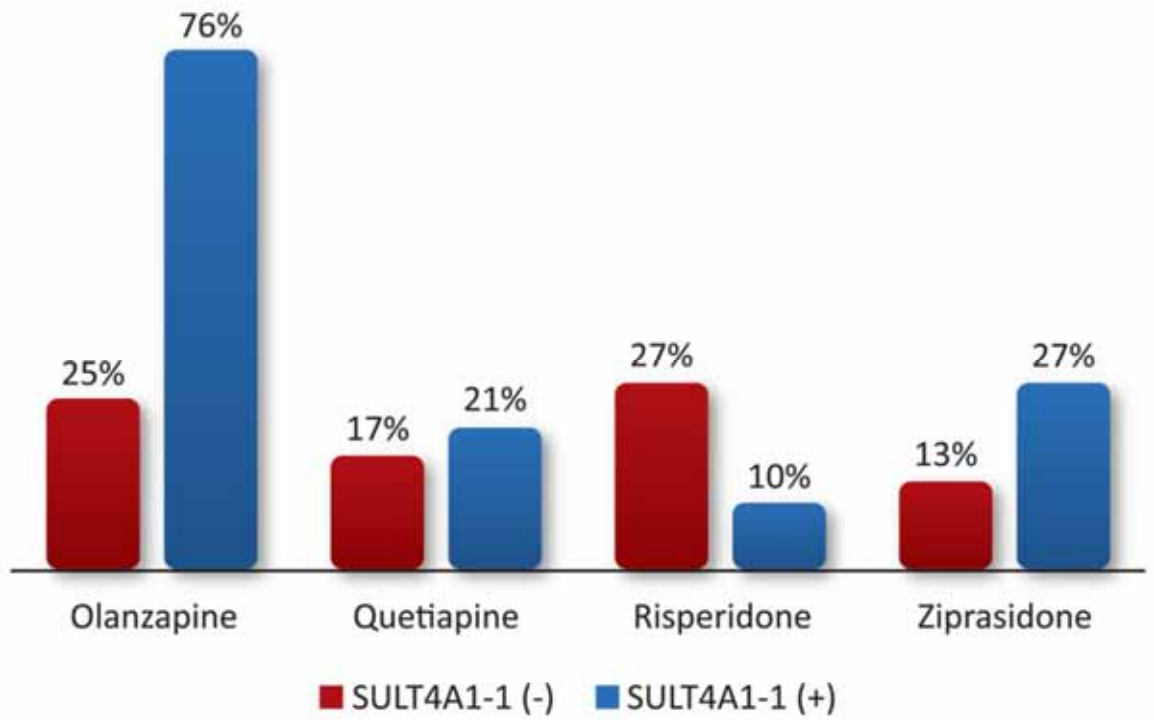
- Val/Val genotype is associated with 3-fold increased responder rate to SSRIs versus Val/Met or Met/Met (68.1% versus 44%; adjusted-OR: 3.04, IC95% [1.05; 9.37], p=0.04).
- Met carriers respond better to SNRIs or TCAs as compared to Val/Val (33.3% versus 60.9%, adjusted-OR: 0.27, IC95% [0.09; 0.76], p=0.02).



Colle et al. 2015 J Affect Disord.175:233-40

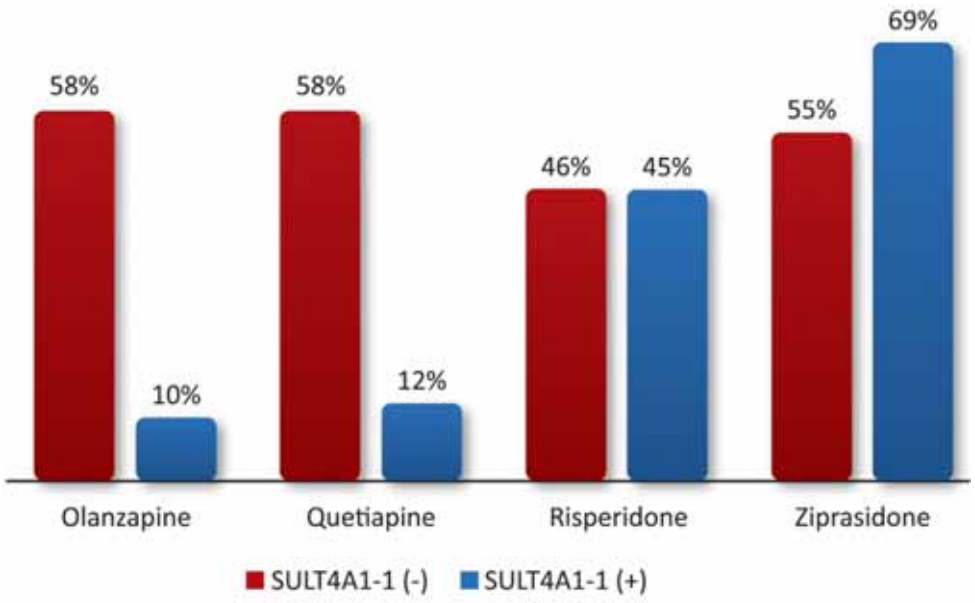
Interaction of BDNF Val66Met polymorphism and antidepressant classes (SSRI versus SNRI/TCA) on responder rates 3 months post-treatment.
Responders: decrease in the Hamilton Depression Rating Scale score of at least 50% from baseline to 3 months; SSRI: Serotonin Selective Reuptake Inhibitor; SNRI/TCA: Serotonin and Norepinephrine Reuptake Inhibitor and tricyclic antidepressants; * : p<0.05 in multivariate model adjusted for propensity-score deciles; **:p<0.05 in multivariate model adjusted for age and drug naives

