Pharmacogenetic Testing for Precision Medicine: The Future is Now

Angela Solis, RPh, Clinical Pharmacist
Martin’s Compounding and Wellness Pharmacies
Dripping Springs, TX
DISCLOSURES

“I declare that I have no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”

The American College of Apothecaries is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

At the conclusion of this program, the participating pharmacist or technician will be able to:

– Objective #1: Demonstrate how genetic information can predict how a patient may respond to drugs.
– Objective #2: Describe how pharmacogenetics affect drug clearance, efficacy, and toxicity.
– Objective #3: Identify patient groups with greatest potential benefit for pharmacogenetic testing
– Objective #4: Characterize the relevance of drug-drug and drug-gene interactions.
Predictive Pharmacogenetics

We are at an evolutionary moment of the human species.
Now, for the first time in history…

• We can predict with increasing precision who is more likely to develop specific diseases.
• We can predict who will respond positively, or negatively, to a particular drug or supplement therapy.
• We can predict which drugs or nutrients are optimal for a specific individual’s treatment, health, and well-being.
What is DNA?

- DNA is a molecule that encodes the genetic instructions used in the development and functioning of all known living organisms.
- In other words: The blueprint of every living organism.
What is a SNP?

• To make new cells, an existing cell divides in two. But first it copies its DNA so the new cells will each have a complete set of genetic instructions.

• Cells sometimes make mistakes during the copying process. These lead to variations in the DNA sequence at particular locations, called **single nucleotide polymorphisms**, or SNPs (pronounced "snips").
What are the consequences of SNPs?

- SNPs can generate biological variation between people by causing differences in the recipes for proteins that are written in genes.
- Those differences can in turn influence a variety of traits such as appearance, disease susceptibility or response to drugs.
- While some SNPs lead to differences in health or physical appearance, most SNPs seem to lead to no observable differences between people at all.
DNA is passed from parent to child, so SNPs may come from parents

Homozygous means the same and Heterozygous means different

• A homozygous organism for a particular trait is described to possess either a pair of dominant alleles (e.g. AA)

• or a pair of recessive alleles (e.g. aa)

• Heterozygous organism for a particular trait is described to possess one dominant allele and one recessive allele. (e.g. Aa)
What Is Genomics?

• The study of all of the nucleotide sequencing in the chromosomes of an organism.

• Experts in genomics strive to determine complete DNA sequences and perform genetic mapping to help understand disease.

• Knowledge about genes has led to the emergence of functional genomics, a field concerned with trying to understand the pattern of gene expression.
Genetics & Pharmaceuticals

- 50% of all medications prescribed are processed by genetic-specific enzymes
- More than 75% of the population have genetic variations (SNPs) that increase their risk for ADRs (Adverse Drug Reactions)
Pharmacogenetic Variances

- Medicines most commonly associated with ADRs are 8 times more likely to undergo metabolic pathways which have genetic variance
- Polypharmacy exacerbates the phenomenon
  - 40% of individuals over age 65 take 5 or more medications
Fourth Leading Cause of Death in U.S.

- 2.2 MILLION severe adverse drug reactions per year
- 180,000 deaths per year caused by prescribed drugs
- $3.5 billion annually in extra medical costs due to ADRs
- COST LEADER for malpractice payouts
- AVOIDABLE medical problem!

Sources: U.S. CDC and JAMA
Precision Medicine

Supporting the cracks (SNPs) in the genetic foundation using targeted prescribing based on pharmacogenetics can dramatically increase a patient’s outcomes.
Genetics affect drug clearance
Range of response from non-response to toxicity

Drug Serum Levels

Days

Drug
Serum
Levels

© 2015 American College of Apothecaries.
Medication Dosing

Advertised Dose Without Genetics

Proper Dose With Pharmacogenetics

© 2015 American College of Apothecaries.
Cytochrome P450’s are drug-metabolizing enzymes

- Major drug metabolizers: 2D6, 2C9, 2C19, 3A4/5
- Minor drug metabolizers: 2B6, 1A2, 2A6, 2C8, 2E1
- Location: Hepatocytes, Intestinal lumen, Blood brain barrier, Placenta, etc.
Representative Drug-Gene Interactions Identified by FDA in Package Inserts

<table>
<thead>
<tr>
<th>CYP 2D6</th>
<th>CYP 2C9</th>
<th>CYP 2C19</th>
<th>CYP 3A4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>Warfarin</td>
<td>Clopidogrel</td>
<td>Select Benzodiazepines</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Phenytoin &amp; Valproic Acid</td>
<td>Carisoprodol</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>SSRIs &amp; TCAs</td>
<td>Fluoxetine</td>
<td>Diazepam</td>
<td>Cyclosporine &amp; Tacrolimus</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Sulfonylureas</td>
<td>Proton pump inhibitors</td>
<td>Statins</td>
</tr>
<tr>
<td>Opioids</td>
<td>NSAIDs</td>
<td>SSRIs &amp; TCAs</td>
<td>Oral Contraceptives</td>
</tr>
</tbody>
</table>
Drug Metabolism Phenotypes

