Aligning Rx with DNA

A PATIENT CENTERD CARE PLAN PRESCRIBING TOOL

RETHINKING YOUR APPROACH

PHARMSCRIPT

"Empowerment At The Source of Treatment"

Metabolic Validation Testing & Geriatrics

- Elderly patients on average receive 4-10x as many medications as the normal healthy population

- Elderly patients are more sensitive to the side effects of medications

- Elderly patients are dealing with more chronic health conditions

- Consequences of side effects and adverse events carry greater morbidity and mortality in the elderly

Statistics to Consider

Medicare Prescriptions:

198 million in 2010 – for behavioral medications

annual increase rate of (9.3% est.)

992 million in 2010 – for all medications

Re-Hospitalization:

22% of behavioral patients

24% of cardiovascular patients

74% are on more than 3 medications

Adverse Drug Reactions:

2.2 million annually

76% of hospitalized patients

106,000 deaths annually

Cost to health US health system - $136B annually

Drug Label Warnings for Pharmacogenomics:

190+ medications

Challenges: Medication Management

Efficacy

•50% of patients do not respond to first treatment (STAR*D)[1]

Noncompliance

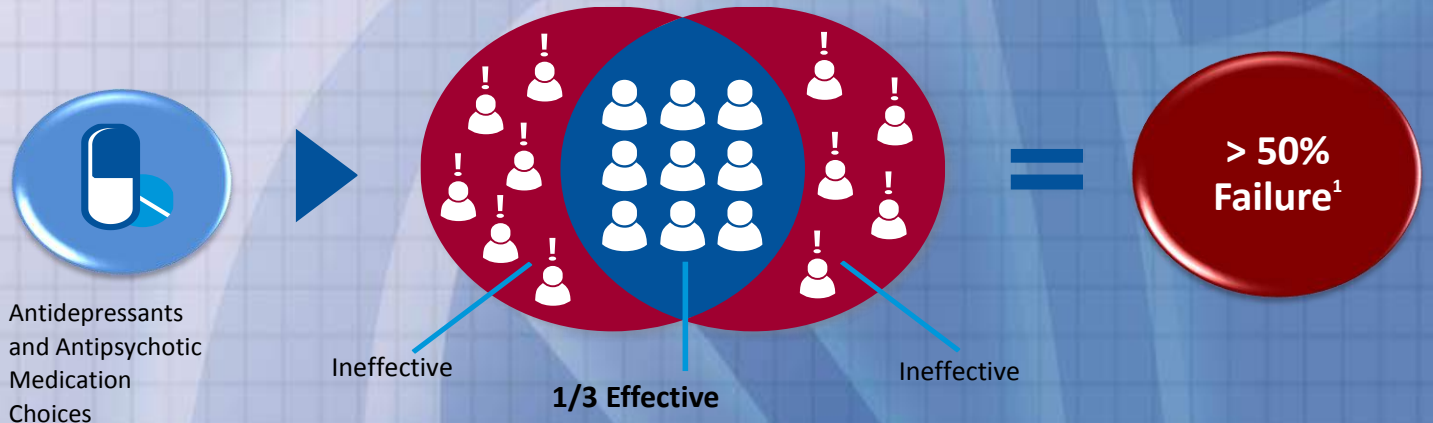
•Up to 70% of patients on antidepressants are noncompliant[2]

Polypharmacy

•Additional provider, prescribing additional medications increased odds of an adverse drug reaction by 29 percent[3]

Side Effects

•Dropout rates in SSRI trials can be as high as 23%[4]



[1] Trivedi MH, Rush AJ, Wisniewski SR, 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] Sabaté E: Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland, World Health Organization, 2003.
[3] Green JL et al. *Am J Geriatr Pharmacoghter*. 2007. Mar;5(1):31-39
[4] Mojtabai et al. National Trends in Psychotropic Medication Polypharmacy in Office-Based Psychiatry. *Arch Gen Psychiatry*. 2010;67(1):26-36

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Tolerability of Psychiatric Medication

- Side effects and patient frustration
- Cost of medications
- Suboptimal drug regimens[1]
- "Trial and error" prescribing

Each additional provider prescribing medications increased odds of an adverse drug event by 29%[2]

[1] New England Healthcare Institute (NEHI). Thinking Outside the Pillbox: A System-wide Approach to Improving Patient Medication Adherence for Chronic Disease.August 2009

[2] Green JL et al. *Am J Geriatr Pharmacoghter*. 2007. Mar;5(1):31-39.