SULT4A1 Status Impacts Response to Olanzapine



Percentage of SUL4A1-1 positive and negative Caucasian patients that achieved clinically significant response in Phase I of the CATIE Study

Treating SULT4A1-1 Positive Patients With Olanzapine or Quetiapine Reduced the Risk of Hospitalization by Over 80% in the CATIE Study

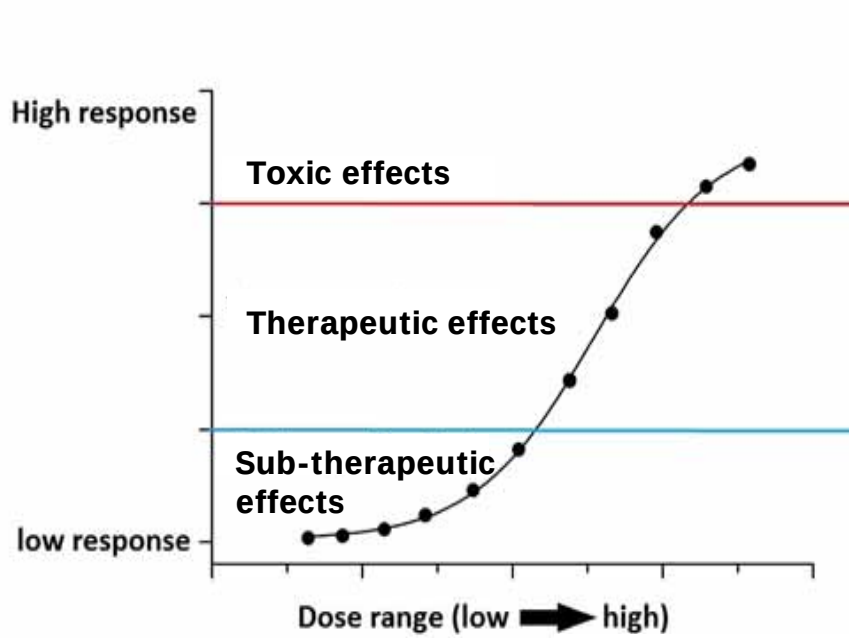


Percentage of SUL4A1-1 positive and negative Caucasian patients who returned to the hospital within one year after starting a new antipsychotic therapy in the CATIE Study

General Principles of Pharmacology—The Dose-Response Relationship

- Drug exposure determines the response or impact of the drug (and its metabolites) for/on the person taking it.
- The greater the exposure or dose, the greater the response.
- Well-accepted and proven laws of therapeutics.

Dose Relationship Between Blood Concentrations of Drug and Efficacy and Toxicity (Single-Dose)



