

Pharmacogenetics

PGX TESTING

Field of Pharmacogenetics

- ▶ Study of how genes affect an individual's response to drugs. Combines pharmacology and genomics
 - ▶ Develops an effective and safe medication plan specific to each patient's DNA
- ▶ All drugs are taken through several biochemical pathways to be broken down after a patient takes them
 - ▶ All pharmaceutical companies by law must pronounce the exact biochemical marker through which our body breaks down the medication

Pharmacogenetics

**The right drug for
the right patient at
the right dose.**

Field of Pharmacogenetics

- ▶ Enables personalized therapeutic decisions for patients suffering from some of the most prevalent clinical conditions in the United States
 - ▶ Cardiovascular disease
 - ▶ Neuropsychiatric disorders
 - ▶ Pain
- ▶ PERSONALIZED medicine

How is this done?

- ▶ Patients DNA is taken and analyzed based upon an algorithm based bioinformatics platform
- ▶ Tool to assist healthcare providers in identifying the optimal drugs for the patients
- ▶ Also provides feedback on a dosage of medications
- ▶ Completion of the human genome project in 2001
 - ▶ In which it is predicted that by 2020 pharmacogenetics approach to predicting drug responsiveness would be a standard practice

Why perform Pharmacogenetic testing

- ▶ **To identify the likelihood of an ADE**

- ▶ An estimated 20-30% of pain patients have a genetic opioid (GOMD) metabolic defect.

- ▶ Tennant, Forest, MD, DPH

- <http://www.practicalpainmanagement.com/treatments/pharmacological/opioids/making-practical-sense-cytochrome-p450>

- ▶ 2.2 billion ADE occur yearly with over 100,000 cases resulting in death.

- ▶ U.S. Food and Drug Administration Development Resources

- <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm>

Why perform Pharmacogenetic testing

▶ To increase drug efficacy.

- ▶ Only 58% of patients who take prescription pain medication receive relief.
 - ▶ Peter D. Hart Research Associates, Americans Talk About Pain: A Survey Among Adults Nationwide (August 2003):7
- ▶ Patients with reduced-function alleles have a 3.5-8 times greater risk of major adverse cardiovascular events, with greatest risk in poor metabolizers of Plavix.
 - ▶ Tabassome Simon, M.D. et. al. Genetic Determinants of Response to Clopidogrel and Cardiovascular Events. N Engl J Med 2009; 360:363-375
- ▶ Drug treatment of psychiatric disorders is troubled by severe adverse effects, low compliance and lack of efficacy in about 30 percent of patients.
 - ▶ Arranz, M.J. et al, Pharmacogenetics for the Individualization of Psychiatric Treatment, American Journal of Pharmacogenomics 2001;1(1):3-10

One size does not fit all

- ▶ Pharmacogenetic testing allows you to easily identify metabolizer status
- ▶ There are **5 genes** in the body that metabolize **75% of all medication prescribed**
- ▶ There are **43 medications** on the market with **black box label warnings due to genetic metabolizer status** (Codeine, Coumadin, Plavix, Coreg, Valium)
- ▶ CYP2D6 metabolizes roughly 30% of all medications prescribed
- ▶ Pharmacogenetic testing is standard of care at Harvard, Mayo Clinic, Vanderbilt, Scripps, Columbia

American Medical Association

“These advancements in personalized medicine rely on knowledge of a patient’s genotype and influences his or her phenotype.

Using the principles of personalized medicine, healthcare providers may be better equipped to move beyond the “one-size-fits-all” that defined much of patient care in the past, to care that is appropriate for unique patient subgroups.”

<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/news.page>

Pharmacogenomics:

Increasing the safety and effectiveness of drug therapy



FDA

“We’ve learned that **this trial-and-error approach leads to patient dissatisfaction, poor clinical outcomes, and greater expense, especially for chronic diseases.**

But in many situations this empirical approach is the best approach we have. Personalized medicine aims to streamline clinical decision making by using biological information available through a genetic test or biomarker, and then saying, ‘based on this profile, **I think you’re more likely to respond to Drug A or Drug B, or less likely to have an adverse reaction with Drug C.**’

The idea is to get patients on the right medication and to get them on it sooner.”

Issam Zineh is Director, Office of Clinical Pharmacology (OCP), Center for Drug Evaluation and Research/ FDA

Media

- ▶ Time, Fortune, Forbes, Huffington Post, New York Times, US Health have published articles in the last 18 months detailing the future of this field
- ▶ FDA has been aggressive in providing genetic labeling on new drugs, and the Clinical Pharmacogenetic Implementation Consortium (CPIC), formed in 2009, provides comprehensive reviews and guidelines on the clinical use of pharmacogenetics information
- ▶ Cost in 2001 to map an entire genome well over \$10,000,
- ▶ President Obama in state of union address mentioned \$215 billion precision medicine initiative