What is Pharmacogenomics ?

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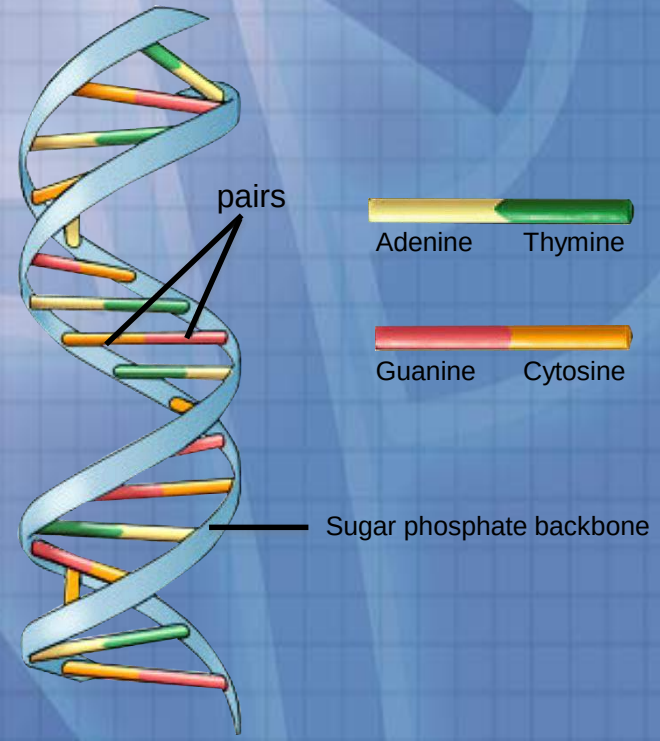
Pharmacogenomics

- The study of how a person's *individual* DNA affects their response to medication



U.S. National Library of Medicine

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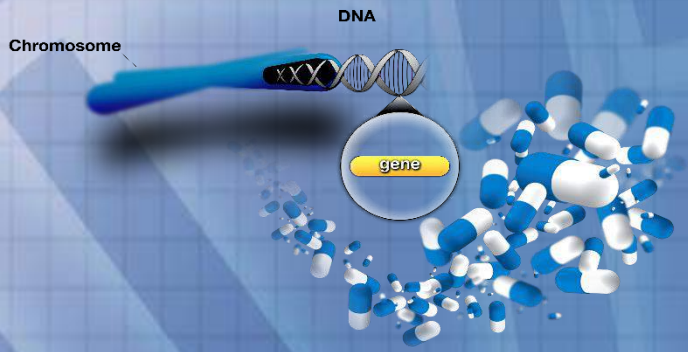
Standard Factors & New Approach to Medication Selection