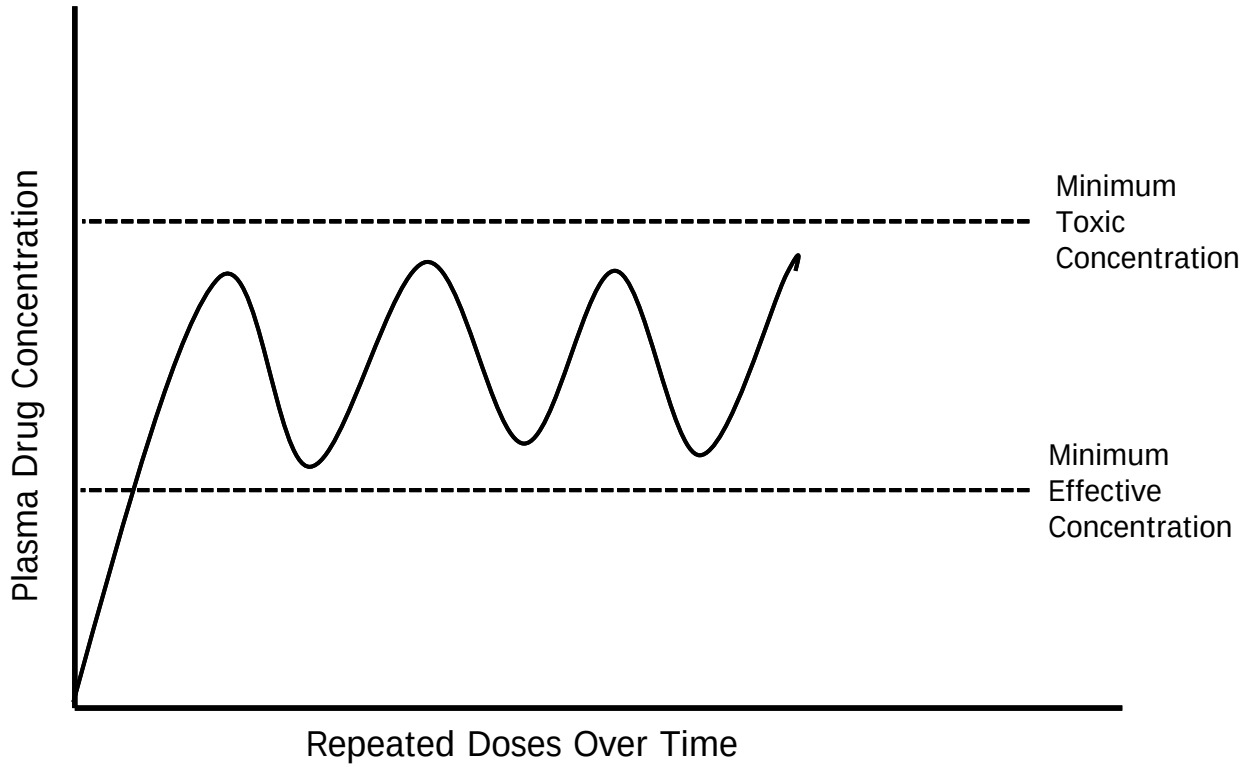
Pharmacogenetic Metabolic Markers

- Cytochrome P450 Hepatic Isozymes
  - Modify drugs so that they are polar and can be eliminated by the kidneys (e.g., hydroxylation).
- CYP isozymes that are important in the metabolism and elimination of commonly prescribed drugs include CYP2D6, CYP2C9, CYP2C19, CYP3A4, CYP3A5, CYP2B6 and CYP1A2.

Metabolizer Phenotypes and Rates of Drug Metabolism

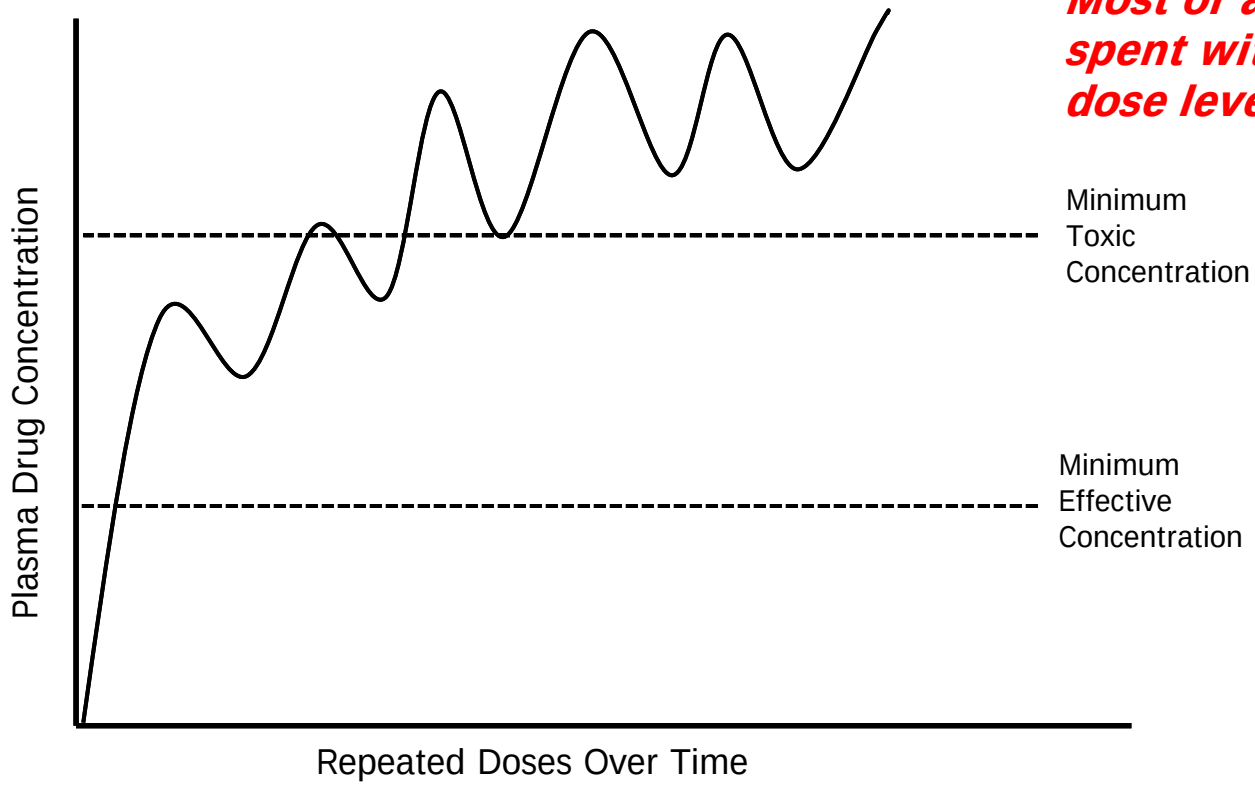
- Variation in the metabolic genes CYP2D6, CYP2C9, CYP2C19, CYP3A4/5, CYP2B6, and CYP1A2 can lead to higher or lower concentrations of drugs. Since recommended dosing assumes normal metabolism, individuals with genetic variants that impact drug metabolism may require dose adjustments or, in some cases, should avoid drugs impacted by genetic variants.

