Introduction

Personalized Medicine/Pharmacogenetics

Pharmacogenetics’ Role in Treatment Plan Options

Clinical Application

Pain Management
Behavioral Health
- Identify individuals that would benefit from testing
- Application examples
- Personalized Medicine in practice

Logistics

Panels to screen/Medical Necessity
Interpretive Reports
Coverage Details

Questions and Answers

Objectives

- Define Pharmacogenetics
- Identify clinical application of pharmacogenetics
- Identify medical necessity requirements
- Identify panels of pharmacogenetics
Pharmacogenetics is the study of how our genes affect our response to drugs. Every human has a genetic code that is unique to them alone.

Variances in the genes that play a role in medications can:
- Be of no consequence to the drug’s safety and efficacy
- Render a medication useless
- Result in a medication causing serious adverse reactions

Overview of Pharmacogenetics

Biochemical and Physiological Effects of Drugs
Pharmacokinetics and Pharmacodynamics

Pharmacokinetics
• What the body does to a drug
• Think metabolism, bioavailability
• Converting Pro-Drug to active agent
• Washing the active agent out of the body

Pharmacodynamics
What the drug does to the body
• Think therapeutic, sub-therapeutic or toxic

Pharmacogenetic DNA Breakdown
Cytochrome P450 Enzymes
More than 50 enzymes in CYP450

CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
90% of drugs are metabolized by these 6 enzymes

Pharmacogenetics

Links differences in gene structure (inherited variation) to drug metabolism and response

Genetic Variation Drug metabolism & response

Genotype Phenotype

SO WHY IS THIS IMPORTANT?

Phenotypes
Categories of people with specific CYP450 variants (polymorphisms)

- **Effective Metabolizer (EM):**
  - Normal Genetics
    - Two Good Copies of the genetic code required for metabolism

- **Intermediate Metabolizer (IM):**
  - Reduced enzymatic activity
    - 1 Good Copy and 1 Bad Copy of code required for metabolism
    - May render the drug a No Go or require a dose adjustment

- **Poor Metabolizer (PM):**
  - Complete lack of enzymatic activity
    - 2 Bad Copies code required for metabolism
    - Usually renders a drug a No Go

- **Ultra Rapid Metabolizer (UM):**
  - Higher than average enzymatic activity
    - 2 Bad Copies causing much higher than normal metabolism
    - May render the drug a No Go or require a dose adjustment

Phenotypes
Categories of people with specific CYP450 variants (polymorphisms)

Incidence of Variants in the Population

<table>
<thead>
<tr>
<th>Gene</th>
<th>EM</th>
<th>IM</th>
<th>PM</th>
<th>UM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>53%</td>
<td>35%</td>
<td>10%</td>
<td>2%</td>
<td>47%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>36%</td>
<td>12%</td>
<td>4%</td>
<td>28%</td>
<td>64%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>57%</td>
<td>40%</td>
<td>3%</td>
<td>NA</td>
<td>43%</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>87%</td>
<td>12%</td>
<td>1%</td>
<td>NA</td>
<td>13%</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>1%</td>
<td>18%</td>
<td>81%</td>
<td>NA</td>
<td>99%</td>
</tr>
</tbody>
</table>

Are variants rare or common?

1. Pharmacogenetics Knowledge Base Implementation: www.pharmgkb.org
Examples

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Metabolic Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen**</td>
<td>Acetaminophen</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Carisoprodol**</td>
<td>Soma</td>
<td>CYP3A4/CYP3A5</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol</td>
<td>CYP3A4/CYP3A5</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Voltaren</td>
<td>CYP2C9/CYP3A4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac</td>
<td>SERT inhibition</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Cipla</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Hydrocodone**</td>
<td>Hydrocodone</td>
<td>CYP2C9/CYP3A4</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Sombратol</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Lithium</td>
<td>Lithobid</td>
<td>CYP2C9/CYP3A4</td>
</tr>
<tr>
<td>Metformin</td>
<td>Novo</td>
<td>CYP2C9/CYP3A4</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Ibesone</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Omeprazole**</td>
<td>GastroStat</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Benicar</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Oxybutynin**</td>
<td>Ditropan</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Oxycodone**</td>
<td>OxyContin</td>
<td>CYP2C19/CYP3A4</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Benicar</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Timolol</td>
<td>Timoptic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Zemurc</td>
<td>CYP2C9</td>
</tr>
</tbody>
</table>

