Pharmacogenomics and Pain Management

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Pharmacogenomics

- Pharmacogenomics is the study of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup.
Genes and Drugs
• How do we know if a patient will respond to a drug?

• What are the response rates for different classes of drugs?

• How are doses determined?

• Why does drug response vary?

• Genetic variation
  • What is it?
  • How do you measure it?
  • How extensive is it?
  • Pharmacogenomics: genetic variation and drug response

• Examples
  • Gefitinib
  • Warfarin

• Pharmacogenomics - costs and benefits
How do we know if a patient will respond (or have an adverse response) to a drug?

(we don’t)
• How do we know if a patient will respond to a drug?

• **What are the response rates for different classes of drugs?**

• How are doses determined?

• Why does drug response vary?

• Genetic variation
  • What is it?
  • How do you measure it?
  • How extensive is it?
  • Pharmacogenomics: genetic variation and drug response

• Examples
  • Gefitinib
  • Warfarin

• Pharmacogenomics - costs and benefits
Pharmacokinetics
The principles of ADME

Absorption
How will it get in?

Metabolism
How is it broken down?

Distribution
Where will it go?

Excretion
How does it leave?

Liver

Medicine

Transporters
Dose determination

- Phase I clinical trials (safety)
  - 20 to 80 healthy volunteers
  - Determine max tolerable dose

- Phase II clinical trials (efficacy)
  - Several hundred patients
  - Estimate therapeutic dose range

- Drugs approved with a specific indication and dose range
Dose determination

• Phase III monitoring.

• Dose that patients actually receive depends on...
  • Prior treatment history of patient (drug naïve?)
  • Physicians experience with prescribing drug
  • Empirical knowledge of appropriate dose
  • In practice – start low, ramp to ~80% of recommended dose before trying different drug
  • Liability issues

• No clinical trials are done to study dose escalation

• Therapeutic drug monitoring
Potential causes of variability in drug effects:

• Pathogenesis and the severity of the disease being treated.

• Drug interactions from concomitant treatments (plasma protein binding, metabolism)

• Individual’s age, gender, lifestyle (including environmental factors), behavior, nutritional state, renal and liver function, and concomitant illnesses.

• Genetic variation
A patient’s response to a drug may depend on factors that can vary according to the alleles that an individual carries, including:

**Pharmacokinetic factors**
- Absorption
- Distribution
- Metabolism
- Elimination

**Pharmacodynamic factors**
- Target proteins
- Downstream messengers
Phase I metabolism (oxidation by CYP450s)

Over 1000 CYP450 enzymes identified (50 active enzymes in human). Expressed mainly in liver.

Multiple alleles with different frequencies in different ethnic groups

P450 enzymes oxidize drugs or other xenobiotics in order to:

1. increase polarity, and enhance excretion (decrease resorption in distal nephron)
2. convert to substrate for phase2 metabolism

\[
RH + O_2 + NADPH + H^+ \xrightarrow{CYP450} ROH + H_2O + NADP^+ 
\]
CYP3A4
- most important (50%)
- inducible

CYP2D6
- next in line (20%)
- not inducible

CYP2C9 and 2C19
- next (15%)
- inducible

* Functional allelic variants. There are 70 identified functional variants of CYP2D6 alone
Phase II metabolism (conjugation)

Substrate is phase I reaction product, or other endogenous compound (e.g. steroid hormones)

Conjugation of highly polar glucuronide enhances water solubility/decreases lipid solubility and thereby promotes excretion

Fewer genes and functional variants than P450s
EM = extensive metabolizers
PM = poor metabolizers

Distribution of metabolic efficiency

Metabolic ratio = [parent]/[metabolite]
Variation in the genome most relevant to pharmacogenomics:

- Insertions/deletions (small and large)
- Single nucleotide polymorphisms (SNPs)
Copy Number Polymorphisms in Human Genome

- gains
- losses

- 39 healthy unrelated individuals
- 255 loci
- 24 variants present in >10% of individuals

