THE FUTURE IS NOW! REVOLUTIONIZING MEDICINE THROUGH THE USE OF PHARMACOGENETICS

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PGX TESTING AKA PHARMACOGENETICS


PERSONALIZED MEDICINE IS IMPACTING THE WORKERS COMPENSATION INDUSTRY FROM ALL ANGLES: SCIENTIFICALLY, FINANCIALLY, COMPLIANTLY, OBJECTIVELY AND COMPASSIONATELY!
It's far more important to know what person the disease has than what disease the person has. - Hippocratesi

> 4.5 BILLION PRESCRIPTIONS A YEAR IN THE U.S. [1]

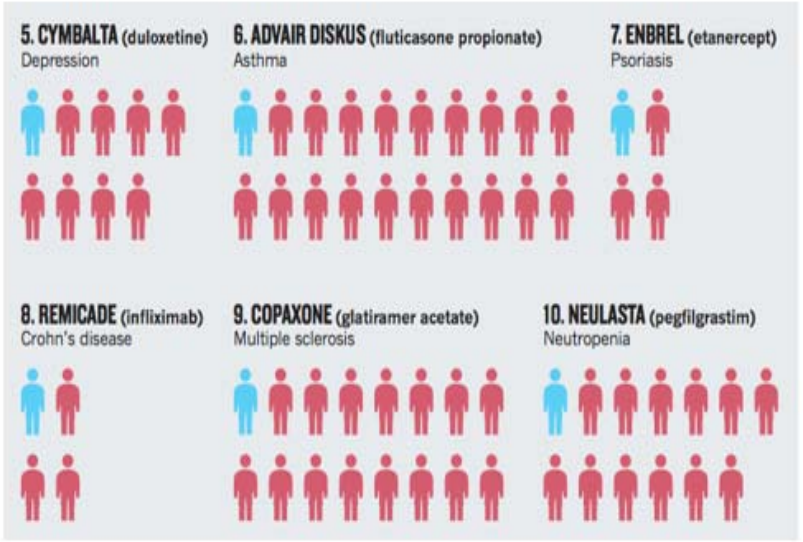
- At least 50% of patients do not receive the proper medication or endure trial and error to find the right prescription[2]
- $136 billion annual cost in adverse drug reactions (ADRs)

Yet, 99% of people have actionable genetic variants that help predict medication response

1. According to IMS Institute for Healthcare Informatics
2. Spear BB, Heath-Chiozzi M, Huff J. Trends Mol. Med.7, 201–204 (2001).

THE VALUE OF MEDICATION RESPONSE TESTING

For every **person** a medication helps, from **3 to 24** people don't benefit at all



Trial and error prescribing in search of the right medication is:

- Inefficient
- Inconvenient
- Expensive
- Dangerous

There is a better way

IMPRECISION MEDICINE

PHARMACOGENOMICS

The study of genetic variations that influence individual response to drugs (receptors)

INDUSTRY CHALLENGE	PGX VALUE ADD
ONE SIZE FITS ALL	INDIVIDUALIZED RESULTS & IMPROVED EFFICACY
60% OF IW RECEIVING MEDS DO NOT RESPOND COMPLETELY TO RX & UP TO 30% DO NOT RESPOND AT ALL	IMPROVED RX COMPLIANCE
ADVERSE DRUG REACTIONS (ADRS) & ADVERSE DRUG EFFECTS (ADES) *OPIOID PAIN ANALGESICS ARE MOST COMMON CONTRIBUTOR OF ADE'S	ENSURE MAXIMUM EFFICACY & THAT THE PATIENT IS TAKING THE APPROPRIATE MEDICATION
ADVERSE DRUG REACTIONS (ADRS) & ADVERSE DRUG EFFECTS (ADES) = 4TH LEADING CAUSE OF DEATH IN US YRLY.	ELIMINATE UNNECESSARY ADR/ADE RISKS

PAIN MANAGEMENT

- Acute pain
  - First 30 days on new opioid likely critical. Dose reductions may be as informative as med changes
  - Sound management in acute phase establishes clinical foundation for chronic pain later on
- Chronic pain
  - Unmanaged chronic pain can contribute to workplace injury, morbidity
  - Costs elevated early on and never return to baseline
- Data from large 2000 person retrospective study examining link between opioids and ADRs nearly complete