The Need for Pharmacogenetic Testing

- There can be wide variability in patient response to commonly prescribed medications:
  - Medication achieves goal and does not harm patient
  - Medication achieves goal, however, also causes an Adverse Drug Reaction
  - Medication does not achieve goal and causes an Adverse Drug Reaction
  - Medication does not achieve goal and does not cause Adverse Drug Reaction
- Genetics is estimated to account for 20-95% of the variability in drug effects

Genetic Variability (1998;8:283-289)

Individualized Therapy

All patients with same diagnosis (not all respond to therapy)

- Maybe just right (no such thing as a curemone dose)
- Treat with conventional dose

Genetic variability

Sub-therapeutic (insufficient response)
Simplistic Approach

Each person receives either a GOOD or BAD Genotype from both Mother and Father.

**Effective Metabolizer** – Received **TWO GOOD**

**Intermediate Metabolizer** – Received **ONE BAD ONE GOOD**

**Poor Metabolizer** – Received **TWO BAD**

**Ultra Rapid Metabolizer** – Received **TWO BAD**

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Adverse Drug Reactions

~60% of meds in top 20 list causing ADRs are linked to a genetic variation

122 drugs have FDA box warnings related to genetics

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Gene Variances

These Genes are responsible for the metabolism of approximately 85% of medications

<table>
<thead>
<tr>
<th>Gene</th>
<th>% of Effective Metabolizers</th>
<th>% of Intermediate Metabolizers</th>
<th>% of Poor Metabolizers</th>
<th>% of Ultra Rapid Metabolizers</th>
<th>VARIANTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D6</td>
<td>53</td>
<td>35</td>
<td>10</td>
<td>2</td>
<td>47%</td>
</tr>
<tr>
<td>2C19</td>
<td>36</td>
<td>32</td>
<td>4</td>
<td>28</td>
<td>64%</td>
</tr>
<tr>
<td>2C9</td>
<td>57</td>
<td>40</td>
<td>3</td>
<td>NA</td>
<td>43%</td>
</tr>
</tbody>
</table>
Pain Management

CYP2D6

- Cost of healthcare for chronic pain patients exceeds cost of treating patients with coronary artery disease, cancer and AIDS.
- **Opioid Medications**
  - 120M prescriptions for hydrocodone and oxycodone alone
  - Opioid poisoning accounts for more fatalities than either heroin or cocaine
  - Response rate of only 50% to 60% partly due to genetic variances in patients
  - Increased regulatory oversight

<table>
<thead>
<tr>
<th>Clinical Fact</th>
<th>Economic Implication</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to opioids can vary as much as 40-fold among patients. Blood concentrations of opioids does not predict analgesia. Pain medications are involved in 30% of all adverse drug events involve pain medications.</td>
<td>Adverse drug events cost an average of $5,189 per hospital day. Patients with adverse drug events average 8-12 additional hospital days at cost of $16,000 to $24,000</td>
<td>2,3,4</td>
</tr>
<tr>
<td>80% of patients reporting adverse drug reactions had impaired 2D6 metabolism</td>
<td>Adverse drug events cost an average of $5,189 per hospital day. Patients with adverse drug events average 8-12 additional hospital days at cost of $16,000 to $24,000</td>
<td>2,3,4</td>
</tr>
<tr>
<td>5% of patients taking oral opioids experience at least one adverse event or adverse effect.</td>
<td>Adverse drug events cost an average of $5,189 per hospital day. Patients with adverse drug events average 8-12 additional hospital days at cost of $16,000 to $24,000</td>
<td>2,3,4</td>
</tr>
<tr>
<td>20% of preventable adverse drug events were associated with analgesics.</td>
<td>Increased length of stay by 2.3 days and costs by $5,368</td>
<td>5</td>
</tr>
</tbody>
</table>