SNPs are the most commonly occurring genetic differences

ACGCCTTGACGAAGCTTAC
ACGCCTTGACGATGCTTAC

SNPs are single base pair positions in genomic DNA at which different sequence alternatives (alleles) exist wherein the least frequent allele has an abundance of 1% or greater.
SNPs are estimated to occur throughout the genome at a rate of between 3 and 6 per 1000 base pairs

- Any individual selected at random contains ~25% of human variation
- ~90% of snps in any given individual are present in pop’n at large
- There are expected to be a total of 10-20M SNPs in human population
Biochemistry of SNP Genotyping

- **5’-T**
- **5’-C**

Ligase

- **5’-T** Match, ligation
- **5’-G** Mismatch, no ligation

- **5’-A**
- **5’-T** Allele-specific oligonucleotide probes

Match stable

- **5’-G**

Mismatch unstable

- **5’-A**
- **5’-T** A/G SNP

Minisequencing primer

- **5’-A** Single nucleotide extension
- **5’-G** No extension

Restriction enzyme

- **5’-A** Cleavage
- **5’-T**
- **5’-G** No cleavage
Pharmacogenomics

• Also known as pharmacogenomics testing, allows physicians to determine a patient’s genetic make-up and how that will affect an interaction with a specific medication.

• No longer a need to experiment with different medications and dosages for a patient. Greatly reduces the chances of adverse drug reactions.
Manipulating Therapeutic Outcomes

Patient population with same disease phenotype

Genotyping

Patients carrying markers for drug toxicity or non-response

Patients carrying markers for "normal" response to drug therapy
TOXICOLOGY TESTING

Toxicology testing reduces medical practice liabilities for physicians as they can accurately determine what is in a patient’s body and how that can affect any prescriptions. Physicians can monitor patients who have a history of addiction or drug abuse while these patients are on Schedule II or III prescriptions. Toxicology testing is an accurate way to determine which medications or illicit drugs a patient is or isn’t taking.
POLYPHARMACY TESTING

Polypharmacy has become a major problem in the nation as it has climbed to the fourth leading cause of death in the country.
Pharmacogenetic Comprehensive Report Created for: PATRICIA ISHERWOOD

Current Patient Medications

**Current Medications List:**
- Bupropion, Fluoxetine, Aurosemis, Levodopa, Tetrabenazine, Tramadol

Medications Affected by Patient Genetic Results

| Condition | Medication | Genotypic Test Results | Genotypic Test Results for...
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<thead>
<tr>
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<td>N/A</td>
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Genotoxic Test Results

**Genotoxic Test Results for:**
- N/A

Version: Mar 01, 2018

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<tr>
<th>Category</th>
<th>Standard Prophylaxis</th>
<th>Use With Caution</th>
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<tr>
<td><strong>Alpha-Blockers for Benign Prostatic...</strong></td>
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<tr>
<td><strong>Angiotensin II Receptor Antagonists</strong></td>
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<td><strong>Antidepressives</strong></td>
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<td><strong>Anti-ADHD Agents</strong></td>
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<td><strong>Antihypertensives</strong></td>
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<tr>
<td><strong>Anticoagulants</strong></td>
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</table>

- **Potentially Impacted Medications**
  - **Alpha-Blockers for Benign Prostatic...**
    - Alfuzosin (Uroxatral)
    - Doxazosin (Cardura)
    - Silodosin (Rapotof)
    - Tamsulosin (Hallow)
    - Tamsulosin (Himali)
  - **Angiotensin II Receptor Antagonists**
    - Amlodipine (Efadil, Edarbyclon)
    - Candesartan (Atacand)
    - Lisinopril (Fixamin)
    - Iloprost (Adempas)
    - Lesartan (Cozaar, Hyzaar)
    - Lisinopril (Miconic)
    - Telmisartan (Micardis)
    - Valsartan (Diovan, Entresto)
  - **Antidepressives**
    - Nefazodone (Serzone, Interven)
  - **Anti-ADHD Agents**
    - Atomoxetine (Strattera)
    - Duloxetine (Cymbalet)
    - Guanfacine (Intuniv)
  - **Antianginal Agents**
    - Ranolazine (Ranexa)
  - **Antihypertensives**
    - Flecainide (Tamboor)
    - Methadone (Methadone)
    - Propafenone (Rythmol)
  - **Anticoagulants**
    - Apixaban (Eliquis)
    - Dabigatran (Eliquis)
    - Edoxaban (Savaysa)
    - Fondaparinux (Arixtra)
    - Rivaroxaban (Xarelto)
    - Warfarin (Coumadin)
Hydrocodone (Vicodin)

- **Hydrocodone**: A specific drug name.
- **Vicodin**: Another specific drug name.