+ Pharmacogenomics =



Personalized Medication Selection

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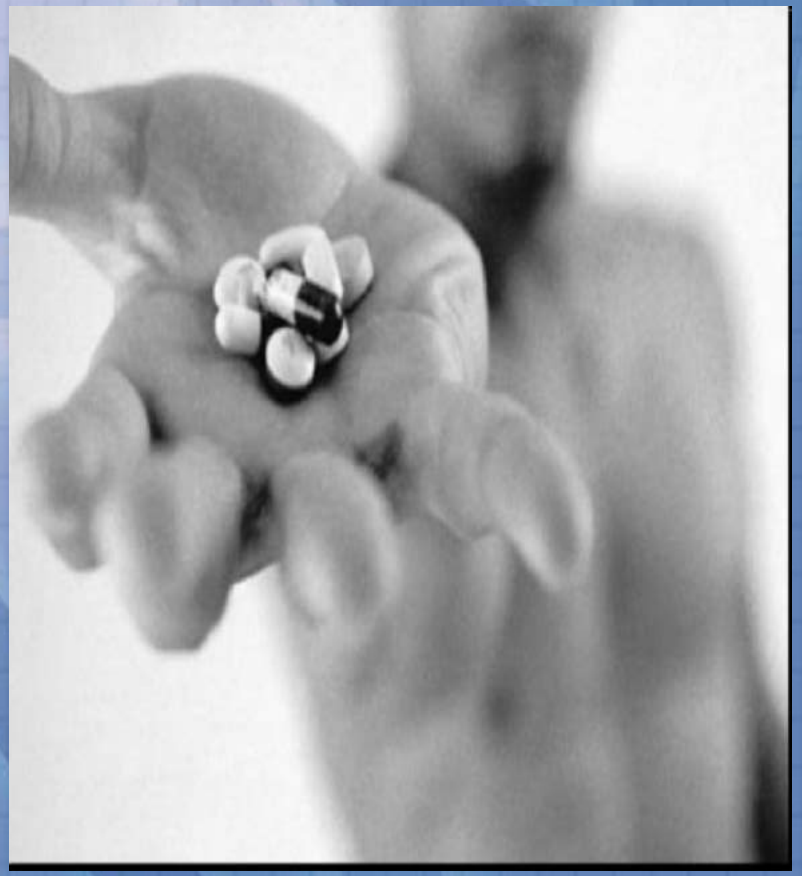
Pharmacogenomics/Personalized Medicine

Right drug, right dose, right patient

Choice of therapy (drug) is predicted by specific genetic changes that can be tested clinically



Intrinsic Variability in Drug Response

"Empowerment At The Source of Treatment"

CYP450 Metabolizer Phenotypes

- Ultrarapid (UM) : Rapid rate of metabolism
- Extensive (EM) : Normal metabolism
- Intermediate (IM) : Reduced rate of metabolism
- Poor (PM) : Slow rate of metabolism

Prevalence of Genetic Variants
Ethnicity Comparisons
Genetic Variant Prevalence CYP2C19 and 2D6

Reduced or No Response to 2C19 Medication (general %)

25% Caucasian

30% Black

40% - 50% Asian

Reduced or No Response to 2D6 Medication (general %)

15-20% Caucasian
20-25% Black
40% - 50% Asian

"Pharmacogenetics (PGx), the study of variations of DNA and RNA characteristics as related to drug response, is one of the most exciting areas of personalized medicine today. The field arises from the convergence of advances in pharmacology (the science of drugs) and genomics (the study of genes and their functions). Patients typically have variability in response to many drugs that are currently available. It can be difficult to predict who will benefit from a medication, who will not respond at all, and who will experience adverse effects. PGx seeks to understand how differences in genes and their expressions affect the body's response to medications.

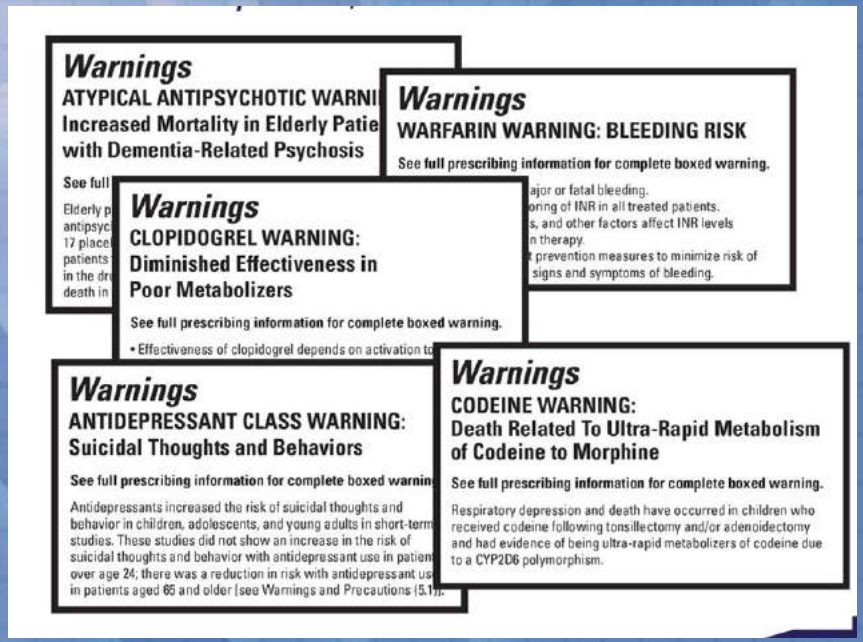
More specifically, PGx uses information (such as DNA sequence, gene expression, and copy number) for purposes of explaining inter individual differences in drug metabolism (pharmacokinetics) and physiological drug response (pharmacodynamics), identifying responders and non responders to a drug, and predicting the efficacy and/or toxicity of a drug.