References
1. Relationship between the measurement of pain using visual score analog and morphine requirements during postoperative intravenous morphine therapy. Anesthesiology 2003;98(6):1415-1421.

Behavioral Health

CYP2C19, SULT4A1

- 23 Million Americans taking Behavioral Health medications
- 253.6 million prescriptions in 2010

- **Anxiety/Depression**
  - 63% of patients fail to achieve remission on first line SSRI therapy
  - 16.35% withdraw due to drug intolerance

- **Schizophrenia**
  - 65,000 hospitalizations for schizophrenia and related disorders
  - Average length of stay is 7.1 days
  - Treating SULT4A1 positive Caucasian patients with olanzapine or quetiapine reduced the risk of hospitalization by over 80%.
## Treatment Resistant Depression

<table>
<thead>
<tr>
<th>Clinical Facts</th>
<th>Economic Implications</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRD occurs in 10% to 15% of patients with diagnosis of depression</td>
<td>TRD increases medical costs: $6,852 annually versus $31,980 annually</td>
<td>3</td>
</tr>
<tr>
<td>TRD patients are 90% more likely to be hospitalized</td>
<td>TRD hospitalisation increases medical costs: $6,512 annually versus $42,344 annually</td>
<td>2</td>
</tr>
<tr>
<td>Patients with depression diagnosis and P450 identified variants have 50% greater health care visits and 4 times greater disability claims</td>
<td>Depression diagnosis with P450 identified variants increased medical costs: $5,188 higher than patients with depression diagnosis and no P450 identified variants</td>
<td>3</td>
</tr>
</tbody>
</table>

### References
3. A retrospective study of healthcare utilization that could have been avoided through P450 Pharmacogenomics predicts health insurance utilization of outpatients with anxiety and depression. Med Psychiatry 2005;2:160.

## Psychosis

<table>
<thead>
<tr>
<th>Clinical Fact</th>
<th>Economic Implication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia patients have a 30% to 50% probability of readmission following initial hospitalisation.</td>
<td>Rehospitalization patients: 28% or twice the medical costs compared to patients not requiring rehospitalisation</td>
<td>1</td>
</tr>
<tr>
<td>SUL7 negative patient taking clozapine have 65% relapse vs 11% SUL7 positive.</td>
<td>$7,786 in recent relapse versus $38,134 to $31,549 if recent relapse</td>
<td>1</td>
</tr>
<tr>
<td>SUL7 negative patient taking clozapine have 58% relapse vs 52% SUL7 positive.</td>
<td>$2,596 in recent relapse versus $38,134 to $31,549 if recent relapse</td>
<td>1</td>
</tr>
<tr>
<td>74% of patients stop taking their prescribed antipsychotic medication at 3 months due to lack of efficacy or ability to tolerate the medication</td>
<td>Cost to treat relapse is $38,561</td>
<td>2,3</td>
</tr>
</tbody>
</table>

### References
1. Impact of SULT on hospitalization for psychotic disorder. Lu et al. Prim Care Comp 2012;14(3) and Ascher et al. JAMA 2010;303:2.

## Practice Model

The Practice Model of Personalized Medicine involves understanding a patient's unique genetic coding, environment characteristics, physical characteristics, and unique patient characteristics to develop personalized medications that cater to the patient's specific needs. This approach enhances efficacy and safety in treatment while reducing costs associated with ineffective medications.
Typical Agency Hospice Pain Management

- Pain is part of the hospice process
- Standard Pain Management for All patients unless contraindicated by terminal diagnosis
- Change and dosage adjustments as pain is uncontrolled
- Family Concern with comfort
- Patients unable to report pain levels

Hospice Pain in hospice patients is inevitable.