Reduce Healthcare Costs

- ▶ The US healthcare system spent roughly 300 billion on prescription drugs in 2014 with that number expected to exceed 450 billion in 2022
- ▶ 2.2 billion ADE occur yearly with over 100,000 cases resulting in death
- ▶ 90% of the population 65 years and over (38 million patients) take a minimum of 1 prescription medicine and half of that population take 5 or more prescription drugs
- ▶ Polypharmacy- occurs in 90% of patients in your settings.
- ▶ Reduces overall cost of prescription drugs by enabling better drug selection
- ▶ Re-hospitalizations reduction

- ▶ Looked at 1 year of savings of patients after pharmacogenetic test was administered.
- ▶ Study look only at psychiatric medications
- ▶ Saved a total of 1035.60 per patient on pharmacy costs alone

Original article

Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation

Joel G. Winner, Joseph M. Carhart, C. Anthony Altar, Josiah D. Allen, Andrew G. Marshak, Bryan M. Dechairo

Assurex Health, Mason, OH, USA

Seth Goldfarb, Gabriela Lavezzari, Kelly K. Parsons, Susan Garavaglia

Express Scripts, St. Louis, MO, USA

Address for correspondence:

Joel G. Winner MD, 2595 Canyon Blvd, Ste 100, Boulder, CO 80302, USA. Tel: +1 720 920 9174;

Fax: +1 720 920 9307;

genewinner@gmail.com

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Adherence – Combinatorial pharmacogenomic testing – Mental health – Pharmacogenomics – Pharmacy spend

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Abstract

Objectives:

The objective of this project was to determine pharmacy cost savings and improvement in adherence based on a combinatorial pharmacogenomic test (CPGx*) in patients who had switched or added a new psychiatric medication after having failed monotherapy for their psychiatric disorder.

Research design and methods:

The prospective project compared 1 year pharmacy claims between a GeneSight CPGx guided cohort and a propensity-matched control group. Patients were project eligible if they augmented or switched to a different antidepressant or antipsychotic medication within the previous 90 days. Following the medication switch or

How Healthcare providers have always prescribed medications

- ▶ Significant risk , health concerns and unnecessary costs associated with the trial and error manner in which physicians prescribe medications
 - ▶ Without knowledge of the patients genetic profile
- ▶ How doctors are taught in medical school and how they've prescribed medication for one hundred years
- ▶ One size fits all approach to patient care has shifted to a personalized approach of right drug for the right patient at the right time

Testing Profile

- ▶ Cytochrome P450 genes code for enzymes responsible for 80% of drug metabolism, genetic variation of these genes alone is estimated to influence 25% of all drug therapies
 - ▶ 15 others genes and 155 variants tested
- ▶ Clinically significant alterations in genes result in four phenotypes
- ▶ Patients metabolic phenotype and its impact on drug metabolism can empower clinical treatment, increase drug efficacy and reduce adverse events

Phenotypes

- ▶ **Normal metabolizers**- 2 function genes and have normal enzyme activity. Standard medication dosing is appropriate
- ▶ **Poor metabolizer**- severely reduced or no functional capacity to metabolize, at high risk for side effects due to toxic drug accumulation- require changes in medication dosages and medications
- ▶ **Intermediate metabolizer**- reduced capacity to metabolize drugs- may require changes
- ▶ **Ultra-rapid metabolizers**- carry multiple copies of the same gene, causing elevated activity. These patients may need increased or decreased in order to offset higher rate of metabolism

ABNORMAL

Ultra Rapid Metabolizers (UM)

- » Increased risk of toxicity from a prodrug due to excessive formation of active metabolites. Consider reducing the starting dose and monitor for ADE.
- » Increased risk of treatment failure from nonprodrugs, consider starting at a higher dose and monitor for lack of efficacy.

NORMAL

Extensive Metabolizers (EM)

- » Normal drug metabolism should be expected.

ABNORMAL

Intermediate Metabolizers (IM)

- » Avoid inhibitors, which would functionally result in poor metabolizer ability.
- » Inducers may improve metabolism.
- » Inconclusive and varied data, often a reduced dose is suggested with close monitoring for ADE.

ABNORMAL

Poor Metabolizers (PM)

- » Unlikely to benefit from a prodrug, consider an alternative drug.
- » Increased risk of toxicity from non-prodrugs, consider reducing the starting dose and monitor for ADE.

Suggested dose adjustments based on CYP2D6 phenotype

PERCENT OF STANDARD DOSE				
DRUG	POOR METABOLIZERS	INTERMEDIATE METABOLIZERS	EXTENSIVE METABOLIZERS	ULTRA-RAPID METABOLIZERS
Imipramine (Tofranil)	30	80	130	180
Doxepin (Sinequan)	35	80	130	175
Trimipramine (Surmontil)	35	90	130	180
Despramine (Norpramin)	40	80	125	170
Nortriptyline (Pamelor)	55	95	120	150
Clomipramine (Anafranil)	60	90	110	145
Paroxetine (Paxil)	65	85	115	135
Venlafaxine (Effexor)	70	80	105	130
Amitriptyline (Elavil)	75	90	105	130
Bupropion (Wellbutrin)	90	95	105	110
Perphenazine (Trilafon)	30	80	125	175
Haloperidol (Haldol)	75	95	100	115
Olanzapine (Zyprexa)	60	105	120	150
Risperidone (Risperdal)	85	90	100	110