FDA's Center for Drug and Evaluation and Research (CDER) has supported pharmacogenomics for more than a decade by providing regulatory advice, reviewing applications, and developing policies and processes centered on genomic and individualized therapeutics."

-- Margaret A. Hamburg M.D., Commissioner of FDA

The FDA and Leading Medical Organizations Have Called For:

- Pharmacogenetic testing in clinical trials
- Pharmacogenetic dosing guidance within each prescription drug's prescribing information
- Recognition that adverse drug reactions are due to genetically caused decreases in drug metabolism
- Black Box warnings calling out risks related to metabolic phenotypes



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Sept 2013
FDA Update to Clopidogrel Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PLAVIX safely and effectively. See full prescribing information for PLAVIX.

PLAVIX (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS
See full prescribing information for complete boxed warning.

- **Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)**
- **Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)**
- **Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)**
- **Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)**

RECENT MAJOR CHANGES

Warnings and Precautions (5.6)	09/2013

INDICATIONS AND USAGE

Plavix is a $P2Y_{12}$ platelet inhibitor indicated for:

- Acute coronary syndrome
  - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (1.1)
  - For patients with ST-elevation myocardial infarction (STEMI), Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. (1.1)
- Recent MI, recent stroke, or established peripheral arterial disease. Plavix has been shown to reduce the combined endpoint of new ischemic stroke, new MI, and other vascular death. (1.2)

DOSAGE AND ADMINISTRATION

- Acute coronary syndrome (2.1)
  - UA/NSTEMI: 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75–325 mg once daily)
  - STEMI: 75 mg once daily, in combination with aspirin (75–325 mg once daily), with or without a loading dose
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg, 300 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

WARNINGS AND PRECAUTIONS

- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)
- Bleeding: Plavix increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of Plavix and aspirin is not more effective than Plavix alone, but increases major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.5)
- Allergic cross-reactivity among thienopyridines has been reported. (5.6)

ADVERSE REACTIONS

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Nonsteroidal anti-inflammatory drugs (NSAIDs): Increases risk of gastrointestinal bleeding. (7.2)
- Warfarin: Increases risk of bleeding. (7.3)