- Prescription cost associated with pain medications that need adjusted and changed is potentially avoided with pharmacogenetics.
- As pain medication doses are increased higher risk for injuries such as falls associated with decreased awareness,
- Dosing patients accurately for the most effective pain management decreases this risk for patients with genetic variances.

Same Diagnosis - Same Medications: Different Outcomes

Current Data Results

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of cases in which results indicated change in medication selection</td>
<td>73.8%</td>
</tr>
<tr>
<td>% of cases in which results indicated change in medication dosage</td>
<td>53.1%</td>
</tr>
<tr>
<td>Average savings of Medications Discontinued</td>
<td>$317.13</td>
</tr>
<tr>
<td>Average Savings of Medications that were changed</td>
<td>$314.40</td>
</tr>
<tr>
<td>% of cases in which patient/family felt as though test was beneficial</td>
<td>97.5%</td>
</tr>
<tr>
<td>% of cases in which physician felt as though test was beneficial for patient</td>
<td>96.9%</td>
</tr>
</tbody>
</table>
Testing

Non-Invasive Buccal Swab
Results Available within 5-7 Days
Lifetime Test – Your Genetics Remain The Same
Variance Can Identify Possible Variance in family

Results

Drugs with Consensus Recommendations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Phenotype</th>
<th>Drug</th>
<th>Consensus Based Action Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Intermediate Metabolizer ≤ 2% of the population</td>
<td>Dosage / Avoid</td>
<td>Avoid / Dosage Adjustment</td>
</tr>
<tr>
<td></td>
<td>Poor Metabolizer ≤ 0.1% of the population</td>
<td>Dosage / Avoid</td>
<td>Avoid / Dosage Adjustment</td>
</tr>
<tr>
<td></td>
<td>Ultra rapid Metabolizer ≥ 10% of the population</td>
<td>Dosage / Avoid</td>
<td>Avoid / Dosage Adjustment</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Therapeutic Implications (adapted from published resources)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Avoid</td>
</tr>
<tr>
<td></td>
<td>Codeine**</td>
</tr>
<tr>
<td></td>
<td>Tramadol**</td>
</tr>
<tr>
<td></td>
<td>Amphetamine</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
</tr>
<tr>
<td></td>
<td>Benzphetamine</td>
</tr>
</tbody>
</table>
Top Three Tested Panels

- Pain Management
- Behavioral Health
- Cardiac

Medical Necessity

Clinical Algorithm Examples

Treatment Resistant Depression:
- Diagnosis of Treatment Resistant Depression
- Taking more than 1 depression and/or anxiety medication

Bipolar-Schizophrenia:
- Diagnosed as “uncontrolled”
- Hospital Admission within past 6 months

Taking any of the following medications:
- Taking 2 or more of following medications: venlafaxine, risperidone, amitriptyline, mirtazapine, nortriptyline, zuclopenthixol, doxepin, aripiprazole, clomipramine, haloperidol, zuclopenthixol, paroxetine, atomoxetine, sertraline, citalopram, citalopram, phenytoin, olanzapine, ziprasidone, quetiapine
What is Pharmacogenetics?
The study of how our genes affect our response to drugs

What is Pharmacokinetics? Pharmacodynamics?
What the body does to a drug / What a drug does to the body

How Many Phenotypes are there?
Effective, Intermediate, Poor, Ultra

Explain Pharmacogenetic Testing
Does Insurance Cover Pharmacogenetic Testing?
Yes with Medical Necessity

What are the Top three Panels?
Cardiac, Pain, Behavioral

Is Pharmacogenetics the answer to all?
No it is a tool to supplement current medical practices

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Questions / Answers

For further information, please feel free to contact me directly:

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