Normal Metabolism of Drug



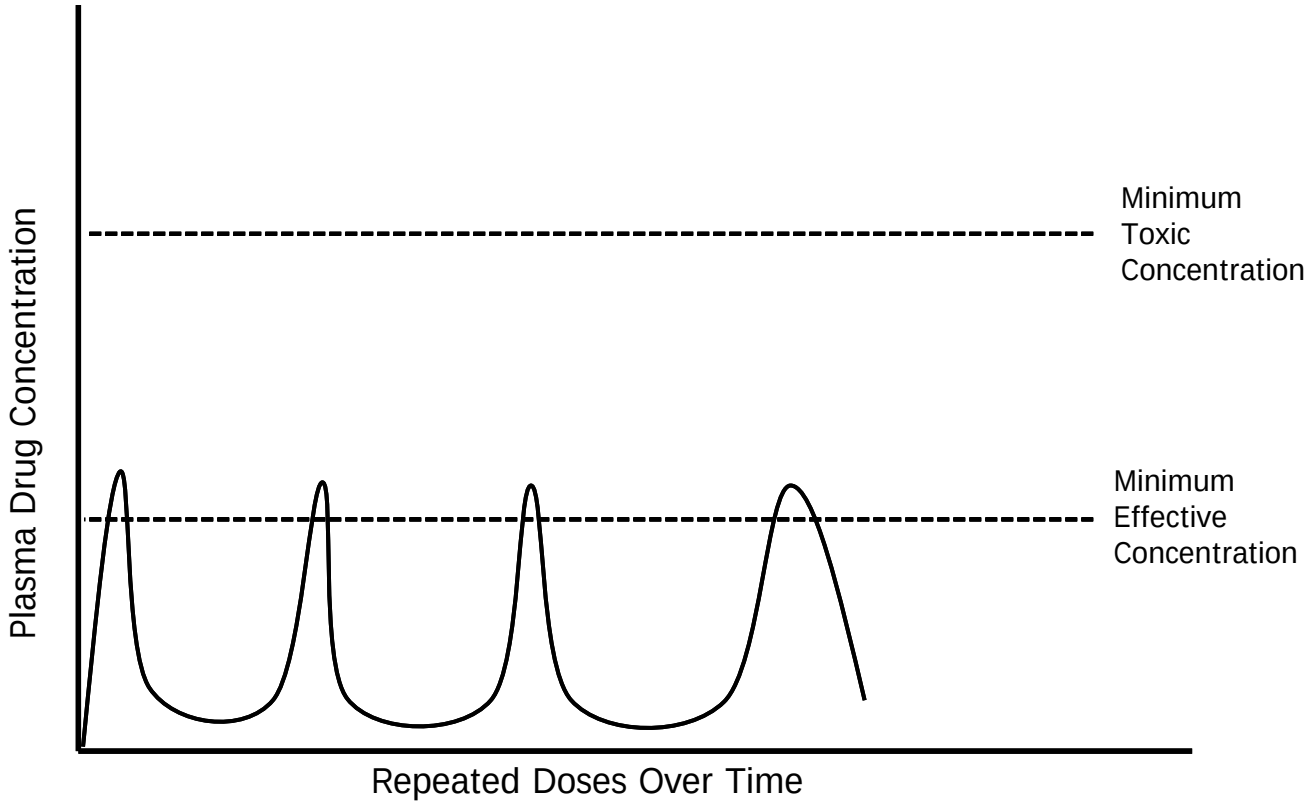
Most or all of time spent with safe and effective levels

Poor Metabolism of Drug



Most or all of time spent with toxic dose levels

Ultra Rapid Metabolism of Drug



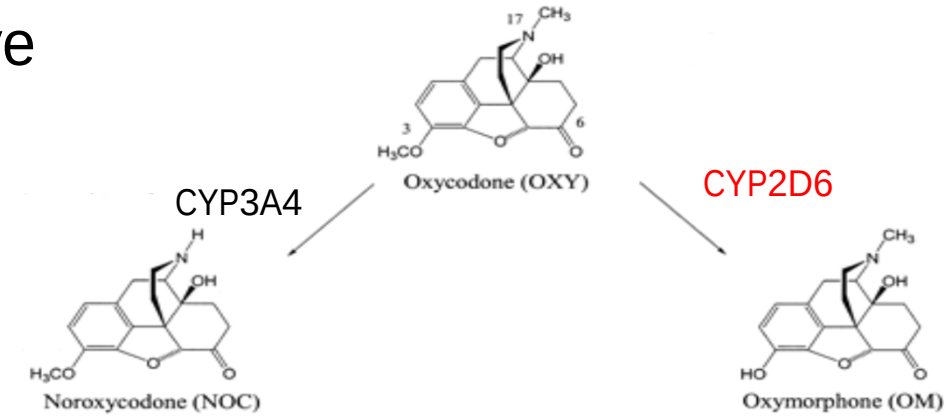
Most or all of time spent with levels below efficacious dose

Genetic-Based Alterations in Drug Metabolism Are *Very* Common

Gene	Extensive Metabolizer (NORMAL)	Intermediate Metabolizer (Impaired)	Poor Metabolizer (Elevated Risk)	Ultra-rapid Metabolizer (Elevated Risk)
2D6	53%	35%	10%	2%
2C19	36%	32%	4%	28%
2C9	57%	40%	3%	NA
3A4	87%	12%	1%	NA

Codone Oral Opiates and CYP2D6 Metabolism

- If CYP2D6 function is impaired, oxycodone is not converted to its active metabolite but is instead converted by CYP3A4/5 into an inactive metabolite.