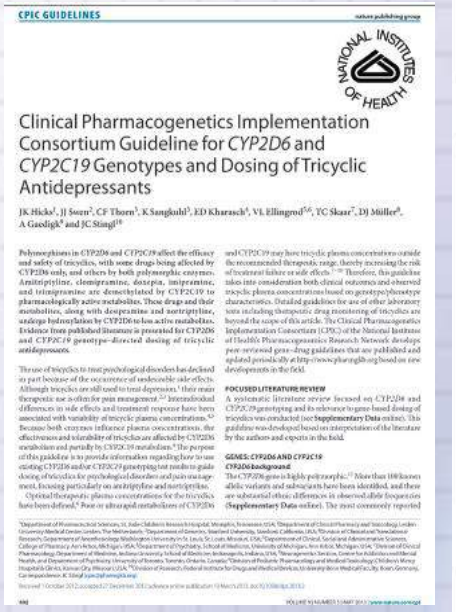
USE IN SPECIFIC POPULATIONS

Nursing mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 09/2013

PGx Awareness – Clinical Guidelines



CPIC GUIDELINES

Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants

		Prodrug	Enzyme	Ultra-Rapid Metabolizer	Intermediate Metabolizer	Poor Metabolizer
PAIN	Codeine	Yes	CYP2D6	Alternative Drug	Alternative Drug	Alternative Drug
	Oxycodone	No	CYP2D6	Alternative Drug	Alternative Drug	Alternative Drug
	Hydrocodone	Yes	CYP2D6	Use with Caution	Use with Caution	Use with Caution
	Tramadol	Yes	CYP2D6	Decrease Dose	Increase Dose	Alternative Drug
	Methadone	No	CYP3A4 & CYP2C19	Decrease Dose	Decrease Dose	Alternative Drug
	Carisoprodol	No	CYP2C19	Standard Dose	Use with Caution	Use with Caution
	Duloxetine	No	CYP2D6	Use with Caution	Use with Caution	Decrease Dose
ANTIDEPRESSANT	Citalopram	No	CYP2C19	Standard Dose	Standard Dose	Decrease Dose
	Venlafaxine	No	CYP2D6	Use with Caution	Use with Caution	Use with Caution
	Citalopram	No	CYP2C19	Standard Dose	Standard Dose	Decrease Dose
	Paroxetine	No	CYP2D6	Alternative Drug	Increase dose	Increase dose
	Sertraline	No	CYP2C19	Alternative Drug	Standard Dose	Decrease dose
	Amitriptyline	No	CYP2D6	Increase Dose	Decrease Dose	Decrease Dose
	Amitriptyline	No	CYP2C19	Alternative Drug	Standard Dose	Decrease Dose
	Imipramine	No	CYP2D6	Increase Dose	Decrease Dose	Decrease Dose
	Imipramine	No	CYP2C19	Alternative Drug	Standard Dose	Decrease Dose
	Nortriptyline	No	CYP2D6	Increase Dose	Decrease Dose	Decrease Dose
	Doxepin	No	CYP2D6	Alternative Drug	Decrease dose	Decrease dose
	Clomipramine	No	CYP2D6	Increase Dose	Decrease Dose	Decrease Dose
ANTIPSYCHOTIC	Clomipramine	No	CYP2C19	Alternative Drug	Standard Dose	Decrease Dose
	Haloperidol	No	CYP2D6	Alternative Drug	Decrease Dose	Decrease Dose
	Risperidone	No	CYP2D6	Alternative Drug	Use with Caution	Decrease Dose
	Aripiprazole	No	CYP2D6 & CYP3A4	Use with Caution	Use with Caution	Decrease Dose
	Clozapine	No	CYP1A2 & CYP3A4	Use with Caution	Use with Caution	Decrease Dose
	Iloperidone	No	CYP2D6 & CYP1A2	Use with Caution	Use with Caution	Decrease Dose
	Perphenazine	No	CYP2D6	Use with Caution	Use with Caution	Decrease Dose

1Hicks CPIC TCA Guidelines Clin Pharmacol ther 2013
2Crews CPIC Codeine Guidelines Clin Pharmacol Therp 2011

"Empowerment At The Source of Treatment"

KEY DATA POINTS FROM CLINICAL TRIALS AND STUDIES

"Empowerment At The Source of Treatment"

Variability in Medication Response

-- Six CYP450 enzymes metabolize approx. 90% of medications

CYP2D6, CYP2C19, CYP2C9, CYP3A4, CYP1A2, CYP2E1

Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions and adverse effects. Am Fam Physician. 2007; 76(3):391-6.

-- CYP450 genetic variability alters response to 1 in 4 medications

Ma JD, Lee KC, Kuo GM. Clinical application of pharmacogenomics. J Pharm Pract. 2012 Aug;25(4):417–27.

Pharmacogenetic Testing (PGx) provides clinically actionable information about how a patient may respond to a specific medication or medication class.

Worldwide Statistics of Gene Variants

-- CYP2D6 = 60% of individuals are UM, PM or IM

-- CYP2C19 = 50% of individuals are UM, PM, or IM

-- MTHFR = 50-60% of individuals have reduced or greatly reduced activity

Sistonen J et al. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenetics and Genomics. 2007;17:93–101.

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.

Botto LD, Yang Q. 5,10-Methylenetetrahydrofolate Reductase Gene Variants and Congenital Anomalies: A Huge Review. Am J Epidemiol. 2000;151(9):862-877.

CYP450 Metabolizer Phenotypes

- Ultrarapid (UM) : Rapid rate of metabolism
- Extensive (EM) : Normal metabolism
- Intermediate (IM) : Reduced rate of metabolism
- Poor (PM) : Slow rate of metabolism

Therapeutic Failures Prevalence and Associated Cost Burden

-- 1 in 5 patients is expected to be a poor responder

Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7(5):201-204.