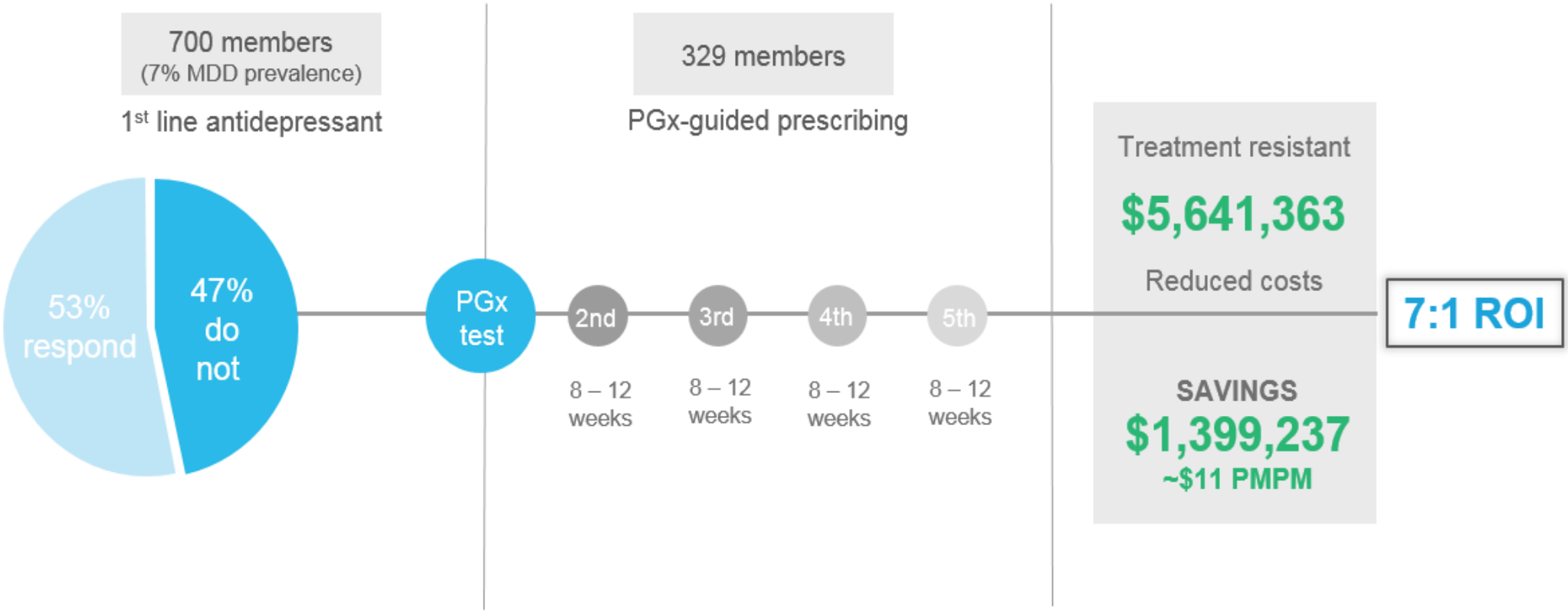
MAJOR DEPRESSIVE DISORDER (MDD): 10,000 LIVES

TRIAL AND ERROR PRESCRIBING DRIVES SIGNIFICANT, AVOIDABLE COSTS

For illustration only

MAJOR DEPRESSIVE DISORDER (MDD): 10,000 LIVES

ONEOME RIGHTMED TEST CAN REDUCE THE GUESSWORK—AND THE COSTS



TESTING SAVES LIVES & MAKES PEOPLE HEALTH IMPACTING ANNUAL WORKE & HEALTHCARE EXPENSES

WHY COMBINE PGX TESTING WITH MEDICARE SET ASIDES?