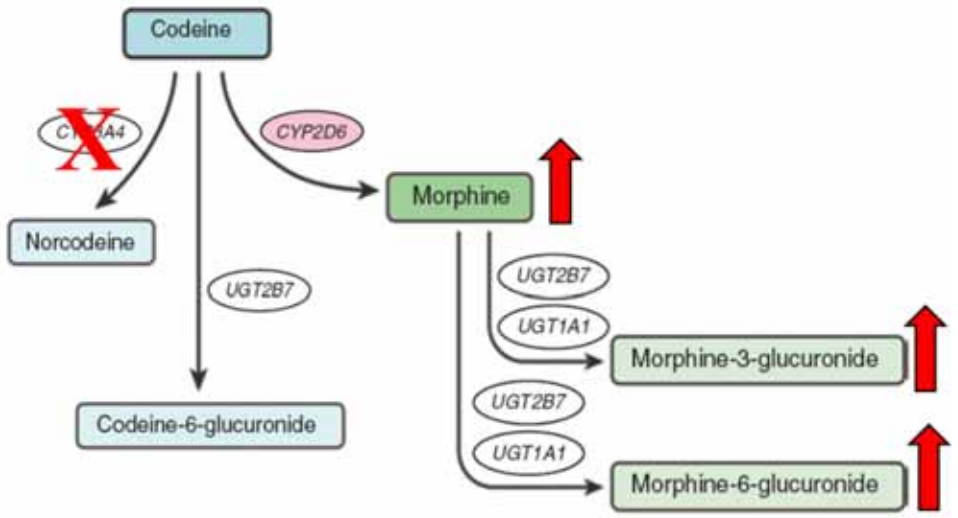


0.33x mu opioid receptor affinity

44x mu opioid receptor affinity

Real-World Case of Metabolism-Induced Opioid Intoxication

- 62-year-old male with CLL and pneumonia treated with clarithromycin, voriconazole and codeine for cough (25 mg 3x/day)
- Coma and respiratory failure on day 4 requiring ventilation and ICU transfer
  - Resolution after naloxone



CYP2D6 phenotype: **UM** **CYP3A phenotype**: **PM**

- (CYP3A inhibition by clarithromycin and voriconazole)
- Morphine values in blood **20-80-fold** higher than expected
- **Acute renal failure** -> accumulation of morphine active metabolites

Gasche Y. et al NEJM 2004, 351: 2827-31

Codeine and CYP2D6 Toxicity

Case	Indication	Codeine Dose	Toxicity
Breastfed Newborn (13 days)	Episiotomy pain (mother)	2x30mg then 2x15 mg	**Death**
Breastfed Newborn	Severe muscle pain	120 mg/day	Mother: sedation, nausea, dizzy; Child: drowsy, poor feeding
Child (2 years)	Tonsillectomy	10-12.5mg, q 4-6 h	**Death**
Child (29 months)	Tonsillectomy	1.75mg/kg	Apnea, unresponsiveness
Child (3 years)	Tonsillectomy	15mg, q 4-6 h	Severe respiratory depression
Child (4 years)	Adenotonsillectomy	8mg, q 5 h	**Death**
Child (5 years)	Adenotonsillectomy	12mg, q 4 h	**Death**
Male (33 years)	Dental pain	60mg	Euphoria, dizzy, blurred vision, epigastric pain