Xie HG, Frueh FW. Pharmacogenemics steps toward personalized medicine. Personalized Medicine 2005; 2(4);325-337

-- Treatment failure can drive up costs by 30%

Olkanski N, Myers MM, Halseth M, et al. The economic burden of treatment-resistant depression.
Clin Ther. 2013;35(4):512-22.

-- Medications are ineffective for 20-75% of patients

Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med 2001;7(5):201-204.

Ross JS, Ginsburg GS. The Integration of molecular diagnostics with therapeutics; Implications for drug development and pathologypractice. Am J Clin Pathol 2003;119:26-36 2

"Empowerment At The Source of Treatment"

Pharmacogenetic Testing Reduces Healthcare Utilization & Costs

- Primary Care (general and specialty) *Reduced*
- Secondary Care Hospital Services *Reduced*
- Psychiatry Hospital Care *Reduced*
- Pharmaceutical Usage *Reduced*

Herbild L, et al. Does Pharmacogenetic Testing for CYP450 2D6 and 2C19 Among Patients with Diagnoses within the Schizophrenic Spectrum Reduce Treatment Costs? Basic&Clin Pharmacol&Toxicol 2013; doi10.1111/bcpt.12093.

Pharmacogenetic Testing Reduces Cost of Care for UMs and PMs vs. Standard Care

Pharmacogenetic testing significantly reduced costs among the extreme metabolizers (poor metabolizers and ultra rapid metabolizers) to 28%.

207 patients

103 not tested

104 tested

Before - $67,064 *

After - $20,532 *

*Avg. mean costs

Herbild L, et al. Does Pharmacogenetic Testing for CYP450 2D6 and 2C19 Among Patients with Diagnoses within the Schizophrenic Spectrum Reduce Treatment Costs? Basic & Clin Pharmacol&Toxicol 2013; doi10.1111/bcpt.12093.

SSRIs fail for almost 1 in 2 patients

-- CYP2D6 and CYP2C19 metabolize almost all SSRIs2

-- CYP2D6 and CYP2C19 are classified as two of the most genetically variable CYP45O enzymes2

Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. Trends Mol Med. 2001 May;7(5):201-4.

Stingl JC, Brockmoller J, Viviani R. Genetic variability of drug-metabolizing enzymes: the dual impact on psychiatric therapy and regulation of brain function. Mol Psychiatry. 2013 Mar;18(3):273-87.

Compare Cost of Treating with Testing vs. Traditional Trial and Error

Behavior Health Medications

- **65% of MDD patients fail their initial medication trial**

  ≥ 75% fail to respond to subsequent medication trials

- **Non-responders cost 2.5 times more overall than responders[1]**

  $17, 128/yr. vs. $6,770/yr.

- **Direct medical costs are 2.5 times higher for non-responders[1]**

  $12,155/yr. vs. $5,755/yr.

1. *Social and economic burden of treatment-resistant major depressive disorder: A comprehensive, systematic analysis of the literature, Mrazek et al.*
2. *Psychiatric pharmacogenomics predict health resource utilization of outpatients with anxiety and depression in a staff model health maintenance organization, Winner et al (Submitted).*

Increased Healthcare Utilization and Costs – ADR's

CYP2D6 Variation Increases ADRs and Treatment Costs

-- Patients with CYP2D6 variants have more ADRs and cost an extra $4000-$6000/year to treat.

-- 30-70% Increase in adverse events

-- 3x Hospital Length of Stay

-- 2x Total hospital charges

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 Pyschopharmacol 2000;20(2):246-251.