- ELIMINATE HOSPITAL READMITTANCE EXPENSES CAUSED BY ADRS
- LOWER THE AMOUNT OF SERIOUS INJURY OR DEATH CAUSED FROM ADRS
- ENSURES PHYSICIANS WRITE THE CORRECT PRESCRIPTIONS THE FIRST TIME
- ADDRESSES **SUBOPTIMAL** MEDICATION DISPENSING THAT RESULTS FROM EMPIRIC PRESCRIBING
- **SUBOPTIMAL** MEANS:
  - MEDICATIONS THAT DONT WORK
  - MEDS THAT PROLONG OR CREATE ADDITIONAL TREATMENT COSTS
  - MEDS THAT CONTRIBUTE OR CAUSE ADRS RESULTING IN SICKNESS, HOSPITALIZATION AND/OR RE-ADMISSION (PENALTY) OR EVENT

PGX REPORT

Thrombophilia Pharmacogenetic Report Created for: Sample Patient

Patient:	Sample Patient	DOB:	2/3/1950
Accession #:	123456	Gender:	Male
Collection Date:	2/23/2015	Received Date:	3/2/2015
Ordered By:	Dr. John Smith	Report Generated:	5/1/2017

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *4, *5, *6, *8, *11, *27
Factor II	20210G>A GG	Normal Thrombosis Risk	20210G>A
Factor V Leiden	1691G>A GG	Normal Thrombosis Risk	1691G>A
MTHFR	677C>T CC	Normal MTHFR Activity	677C>T
MTHFR	1298A>C AA	Normal MTHFR Activity	1298A>C
VKORC1	-1639G>A G/G	Low Warfarin Sensitivity	-1639G>A

Current Patient Medications

Current Medication List: Codeine, Zocor, Bupropion

Medications Affected by Patient Genetic Results

✓ **Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)**

Good Response to Bupropion for Smoking Cessation (ANKK1 DRD2:Taq1A G/G Unaltered DRD2 function) Evidence Level: **Informative**

Smoking Cessation: The patient's genotype result is associated with a positive response with bupropion treatment.

✓ **Bupropion (Wellbutrin, Zyban, Aplenzin, Contrave)**

Normal Response to Bupropion (CYP2B6 *1/*1 Normal Metabolizer) Evidence Level: **Informative**

Bupropion is metabolized to its active metabolite hydroxybupropion by CYP2B6. This metabolite contributes to the therapeutic effects of bupropion when used as a smoking cessation agent or as an antidepressant. Unless other genetic or non-genetic factors are present, individuals who are CYP2B6 normal metabolizers are not expected to have lower blood levels of hydroxybupropion. Bupropion can be prescribed at standard label-recommended dosage.

Codeine (Codeine; Fioricet with Codeine)

Increased Response to Codeine (CYP2D6 *1/*1 XN Ultra-Rapid Metabolizer) Evidence Level: **Actionable**

Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is a ultra-rapid metabolizer, greatly increased morphine levels are expected, and the patient is at high risk of toxicity when taking codeine. Avoid prescribing codeine, and consider an alternative opioid or a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: fentanyl, morphine, hydromorphone, oxymorphone, and tapentadol.

✓ **Zocor (Simvastatin)**

Normal Response to Simvastatin (CYP3A4 *1/*1 Normal Metabolizer) Evidence Level: **Informative**

The genotype result indicates that the patient does not carry the CYP3A4*22 allele (this allele is associated with a decreased CYP3A4 enzyme activity). The patient is expected to achieve an optimal lipid control goal with standard simvastatin dose requirements.

SEE "Guidance Levels" & "Evidence Levels" KEY next page

PG. 2 REPORT

Zocor (Simvastatin)

Normal Myopathy Risk (SLCO1B1 521T>C T/T Normal Function) Evidence Level: **Actionable**

Simvastatin plasma concentrations are not expected to be elevated, and unless other genetic or circumstantial risk factors are present, simvastatin can be prescribed at standard FDA-recommended starting doses and adjusted based on disease-specific guidelines. **The FDA recommends against the use of the 80 mg daily dose unless the patient had already tolerated this dose for 12 months without evidence of myopathy.** Other myopathy predisposing factors include advanced age (≥65), uncontrolled hypothyroidism, renal impairment, high statin dose, comedications, and female gender.

Guidance Levels

#1 Based upon the patient's genotype, a medication has potentially reduced efficacy or increased toxicity or the patient has increased risk for the indicated condition.

#2 Based upon the patient's genotype, guidelines exist for adjusting dosage or increased vigilance or the patient has moderate risk for the indicated condition.

#3 Based on this patient's genotype, the medication can be prescribed according to standard regimens or the patient's risk for the indicated condition is not increased.

