Pharmacogenomics - Moving from the Paradigm of ‘Typical’ to ‘Individual’ in Your Practice

Bethany Reed, RN, MSN
DISCLOSURES

• There has been no commercial support or sponsorship for this program.
• The planners and presenters have declared that no conflicts of interest exist.
• The program co-sponsors do not endorse any products in conjunction with any educational activity.
Boston College Connell School of Nursing Continuing Education Program is accredited as a provider of continuing nursing education by the American Nurses Association Massachusetts, an accredited approver by the American Nurses Credentialing Center’s Commission on Accreditation.
SESSION OBJECTIVES

• Identify more accurately and predict how patients will benefit most from certain classes of medications.
• Discuss how pharmacogenomic directed prescribing reduces the incidence of adverse drug reactions and provides pharmacogenomic benefits to patients.
• Summarize clinical case studies demonstrating how pharmacogenomics is currently being utilized in the primary care healthcare setting.
PHARMACOGENOMICS

Moving from the Paradigm of ‘Typical’ to ‘Individual’
In Your Prescribing Practice
By
Bethany Reed, MSN, AGPCNP-BC
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“If it were not for the great variability among individuals, medicine might as well be a science and not an art.”

William Osler (1892)
OBJECTIVES

• Define pharmacogenomics and its history and future in healthcare
• Describe the goals of testing and the application of pharmacogenomics in the primary care setting
• Review evidence based research to support its use in prescribing practice
• Identify insurance coverage for testing
• Discuss case studies
• Identify impact of the future of provider practice
PHARMACOGENOMICS

• Studying the genetic basis for the difference between individuals in response to drugs.

• Enables personalized therapeutic decisions for patients suffering from some of the most prevalent clinical conditions—cardiovascular disease, neuropsychiatric disorders, pain.

• A healthcare tool for providers to assist in identifying optimal drugs for their patients as well as dosing guidelines based on patient’s genetic make-up, current prescriptions regimen, and other key factors.

• Enables healthcare providers to make timely and evidence based decisions, which can reduce overall cost of patient care by reducing adverse events, optimizing patient’s overall therapeutic regimen and helping to achieve a faster therapeutic response.
<table>
<thead>
<tr>
<th>Year</th>
<th>Individual(s)</th>
<th>Landmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>510 bc G6PD</td>
<td>Pythagoras</td>
<td>Recognition of the dangers of ingesting fava beans, later characterized to be due to deficiency of G6PD</td>
</tr>
<tr>
<td>1866</td>
<td>Mendel</td>
<td>Establishment of the rules of heredity</td>
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<tr>
<td>1906</td>
<td>Garrod</td>
<td>Publication of ‘<em>Inborn Errors of Metabolism</em>’</td>
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<tr>
<td>1932</td>
<td>Snyder</td>
<td>Characterization of the ‘phenylthiourea nontaster’ as an autosomal recessive trait</td>
</tr>
<tr>
<td>1932</td>
<td>Snyder et al.</td>
<td>Discovery of glucose-6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td>1956</td>
<td>Carson et al.</td>
<td>Discovery of glucose-6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td>1956</td>
<td>Caron et al.</td>
<td>Discovery of glucose-6-phosphate dehydrogenase deficiency</td>
</tr>
<tr>
<td>1956</td>
<td>Motulsky</td>
<td>Further refined the concept that inherited defects of metabolism may explain individual differences in drug response</td>
</tr>
<tr>
<td>1957</td>
<td>Kalow &amp; Genest</td>
<td>Characterization of serum cholinesterase deficiency</td>
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<tr>
<td>1957</td>
<td>Vogel</td>
<td>Coined the term pharmacogenetics</td>
</tr>
<tr>
<td>1960</td>
<td>Price Evans</td>
<td>Characterization of acetylator polymorphism</td>
</tr>
<tr>
<td>1962</td>
<td>Kalow</td>
<td>Publication of ‘Pharmacogenetics – Heredity and the Response to Drugs’</td>
</tr>
<tr>
<td>1977/79</td>
<td>Mahgoub et al. and Eichelbaum et al.</td>
<td>Discovery of the polymorphism in debrisoquine hydroxylase s partein oxidase</td>
</tr>
<tr>
<td>1988</td>
<td>Gonzalez et al.</td>
<td>Characterization of the genetic defect in debrisoquine hydroxylase, later termed CYP2D6</td>
</tr>
<tr>
<td>1988–2000</td>
<td>Various</td>
<td>Identification of specific polymorphisms in various phase I and phase II drug metabolizing enzymes, and latterly in drug transporters</td>
</tr>
<tr>
<td>2000</td>
<td>Public-private partnership</td>
<td>Completion of the first draft of the human genome</td>
</tr>
<tr>
<td>2000</td>
<td>The International SNP Map Working Group</td>
<td>Completion of map of human genome sequence variation containing 1.42 million SNPs</td>
</tr>
</tbody>
</table>
FUTURE APPLICATION

- [https://www.pharmgkb.org/page/cpic](https://www.pharmgkb.org/page/cpic)
- [http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm](http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm)

