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

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MSN, APNP, PMHNP-BC &
Karen Cofield RN, CCM, QRP, MSCC, CMSP
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. 

- At least 50% of patients do not receive the proper medication or endure trial and error to find the right prescription.
- $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

THE VALUE OF MEDICATION RESPONSE TESTING
For every **person** a medication helps, from **3 to 24** people don’t benefit at all.

- **1. ABILIFY** (aripiprazole): Schizophrenia
- **2. NEXIUM** (esomeprazole): Heartburn
- **3. HUMIRA** (adalimumab): Arthritis
- **4. CRESTOR** (rosuvastatin): High cholesterol
- **5. CYMBALTA** ( duloxetine): Depression
- **6. ADVAIR DISKUS** (fluticasone propionate): Asthma
- **7. ENBREL** (etanercept): Psoriasis
- **8. REMICADE** (infliximab): Crohn’s disease
- **9. COPAXONE** (glatiramer acetate): Multiple sclerosis
- **10. NEULASTA** (pegfilgrastim): Neutropenia

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)

<table>
<thead>
<tr>
<th>Industry Challenge</th>
<th>PGX Value Add</th>
</tr>
</thead>
<tbody>
<tr>
<td>One size fits all</td>
<td>Individualized results &amp; improved efficacy</td>
</tr>
<tr>
<td>60% of IW receiving meds do not respond completely to Rx &amp; up to 30% do not respond at all</td>
<td>Improved Rx compliance</td>
</tr>
<tr>
<td>Adverse drug reactions (ADRs) &amp; adverse drug effects (ADEs)</td>
<td>Ensure maximum efficacy &amp; that the patient is taking the appropriate medication</td>
</tr>
<tr>
<td>Opioid pain analgesics are most common contributor of ADE's</td>
<td>Eliminate unnecessary ADR/ADE risks</td>
</tr>
<tr>
<td>Adverse drug reactions (ADRs) &amp; adverse drug effects (ADEs) = 4th leading cause of death in US yrly.</td>
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</table>
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

- **700 members** (7% MDD prevalence)
  - 1st line antidepressant
  - 47% do not respond

- **329 members**
  - Trial & error prescribing
  - Treatment resistant
  - 2nd, 3rd, 4th, 5th
  - 8 – 12 weeks each

Treatment resistant: $7,040,600
Total costs

For illustration only
MAJOR DEPRESSIVE DISORDER (MDD): 10,000 LIVES

ONEOME RIGHTMED TEST CAN REDUCE THE GUESSWORK—AND THE COSTS

700 members (7% MDD prevalence)
1st line antidepressant

329 members
PGx-guided prescribing

Treatment resistant
$5,641,363
Reduced costs

SAVINGS
$1,399,237
~$11 PMPM

7:1 ROI
TESTING SAVES LIVES & MAKES PEOPLE HEALTHIER, IMPACTING ANNUAL WORKERS' COMP & HEALTHCARE EXPENSES

**HEALTHCARE PAYER ORGANIZATION MANAGING**

**TOTAL PAYER POPULATION**

$1,000,000

**% OF INITIAL UTILIZATION**

1% = 10,000 PEOPLE

$75.00 = AVERAGE COST PER RX

**SUBOPTIMALSCRIPTS ELIMINATED PER PATIENT PER YEAR**

2

**NO OF CRITICAL HOSPITAL EVENTS CAUSED BY ADRS AVOIDED**

100 (10% OF ITEM 3)

$25,000.00

**TOTAL PAYER POPULATION**

$132,500,000.00

= PROJECTED SAVINGS OVER 5 YRS (MAINTAINING 1%)

$1,325,000,000.00

= PROJECTED SAVINGS OVER 5 YRS (INCREASING TO 10%)
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 don't 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
Thrombophilia Pharmacogenetic Report