Evidence Levels

#1 Actionable - Recommendations based upon publications by international pharmacogenetic expert groups, consortia or regulatory bodies (CPIC, DPWG, FDA, EMA). Recommendations are suitable for implementation in a clinical setting. Guidelines may change as new knowledge arises.

#2 Informative - There are insufficient or contradictory findings documenting the impact of a given genetic polymorphism or drug interaction. Recommendations are informative and implementation in a clinical setting is optional.

Risk Management

Thrombophilia

No Increased Risk of Thrombosis

The patient does not carry the Factor V Leiden G1691A mutation or Factor II G20210A mutation (wild-type).

The patient's risk of thrombosis is not increased (average risk of clotting is about 1 in 1000 for anyone in a year). However, because this test cannot find all of the inherited reasons for abnormal clotting, other factors may affect this risk assessment.

Unless other genetic and/or circumstantial risk factors are present (e.g., smoking or obesity…), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

Hyperhomocysteinemia - Thrombosis

No Increased Risk of Hyperhomocysteinemia

The patient does not carry the MTHFR C677T or MTHFR A1298C mutation (wild-type). MTHFR enzyme activity is normal.

With a normal MTHFR activity, this patient is unlikely to have elevated plasma levels of homocysteine, which is a known risk factor for cardiovascular diseases and thrombosis. Unless other risk factors are present, the patient is not expected to have an increased risk for venous thromboembolism (VTE).

MTHFR enzyme activity is normal.

EXAMPLE 1

Patient had been treating with a psychiatrist for anxiety and depression under his workers comp claim for 6 months and reported not feeling any better with any of the prescribed medications. Patient had been prescribed the following medications; ***Celexa, Lexapro and Effexor*** at different times. The psychiatrist agreed to a PGX test.

Potentially Impacted Medications			
Category	**Standard Precautions**	**Use With Caution**	**Consider Alternatives**
Antidepressants	Desvenlafaxine (Pristiq) Duloxetine (Cymbalta) Fluoxetine (Prozac, Sarafem) Levomilnacipran (Fetzima) Mirtazapine (Remeron) Sertraline (Zoloft) Vortioxetine (Brintellix)		Amitriptyline (Elavil) Citalopram (Celexa) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Escitalopram (Lexapro) Imipramine (Tofranil) Nortriptyline (Pamelor) Paroxetine (Paxil, Brisdelle) Trimipramine (Surmontil) Venlafaxine (Effexor)
Antipsychotics	Aripiprazole (Abilify) Iloperidone (Fanapt) Paliperidone (Invega) Thioridazine (Mellaril)	Clozapine (Clozaril) Olanzapine (Zyprexa) Perphenazine (Trilafon) Pimozide (Orap) Tetrabenazine (Xenazine)	Haloperidol (Haldol) Risperidone (Risperdal)
Benzodiazepines	Clobazam (Onfi) Clonazepam (Klonopin)	Diazepam (Valium)	

EXAMPLE 1 CONT

Escitalopram (Lexapro)

Insufficient Reponse to Escitalopram (CYP2C19 *1/*17 Rapid Metabolizer) Evidence Level: **Actionable**

Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

Venlafaxine (Effexor)

Non-Response to Venlafaxine (CYP2D6 *2/*2 XN Rapid Metabolizer) Evidence Level: **Actionable**

The patient is unlikely to achieve adequate serum levels of venlafaxine and O-desmethylvenlafaxine when taking standard doses of venlafaxine. Consider alternative drug or increase venlafaxine dose to a maximum of 150% of the normal dose and monitor venlafaxine and O-desmethylvenlafaxine plasma concentrations.

Citalopram (Celexa)

Insufficient Response to Citalopram (CYP2C19 *1/*17 Rapid Metabolizer) Evidence Level: **Actionable**

The patient may not respond to usual doses. Monitor plasma concentration and increase dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.

EXAMPLE 2

Patient had been treating with a chronic pain specialist for over a year and had been out of work due to his narcotic use and recent surgery. Patient was taking the following medications; **Hydrocodone, Flexeril and Ultram**. Patient continued to report a pain level of 8-10 despite the increased doses of medication.