Published Clinical Results—Utilizing PGx Guidance

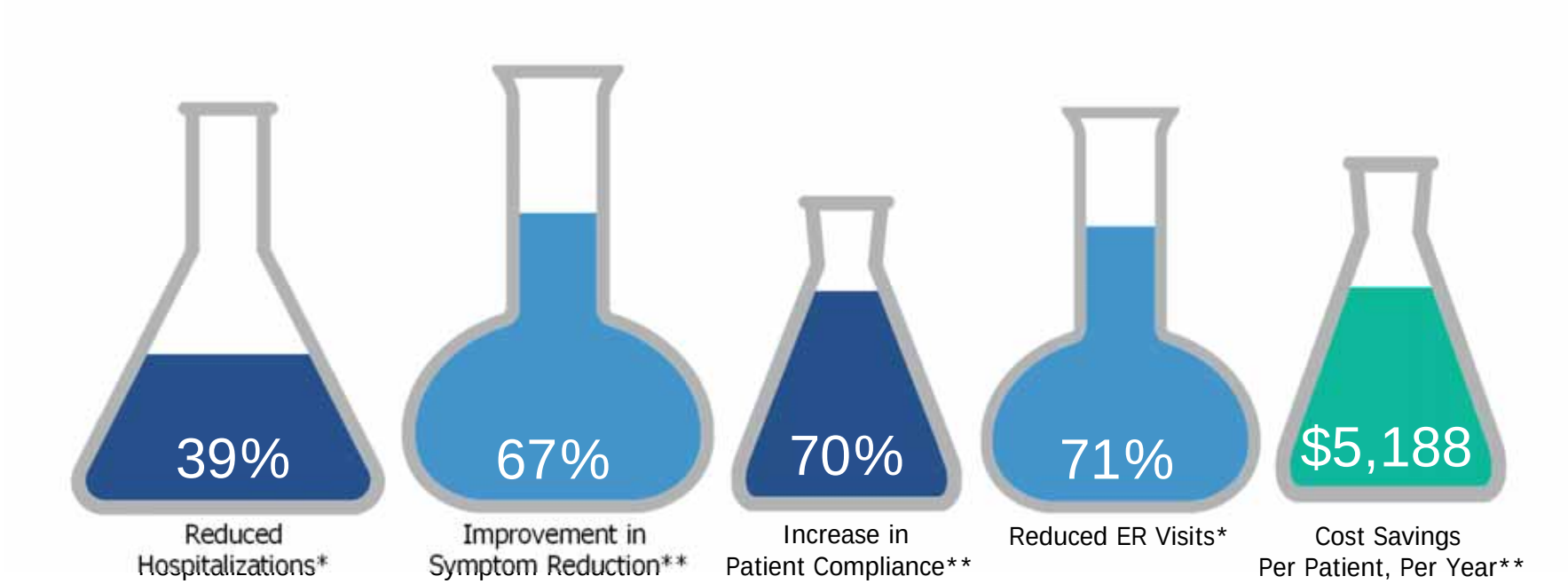
- Multiple published studies have reported:
  - Reducing depression and other symptoms;
  - Decreasing time to symptom relief;
  - Increasing patient compliance to therapeutic regimen, and satisfaction with medications.

PGx Improves Treatment Outcomes in Depression

- A study of 165 subjects diagnosed with major depressive disorder compared 8 weeks of treatment with PGx testing vs. unguided treatment as usual (TAU).
  - Clinical decisions guided by PGx testing improved time to depression symptom relief;
  - Medications identified as genetically optimal were prescribed to patients;
  - A four-fold greater improvement in patients' depression symptoms at week 8 was observed;
  - Positive physician-patient relationship as well as feedback from physician on use of PGx testing.

Hall-Flavin et al., Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. Pharmacogenetics and Genomics 23(10):535-48 · October 2013

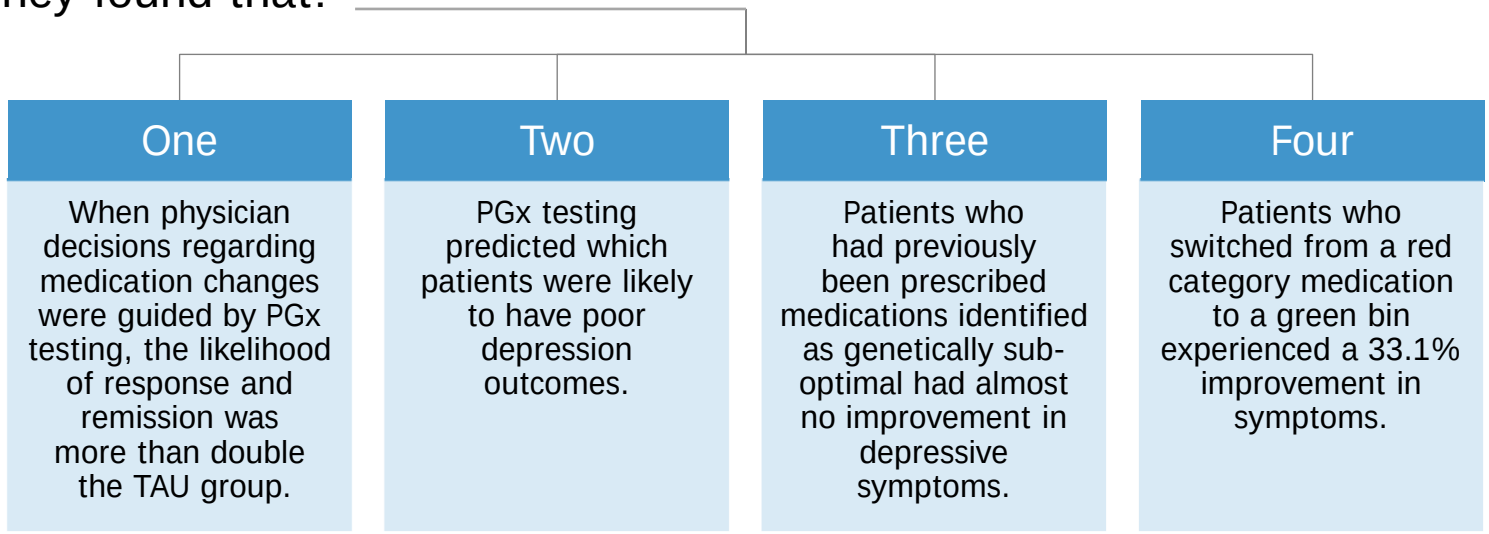
Published Clinical Results— Utilizing Pharmacogenetic Guidance