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

Test Details

<table>
<thead>
<tr>
<th>CYP2C9</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>Alleles Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor II</td>
<td>20210G&gt;A GG</td>
<td>Normal Thrombus Risk</td>
<td>20210G&gt;A</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>1691G&gt;A GG</td>
<td>Normal Thrombus Risk</td>
<td>1691G&gt;A</td>
</tr>
<tr>
<td>MTHFR</td>
<td>677C&gt;T CC</td>
<td>Normal MTHFR Activity</td>
<td>677C&gt;T</td>
</tr>
<tr>
<td>MTHFR</td>
<td>1298A&gt;C AA</td>
<td>Normal MTHFR Activity</td>
<td>1298A&gt;C</td>
</tr>
<tr>
<td>VKORC1</td>
<td>-1635G&gt;A GG</td>
<td>Low Warfarin Sensitivity</td>
<td>-1635G&gt;A</td>
</tr>
</tbody>
</table>

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 (via downregulated DRD2 function)
  Smoking Cessation: The patient's genotype result is associated with a positive response with bupropion treatment.
  Evidence Level: Informative

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

Codeine (Oral, Codeine; Florica; with Codeine)

- Increased Response to Codeine (CYP2D6 *1/*1 Ultra-Rapid Metabolizer)
  Codeine is converted into its active metabolite morphine by CYP2D6. Since this patient is a ultrarapid metabolizer, ideally 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 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.
  Evidence Level: Actionable

Zocor (Simvastatin)

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

Non-myopathy Risk (SLCO1B1 521T>C T/T Normal Function) Evidence Level: Actionable

Statins can cause plasma concentrations 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 on a dose-specific basis. 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, comedication, 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.
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.
**EXAMPLE 1 CONT**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Evidence Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram (Lexapro)</td>
<td>Insufficient Response to Escitalopram (CYP2C19 *1/*17 Rapid Metabolizer)</td>
<td>Actionable</td>
</tr>
<tr>
<td></td>
<td>Monitor plasma concentration and titrate dose to a maximum of 150% in response to efficacy and adverse events or select alternative drug.</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>Non-Response to Venlafaxine (CYP2D6 *2/*2 XN Rapid Metabolizer)</td>
<td>Actionable</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>Insufficient Response to Citalopram (CYP2C19 *1/*17 Rapid Metabolizer)</td>
<td>Actionable</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
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</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Potentially Impacted Medications</th>
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<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td>Fibromyalgia Agents</td>
</tr>
<tr>
<td>Milacipran (Savella)</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
</tr>
<tr>
<td>Cyclobenzaprine (Flexeril, Anrix)</td>
</tr>
<tr>
<td>Metaxalone (Skelaxin)</td>
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<tr>
<td>NSAIDs</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
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<tr>
<td>Flurbiprofen (Ansaid)</td>
</tr>
<tr>
<td>Meloxicam (Mobic)</td>
</tr>
<tr>
<td>Piroxicam (Feldene)</td>
</tr>
<tr>
<td>Opioids</td>
</tr>
<tr>
<td>Alfentanil (Alfenta)</td>
</tr>
<tr>
<td>Butorphanol (Tramadol)</td>
</tr>
<tr>
<td>Fentanyl (Actiq)</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid, Exalgo)</td>
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<tr>
<td>Meperidine (Demerol)</td>
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<tr>
<td>Oxymorphone (Opana, Numorphan)</td>
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<tr>
<td>Sufentanil (Sufenta)</td>
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<tr>
<td>Tapentadol (Nucynta)</td>
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<tr>
<td>Dihydrocodeine (Synaigos-DC)</td>
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<tr>
<td>Hydrocodone (Vicodin)</td>
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<tr>
<td>Methadone (Dolophine)</td>
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<tr>
<td>Morphine (MS Contin)</td>
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<tr>
<td>Oxycodone (Percocet, Oxycontin)</td>
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<tr>
<td>Codeine (Codeine; Fioricet with Codeine)</td>
</tr>
<tr>
<td>Tramadol (Ultram)</td>
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</tbody>
</table>
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 DNA 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. – Hippocrates
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 !!!