### Adverse Response to Hydrocodone

- **Drugs (AHP)**: A mention of another specific drug.
- **Other** (AHP): Another mention of another specific drug.

### Evidence Level: Important

- **Evidence Level**: A classification indicating the importance of the information.

### Possible Sensitivity to Methadone

- **Methadone**: A mention of another specific drug.

### Based on currently available evidence, M-methadone plasma concentrations may increase, resulting in higher risk of cardiac arrhythmias and QTc prolongation.

### Clinical Considerations

- **Clinical Considerations**: A section dedicated to clinical considerations.

### Methadone (Dolophine)

- **Methadone**: A mention of another specific drug.

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Opioids and Pharmacogenomics
Principles

1. Oral administration of analgesics
2. Dosing at regular intervals
3. Prescribe analgesics according to the intensity of the pain as evaluated by a scale of intensity
4. Dosing should be adapted to individual patients
5. Constant attention to detail and planning when prescribing analgesia
<table>
<thead>
<tr>
<th>Chronic pain medications (n. %)*</th>
<th>Overall (n=482)</th>
<th>USA (n=237)</th>
<th>Canada (n=35)</th>
<th>Germany (n=114)</th>
<th>UK (n=96)</th>
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<td>Altaloid</td>
<td>1 (0.2)</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.0)</td>
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<td>Anesthetic</td>
<td>15 (3.1)</td>
<td>5 (2.1)</td>
<td>0 (0.0)</td>
<td>3 (2.6)</td>
<td>7 (7.3)</td>
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<td>Anticonvulsant</td>
<td>112 (23.2)</td>
<td>39 (16.5)</td>
<td>9 (25.7)</td>
<td>38 (33.3)</td>
<td>26 (27.1)</td>
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<td>Antidepressant/SNRIs</td>
<td>52 (10.8)</td>
<td>10 (4.2)</td>
<td>4 (11.4)</td>
<td>20 (17.5)</td>
<td>18 (18.8)</td>
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<td>Barbiturate</td>
<td>1 (0.2)</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
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<td>Benzodiazepine</td>
<td>20 (4.1)</td>
<td>12 (5.1)</td>
<td>4 (11.4)</td>
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<td>Cannabidiol/cannabinoid</td>
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<td>Headache/migraine medication</td>
<td>32 (6.6)</td>
<td>8 (3.4)</td>
<td>1 (2.9)</td>
<td>1 (0.9)</td>
<td>22 (22.9)</td>
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<td>Muscle relaxant</td>
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<td>47 (19.8)</td>
<td>6 (17.1)</td>
<td>13 (11.4)</td>
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<td>NSAID</td>
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<td>3 (8.6)</td>
<td>23 (20.2)</td>
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<td>Opioid</td>
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<td>233 (98.3)</td>
<td>33 (94.3)</td>
<td>89 (78.1)</td>
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<td>Tricyclic antidepressant</td>
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<td>5 (2.1)</td>
<td>1 (2.9)</td>
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<td>Other pain medication</td>
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<td>12 (5.1)</td>
<td>0 (0.0)</td>
<td>30 (26.3)</td>
<td>17 (17.7)</td>
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<td>Most commonly used opioid medications (n. %)</td>
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<td>Codeine</td>
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<td>2 (5.7)</td>
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<td>Fentanyl</td>
<td>42 (8.7)</td>
<td>15 (6.3)</td>
<td>8 (22.9)</td>
<td>11 (9.6)</td>
<td>8 (8.3)</td>
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<td>Hydrocodone or dihydrocodeine</td>
<td>75 (15.6)</td>
<td>69 (29.1)</td>
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<td>6 (6.3)</td>
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<td>Hydromorphone</td>
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<td>6 (2.5)</td>
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<td>76 (15.8)</td>
<td>36 (15.2)</td>
<td>4 (11.4)</td>
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<td>Oxycodone</td>
<td>201 (41.7)</td>
<td>134 (56.5)</td>
<td>22 (62.9)</td>
<td>31 (27.2)</td>
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<td>Tramadol</td>
<td>72 (14.9)</td>
<td>19 (8.0)</td>
<td>3 (8.6)</td>
<td>5 (4.4)</td>
<td>45 (46.9)</td>
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<tr>
<td>Other opioid</td>
<td>68 (14.1)</td>
<td>25 (10.5)</td>
<td>2 (5.7)</td>
<td>32 (28.1)</td>
<td>9 (9.4)</td>
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<td>Comorbid conditions (n. %)</td>
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<td>Hypertension</td>
<td>133 (27.6)</td>
<td>62 (26.2)</td>
<td>11 (31.4)</td>
<td>34 (29.8)</td>
<td>26 (27.1)</td>
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<td>Depression</td>
<td>79 (16.4)</td>
<td>30 (12.7)</td>
<td>6 (17.1)</td>
<td>16 (14.0)</td>
<td>27 (28.1)</td>
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<tr>
<td>Anxiety</td>
<td>56 (11.6)</td>
<td>31 (13.1)</td>
<td>7 (20.0)</td>
<td>4 (3.5)</td>
<td>14 (14.6)</td>
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<td>Diabetes mellitus</td>
<td>48 (10.0)</td>
<td>24 (10.1)</td>
<td>5 (14.3)</td>
<td>9 (7.9)</td>
<td>10 (10.4)</td>
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<td>Hypothyroidism</td>
<td>32 (6.6)</td>
<td>11 (4.6)</td>
<td>4 (11.4)</td>
<td>7 (6.1)</td>
<td>10 (10.4)</td>
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<tr>
<td>Coronary artery disease</td>
<td>18 (3.7)</td>
<td>5 (2.1)</td>
<td>3 (8.6)</td>
<td>6 (5.3)</td>
<td>4 (4.2)</td>
</tr>
</tbody>
</table>
Warfarin (Coumadin)
Warfarin