Summary

Clinical Value of Pharmacogenetic Testing

-- Pharmacogenetic testing is evidence-based and clinically actionable

-- Pharmacogenetics should have significant impact to prescribing

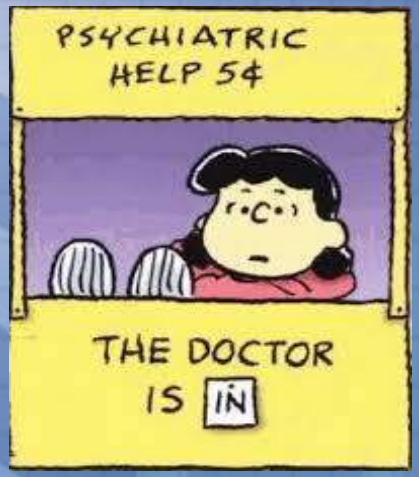
-- Pharmacogenetics should enable significant cost savings and improved patient outcomes

- Medications are commonly used
- Medications incur significant pharmacy spend
- Medications metabolized by genetically variable enzymes

-- Pharmacogenetics should enable significant cost savings and improved patient outcomes

-- Pharmacogenetics should assist in reducing healthcare spend associated with ADRs and therapeutic failures

Benefits to Providers



Pharmacogenetic Testing Helps Providers:

-- Explain or predict unexpected medication outcomes, such as elevated adverse effects, decreased efficacy, or treatment failures

-- Identify patients at higher risk for certain medication interactions

-- Reduce the need for sequential medication trials and prolonged symptoms

-- Give an explanation or rationale for higher than expected doses needed to achieve efficacy

-- 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.

Assisted/Skilled Living Center

Case Studies

"Empowerment At The Source of Treatment"

Case Study 1 -Overview

Residents Tested:	132
On Avoid Use Meds:	23%
Need Dosage Review:	48%
Drug-Drug Warning:	48%

(Missouri Homes)

Case Study 2 - Overview (cont.)

Residents Tested: 112

Data on Patient Population:

•Patients on average were on 21 prescription drugs/OTC's.

•53 of 112 patients were identified with opportunities to replace or reduce prescription therapies on the basis of their genetics or environmental interactions.

Overview (cont.)

On Avoid Use Meds:	31%
Need Dosage Review:	47%
Drug-Drug Warning:	60%

Without knowledge of the patient's genetics, approximately 60% of findings would go undetected by traditional drug review.

PGx Medical's Unique Program

(*Not all labs are the same)*

- Billing Capabilities under CMS guidelines as of June 22, 2015
- Number of Genes Reported Maximize LTC Facilities' care for the residents
- Report Details
  - User Friendly
  - Drug-Drug Interactions
  - Phenotype and Genotype
  - Highlighted current meds
  - Med Class Breakdown vs. Gene Class Breakdown
  - 48 hr. turnaround
  - Etc.

Standard for Pharmacogenetic Testing

Genes Tested (19)

2D6
2C9
2C19
1A2
3A4
3A5
SLC6A4
HTR2A
OPRM1
COMT
Factor II
Factor V
MTHFR
VKORC1
+++

Reports Available (3)

Pain
Depression
Psychiatric
Anxiety
Cardiology
Thrombophilia
Anti Coagulants
ADHD

Reports Include

Patient-Med Specific
Dosing Guidance
Drug-Drug Interaction
Highlighted Medication
Warning Label Alerts
Genotyping
Phenotyping
Clinical Relevance Guide

"Empowerment At The Source of Treatment"

CYP450 Metabolizer Phenotypes

- Ultrarapid (UM) : Rapid rate of metabolism
- Extensive (EM) : Normal metabolism
- Intermediate (IM) : Reduced rate of metabolism
- Poor (PM) : Slow rate of metabolism

Operational Overview

- All Testing must have a physician order
  - Global authorization to Facility
  - Registration of authorized partners – PA, RN, LPN, other
  - Protocol for Testing Established

- Swab Collection
- PGx Assisted Process – training, staffing, etc.
  - In Facility
  - Remote Asst Living (patient home)

Operational Overview (cont.)

- Reports Access / Delivery
  - Portal Access (*Remote*) – multi user log in
  - IT Interface with EHR
  - Other – fax, email, other

- Billing
  - PGx will facilitate all billing
  - MDCR/MDCD – EOB only
  - No Balance Billing
  - Financial Assistance available for any co-pay or deductibles for commercial clients

Partnering with PGx Medical

- Integrity in the testing process
- Operational experience
- Integration experience
- CMS guided medical necessity and billing practices
- Value added service with no capital expenditures from the facility is required
- Local knowledge and expertise

Contact Information

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