*2016 Journal of Medical Economics Four-Month Study of Elderly Patients w/PGx guidance
** 2013 Mayo Clinic Study using PGx guidance treating Depression

PGx Improves Treatment Outcomes in Depression

- A randomized, blinded controlled trial of 49 subjects with a primary diagnosis of major depressive disorder. The study compared 10 weeks of treatment guided by PGx testing with unguided Treatment as Usual (TAU). They found that:



Winner et al., A prospective, randomized double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discovery Medicine 2013;16(89): 219-227

Pharmacogenetic Guidance in Perioperative Medicine

- In a study of 63 consecutive patients undergoing open or laparoscopic colorectal and major ventral hernia surgery utilizing PGx guidance for inter-operative and post-surgical analgesia were compared to 47 patients from the hospital's historical population resulting in:

1. Narcotic modifications of the ERP analgesic program in 80% of patients.
2. Modifications in 56% of patients with respect to NSAID selection.
3. These modifications resulted in excellent analgesia with a **50% reduction in narcotic consumption**, and a **reduced incidence of analgesic related side effects** compared to our standard ERP.

Senagorea et al., Pharmacogenetics-guided analgesics in major abdominal surgery: Further benefits within an enhanced recovery protocol. The American Journal of Surgery 213 (2017) 467e472.

Pharmacogenetic Guidance in Perioperative Medicine

Perioperative Risk and Opioid Management Program

In a signature group, utilizing Perioperative Protocol with molecular screening and genetic guidance documented the following 24-month results on 324 patients:

	WITH Protocol Guidance	WITHOUT Protocol Guidance	Difference
Total Cost	$17,800.00	23,900.00	+$6,100.00
90 Day Readmission Rate	1.9%	10.3%	+8.4%
Patient Satisfaction Score	80%	71%	-9%

Reduction in Opioid Prescriptions: 52%

Patients Who Received NO Prescription Opioids: 17%

Average Patient Received (6) Days of Prescription Opioids

Multigene PGx Panel Reduced Adverse Drug Events in a 6,944-Patient Study

Articles

A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Jesse J Swen, Cathelijne H van der Wouden*, Lisanne EN Manson*, Heshu Abdullah-Koolmees, Kathrin Blagec, Tanja Blagus, Stefan Bohringer, Anne Cambon-Thomsen, Erika Cecchin, Ka-Chun Chaung, Vera HM Deneer, Mathilde Dupui, Magnus Ingelman-Sundberg, Siv Jonsson, Candace Joefield-Roka, Katja S Just, Mats O Karlsson, Liilja Konta, Rudolf Koopmann, Marjolein Kriek, Thorsten Lehr, Christina Mitropoulou, Emmanuelle Rial-Sebbag, Victoria Rollinson, Rossana Roncato, Matthias Samwald, Elke Schaeffeler, Maria Skokou, Matthias Schwab, Daniela Steinberger, Julia C Stingl, Romen Tremmel, Richard M Turner, Mandy H van Rhenen, Cristina L Udovita Fajardo, Vita Dolžan, George P Patrinos, Munir Pirmohamed, Gare Sunder-Plassmann, Giuseppe Toffoli, Henk-Jan Guchelaar, on behalf of the Ubiquitous Pharmacogenomics Consortium†

PGx-guided treatment reduced the adverse drug event rate by 30% at two different time points. Physicians in the study followed the PGx guidance only 69% of the time.