- Anticoagulant of choice in North America for cardiovascular disease, thromboembolic disease, and prophylactic post-surgery application

**Mechanism**
- Activation of coagulation factors II, VII, IX and X by carboxylation requires vitamin K
- VitK generated by VitK-epoxide-reductase.
- Warfarin (and other oral anticoagulants) inhibits this enzyme complex.

- 15th most prescribed drug and 1st in category of accidents and adverse reactions (bleeding)

- Very narrow therapeutic index and individualized dosing mandatory. Effective daily dose 0.5 to 80mg

- Dosing determined by patient history and physical exam, in conjunction with INR (international normalization ratio. In-vitro clotting time versus standard reference)
Warfarin

• genetic factors influencing warfarin response unknown.

• genetic data may help determining correct dose and preventing adverse reactions

• present study: type 14 genes in 1000+ patients and associate variants with warfarin response

Figure 2: Warfarin's Therapeutic Pathway (TDP). PL = platelets or phospholipids; TF = tissue factor; t-PA = tissue plasminogen activator. The lower case “p” indicates inactive “pro” form of the coagulation factors that have not yet been converted to the γ-carboxylated form that can bind calcium. The lower case “a” indicates coagulation factors that have been activated through binding of calcium to the γ-carboxylated glutamic acid residues at the C-terminus of the protein. The fourteen proteins under investigation in this pharmacogenetic study are circled and in bold font.
Summary
Pharmacogenomic Testing Can be used in:

1. Opioid Addiction
2. Genetic mapping
3. Organ-transplant patients
4. Ethnic background
Set up is Easy

1. No Cost to Patient or Physician
2. Covered by Most Insurances
3. Open Portal for Drug Evaluation and Comparison with Drug dosing Recommendations based on pharmacogenomics
4. Access to top Toxicologists in the Field