PGX testing was completed which revealed the following:

Potentially Impacted Medications			
Category	**Standard Precautions**	**Use With Caution**	**Consider Alternatives**
Fibromyalgia Agents	Milnacipran (Savella)		
Muscle Relaxants	Cyclobenzaprine (Flexeril, Amrix) Metaxalone (Skelaxin)	Carisoprodol (Soma) Tizanidine (Zanaflex)	
NSAIDs	Celecoxib (Celebrex) Flurbiprofen (Ansaid) Meloxicam (Mobic) Piroxicam (Feldene)		
Opioids	Alfentanil (Alfenta) Buprenorphine (Butrans, Buprenex) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Meperidine (Demerol) Oxymorphone (Opana, Numorphan) Sufentanil (Sufenta) Tapentadol (Nucynta)	Dihydrocodeine (Synalgos-DC) Hydrocodone (Vicodin) Methadone (Dolophine) Morphine (MS Contin) Oxycodone (Percocet, Oxycontin)	Codeine (Codeine; Fioricet with Codeine) Tramadol (Ultram)

EXAMPLE 2 CONT

Tramadol (Ultram)

Increased Response to Tramadol (CYP2D6 *2/*2 XN Rapid Metabolizer) Evidence Level: **Actionable**

The patient is at high risk of toxicity when taking tramadol at standard dosing. Consider reducing tramadol dose by 30%. Careful monitoring for side effects and weekly titration are recommended. If toxicity, consider alternative opioids other than codeine or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *2/*2 XN Rapid Metabolizer) Evidence Level: **Informative**

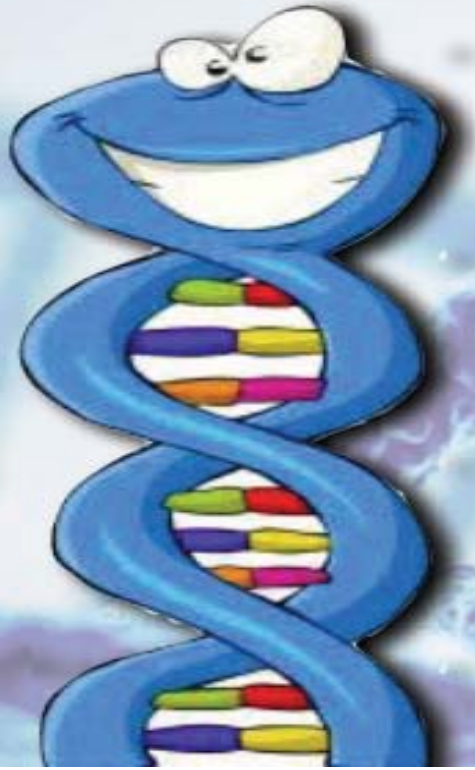
Increased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 rapid metabolizers. Usually, adequate pain relief without an increase in adverse events can be achieved by using standard or lower hydrocodone doses. Other opioids not metabolized by CYP2D6 (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone) may also be considered if excessive side effects are reported.

Cyclobenzaprine (Flexeril, Amrix)

Normal Response to Cyclobenzaprine Evidence Level: **Informative**

Pharmacogenetic guidance: Cyclobenzaprine is excreted primarily as a glucuronide via the kidney and as a N-demethylated metabolite by CYP3A4, CYP1A2, and to a lesser extent CYP2D6. Due to the minor involvement of CYP2D6 in the metabolism of cyclobenzaprine, the polymorphism of this enzyme is not of concern in its the clinical use. No genetically guided drug selection or dosing recommendations are available.

EXACTLY WHAT DOES THE LAB DO WITH MY DNA SAMPLE?



- **DNA IS EXTRACTED (SWAB)**
- **SAMPLES ARE LOADED**
- **REAL TIME PCR** (POLYMERASE CHAIN REACTION - PROCESS OF AMPLIFYING DAN TO MAKE MORE FOR STUDY)SAMPLES ARE LOADED
- **ANALYZE RESULTS** (PROPRIETARY REPORT GENERATION AND GENOTYPE SOFTWARE)

It's far more important to know what person the disease has than what disease the person has. – Hippocratesi

WHEN DO I REFER AN INJURED WORKER FOR PGX TESTING?

- ✓Patient currently taking multiple medications
- ✓Patient taking prescribed meds and is not feeling better
- ✓Patient has been prescribed pain meds, blood thinners, beta blockers or psychiatric meds such as an antidepressant

QUESTIONS?

THANK YOU FOR YOUR PARTICIPATION !!!