Dose-adjustment values were determined by comparing drug concentration, clearance, or exposure data across phenotypes. Values

Cardiovascular

- ▶ Anti-platelet, anti-coagulant, statins, beta-blockers, ACE inhibitors, calcium blockers and hormone therapies
 - ▶ Ten fold inter-patient variability in warfarin dosing required to attain a therapeutic response

The CYP2C9/VKORC1 Warfarin Assay

- ▶ Warfarin is the most widely prescribed oral anticoagulant used to treat various disorders, including venous thrombosis, atrial fibrillation, pulmonary embolism, acute myocardial infarction and following heart valve replacement.
- ▶ US: 3,000,000 new Warfarin prescriptions annually, and increasing.
- ▶ Problem:
 - There is greater than a ten-fold inter-patient variability in the response to Warfarin.
 - Too much Warfarin creates great risk of bleeding (1% to 5 % annually; fatal in 1.1%)
 - Adverse effects of warfarin treatment account for 15% of all severe adverse effects for ALL prescribed drugs.
- ▶ Warfarin is the most widely prescribed oral anticoagulant used to treat various disorders, including venous thrombosis, atrial fibrillation, pulmonary embolism, acute myocardial infarction and following heart valve replacement.

Psychiatric/Anti-Depressant

- **Antidepressants**

- Monoamine Oxidase Inhibitors (MAOIs)
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)
- Tricyclic Antidepressants (TCAs)
- Miscellaneous Agents

- **Antipsychotics**

- Conventional/Typical
- Atypical

- **Central Nervous System (CNS) Agents**

- Stimulants
- Nonstimulants

- **Anxiolytics**

- Benzodiazepines
- Miscellaneous Agents

- **Nonbenzodiazepine Hypnotics**

- **Mood Stabilizers**

Pain Management

- ▶ **Opioids**
- ▶ Non-steroidal
- ▶ anti inflammatory

FDA recommendation

- ▶ Currently has black box warning guidelines for:
 - ▶ 24 psychiatry drugs
 - ▶ 10 cardiovascular
 - ▶ Codeine and morphine
 - ▶ Several oncology, endocrinology , pulmonary and ID drugs
- ▶ These labels provide specific actions that must be taken based on the biomarker information

Testing Process

- ▶ Must be ordered by a healthcare provider
- ▶ Simple 4 step process
 - ▶ Fill out patient information and demographic forms
 - ▶ CAN PRINT out of EMR
 - ▶ Collect sample by swabbing inside patients cheek
 - ▶ Place collection sample and completed forms back into sample envelope
 - ▶ Ship out via next day Fed-Ex
- ▶ Turn around time 48 hours after receiving

What does it cost?

- ▶ Test is covered by Medicare
- ▶ One and done approach, the information received from the test can be used over a life time
- ▶ A person's DNA never changes!

Case Study

- ▶ Private practice in Northern New Jersey has adapted this into their practice for all appropriate patients as part of their patient physicals
 - ▶ To date have done testing on nearly 1000 patients, resulting in 35% percent changes in medication or dosage
- ▶ Narcotics example
 - ▶ MORPHINE

Case Study

- ▶ Nursing home setting in Bridgewater NJ- Beta test site of the 68 patients in long term care 67 qualified for the test resulting in 28 changes to medications
 - ▶ Patient was polypharmacy , elderly in her late 80s, nursing staff have reported several falls, irritable and combative behavior, no appetite, along with heightened signs of depression, increased blood pressure. Patient X was on medications for all of these conditions, all of which were managed but not to the point they should be. Nearly a third of the patients medications were changed after the test results were read and interpreted by the physicians. Note in her chart- due to pharmacogenomics test patient is a completely different person, more cheerful, interactive with fellow patients and all symptoms have greatly decreased of aforementioned conditions
 - ▶ Patient from same facility- been admitted to the hospital 5 times for congestive heart failure, by guidelines given you are supposed to increase the dosages of ACE inhibitor and beta blockers. After doing the test the patient was a non metabolizer of the drug this lead to the constant buildup of it, and it was never broken down in her body .

Case Study

- ▶ 50-year-old Caucasian male
- ▶ ED report:
 - ▶ chest pain
 - ▶ AMI (NSTEMI) one week earlier. Stents Placement
 - ▶ “EKG showed that he has an acute ST elevation in the anterolateral leads consistent with acute myocardial infarction.”
- ▶ Plavix® (75 mg daily) and Aspirin (325 mg daily)
- ▶ One week earlier (NSTEMI):
 - ▶ At that time, he was found to have a totally occluded right coronary artery. He also had significant left coronary artery disease.
- ▶ He underwent initial right coronary artery stent intervention.
- ▶ Follow-up intervention (2 days latter) in his diagonal left anterior descending stent distribution and circumflex distribution.”