- Poor Metabolizers
  2D6 5.1%  2C9 3.4%  2C19 2.3%
- Intermediate Metabolizers
  2D6 36%  2C9 28.2%  2C19 25.4%  3A4 9.4%
- Normal Metabolizers
  • <15% normal for all 3 major enzymes
- Ultra Rapid Metabolizers
  2D6 3.5%  2C19 27.7%  3A5 20.8%

*Based on data on 13,000 patients in U.S. population. Frequencies may vary based on ethnicity.
Clinical Relevance in Prescribing

- Active patient sample
  - Research by Dr. David Durham, Neuropsychiatrist, Clinical Assistant Professor of Psychiatry, Univ. New Mexico School of Medicine
- Total Patients Evaluated: 296
- Testing revealed 101 previously unknown, significant interaction risks in 82 patients (27.7%)
Anticoagulant Study

- Bleeding risk study
  - Revealed importance of gene variant testing in patients prescribed all anti-coagulants
Lab Pharmacogenetic Testing Now Available to Physicians/Patients

- DNA Collection: Saliva Testing
- Available in select MD offices and pharmacies
- Simple procedure
- Results available quickly
- Interpretation necessary
- Growing awareness and demand
- Costs
- Challenges

© 2015 American College of Apothecaries.
Testing Process in Practice Setting

- Doctor writes order for lab test
- Testing available in select pharmacies and MD practices
- Simple procedure: Buccal swab
- Swab and a medication list sent to the lab.
- Lab results may be downloaded into system software or sent as hardcopy.
- Pharmacist or prescriber review; provide summary report of interactions to provider and meet with patient.
Advanced medication management software is available

- Comprehensive drug-gene and drug-drug interaction software
- Incorporates herbals, OTCs, and recreational drugs
- Genotype-based drug and dosage recommendations
- Software is an effective option to factor multi-drug effects and cumulative effects of drug-gene and drug-drug interactions
Case Study #1

Clopidogrel/Fluoxetine patient

- Intermediate metabolizer of CYP2C19 and CYP2D6
- Resulted in non-response to clopidogrel AND adverse effects caused by fluoxetine
Case Study #2

Chronic pain management patient – exhibiting treatment failure

- Poor metabolizer of CYP2D6
- Hydrocodone was not being metabolized to active form, thus non-response
Case Study #3

Pediatric ADHD patient

- Poor metabolizer of 2D6; unknown at the time
- Resulted in seizures caused by amphetamine mixed salts; med had to be changed to methylphenidate
Case Study #4

Tramadol dosed in 5 year old child post-tonsillectomy

- Resulted in adverse response which progressed to coma
  - Response reversed with use of naloxone
- Genotype testing found him to be ultra rapid metabolizer, so tramadol was quickly metabolized to its more potent active metabolite
Case Study #5

Confusion and Alzheimer’s-like symptoms in 78 year old patient

- Genetic testing shows CYP296 Poor Metabolizer
- Drug list includes chlorpheniramine, a major 2D6 substrate
  - Study shows 200% increase in poor metabolizers (Yasuda et al, Br J Clin Pharmacol 53, 519-525, 2002)
- Advised patient to stop chlorpheniramine and discussed alternatives
- Patient called after 3 days to notify that she could think clearly again and feels that she has been in a drug-induced haze
Frequently Asked Questions

- Discrimination based on results?
  - The Genetic Information Nondiscrimination Act (GINA) is U.S. federal legislation that protects Americans from discrimination (in health insurance and employment decisions) on the basis of genetic information.

- Frequency of Testing?
  Permanent lifetime results
Insurance Coverage for Genetic Testing

- Medicare Part B (only for certain diagnoses/drugs)
- Medicare Advantage Plans (only for certain diagnoses with patient Co-Pay)
- Some state Medicaid programs cover
- Some Private Pay Insurance covers; other do not cover yet. Prior authorizations may be necessary.
New Medicare Coverage Guidelines

- CYP2C19 gene variant testing for patients with acute coronary syndromes undergoing percutaneous coronary intervention treatment who are starting, or restarting, clopidogrel (Plavix).

- CYP2D6 gene variant testing in patients with major depressive disorder taking amitriptyline or nortriptyline.

- CYP2D6 testing for patients taking or restarting tetrabenazine doses greater than 50 mg/day
Need More Information?

Angela Solis, RPh
Martin’s Compounding and Wellness Pharmacy at Dripping Springs
100 Commons Rd, Suite 1
Dripping Springs, Tx 78620
angela@cpdwellness.com