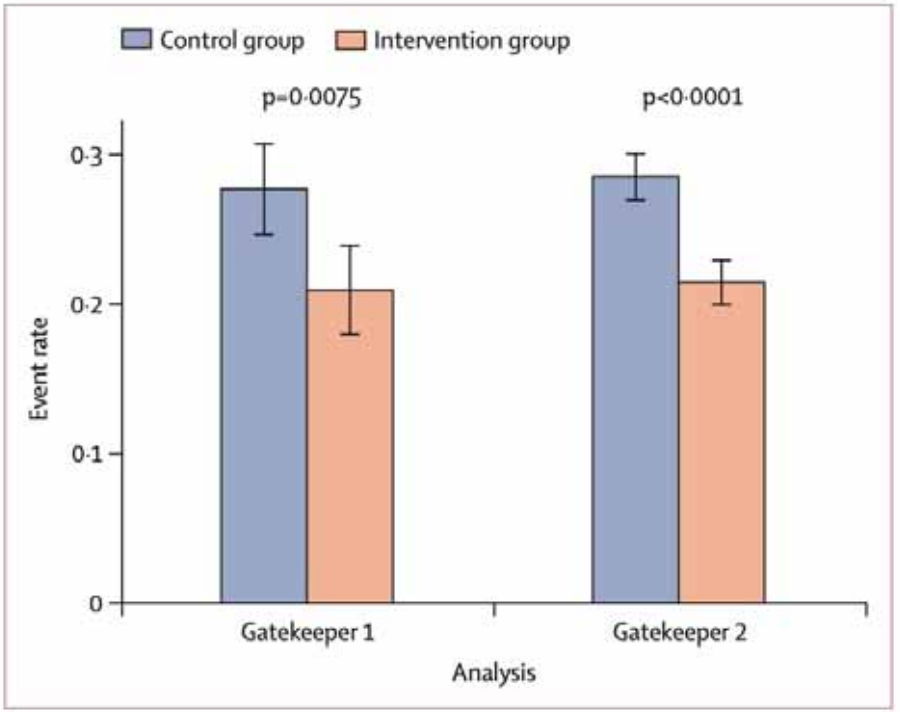
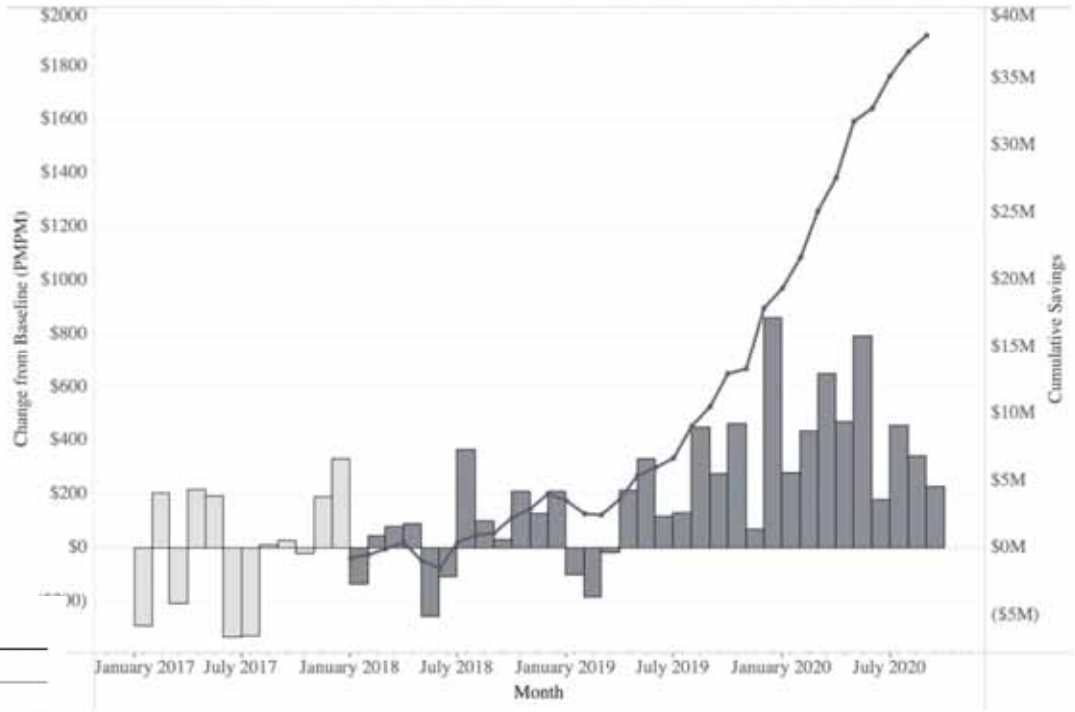


Figure 2: **Frequency of causal clinically relevant adverse drug reactions in patients with an actionable test result**

KY Teacher's Study Shows Large Impact on Outcomes and Costs

- Cumulative savings over 32 months was at $7,000 per member versus control (non-participants).
- Savings averaged $218.34 PMPM for participants.



Journal of Personalized Medicine
MDPI
Article

Real-World Impact of a Pharmacogenomics-Enriched Comprehensive Medication Management Program

Joseph P. Jarvis [1], Arul Prakasam Peter [1], Murray Keogh [1], Vince Baldasare [1], Gina M. Beanland [2], Zachary T. Wilkerson [2], Steven Kradel [1] and Jeffrey A. Shaman [1,*]

[1] Coriell Life Sciences, Philadelphia, PA 19112, USA; (J.P.J.); (A.P.P.); (M.K.); (V.B.); (S.K.)
[2] Know Your Rx Coalition, University of Kentucky, Lexington, KY 40502, USA; (G.M.B.); (Z.T.W.)
* Correspondence:

Table 4. Healthcare resource utilization events avoided in the intervention group.

Healthcare Resource Utilization (Intervention Group)			
Place of Service	HRU Events		
	Expected *	Actual	% Avoided
Outpatient	315,058	309,126	1.9%
Emergency Department	7129	6644	6.8%
Inpatient	13,340	11,351	14.9%

Realizing the Promise of PGx in Clinical Practice

- The greatest utility of PGx is in *prospective drug selection*
- The more relevant genes tested, the more information the physician has to make an optimal drug selection
  - *One gene, one drug doesn't provide adequate guidance*
  - *Combinatorial PGx enables the clinical integration of multiple genes into drug selection*
- Enforce compliance with PGx results

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Session Evaluation

Thank You

"We are in a new era of the life sciences...but in no area of research is the promise greater than in the field of personalized medicine."

Senator Edward M. Kennedy
Remarks on the Senate's Consideration of the Genetic Information Nondiscrimination Act, April 24, 2008