- Interfacing with EMR
- Inpatient application
- Advancing panel options
  - Drug selection for panels
ACADEMIC INSTITUTIONS, HOSPITALS, HEALTHCARE SYSTEMS, & OTHER RESEARCH INSTITUTES

- Baylor College of Medicine
- Cancer Treatment Centers of America
- Cedars-Sinai Medical Center
  - Cleveland Clinic
  - Dartmouth College
- Mayo Clinic College of Medicine
- Mount Sinai Medical School
  - Stanford University
- St. Jude Children’s Research Hospital
- The Johns Hopkins University School of Medicine
CPIC

- Clinical Pharmacogenetics Implementation Consortium
  - Formed in 2009
  - Guidelines are peer reviewed
  - Identify the one barrier to clinical implementation
  - Provides guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs
    - Guideline citations
    - Current list of genes/drugs of interest that are already, or will be, the subject of CPIIC guidelines
  - How to incorporate genomic data into routine clinical practice
  - Evidence based research
FDA

- Table of pharmacogenomic biomarkers in drug labeling
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype specific dosing
  - Mechanisms of drug action
  - Polymorphic drug target and disposition genes
- Presentations and Publications on Pharmagenomics
AMA

- Practical applications of pharmacogenomics today:
  - Cancer and pharmacogenomics
  - Statin therapy and cholesterol reduction
  - SSRI's
  - Cardiovascular risks
- Economics issues from molecule to marketplace:
  - Decrease in the cost of health care because of decreases in:
    - Number of adverse drug reactions
    - Number of failed drug trials
    - Time it takes to get a drug approved
    - Length of time patients are on medication
    - Number of medications patients must take to find an effective therapy
EVIDENCE BASED RESEARCH

IMPLICATIONS IN CLINICAL PRACTICE

• Trial and error—guide the dart
  • Estimate that genetics accounts for up to 95% of variability in drug disposition

• Adverse drug reactions
  • Polypharmacy—elders taking more than five or more prescription drugs

• Prescription drug use costs

• Improve clinical outcomes
  • Reducing total healthcare visits, medical visits, medical absence claims, disability claims

• Reduce overall cost of prescriptions drugs by enabling better drug selection

• Earlier favorable results
CLINICAL SETTINGS

• Long term and post acute care facilities
• Government facilities
• Managed care organizations
• Integrated Delivery System (IDN)
• Providers in multiple specialties
• Primary care providers well poised to utilize the technology
TESTING PROCESS

• Sample collection/requisition form including mediation list, insurance information
• Swab patient’s mouth/buccal epithelium
• Place swab in sterile collection tube
• Submit paperwork and sample to lab and receive report in 24-48 hours
• Reimbursement/billing for review of report with patient
BILLING AND CODING
INSURANCE COVERAGE
PHARMACOLOGICAL ACTIVITY GENOTYPING

• Determines how likely each medication is to produce its intended therapeutic effect.
  • Analyzes key genes that influence how effective important proteins will be at regulating the biological process targeted by medications.
  • The presence and degree of mutations known to occur in the genes that code for metabolizing enzymes, neurotransmitter proteins, transporter proteins can result in treatment failures or increased risk of serious or common adverse reactions.
CYTOCHROME P450 3A4 AND 3A5

Metabolized by CYP3A4 and 3A5

- Opioids—codeine, hydrocodone, oxycodone, fentanyl, buprenorphine, methadone
- Antidepressants—citalopram

CYP3A4 and 3A5 Inducers

- Antiseizure drugs—phenytoin, carbamazepine, phenobarbital
- Herbal supplements—St. John’s Wort

CYP3A4 and 3A5 Inhibitors

- Antibiotics—clarithromycin, erythromycin
- Calcium channel blockers—diltiazem, verapamil
- Antifungals—itraconazole, ketoconazole
- Other—grapefruit juice
### CYTOCHROME P450 2C9-VKORC1

#### Drugs Metabolized by CYP2C9
- Anticoagulants—warfarin
- Antidepressants—amitriptyline, fluoxetine
- NSAID’s—celecoxib, diclofenac, ibuprofen, naproxen, piroxicam, mobic, voltaren
- Oral hypoglycemic agents—glipizide, glimepiride, glyburide, avandia
- Miscellaneous—fluvastatin, rosuvastatin, sulfamethoxazole, tamoxifen, torsemide

#### CYP2C9 Inhibitors
- Antidepressants—sertraline, fluvoxamine
- Antiarrhythmic agent—amiodarone
- Statins—lovastatin, fluvastatin
- Antibacterial—sulfaphenazole, isonlazid

#### CYP2C9 Inducers
- Anticonvulsants—phenobarbital
- Barbiturates—secobarbital
- Antibacterials—rifampin
CYTOCHROME P450 2C19

**Drugs Metabolized by CYP 2C19**
- Anticoagulants—clopidogrel, warfarin, pleta
- Anticonvulsants—phenytoin, primidone
- Antidepressants—amitriptyline, citalopram, clomipramine
- PPI's—lansoprazole, omeprazole, pantoprazole
- Miscellaneous—progesterone, propranolol, warfarin
- Anti-anxiety drugs—diazepam

**CYP 2C19 Inhibitors**
- Antidepressants—fluoxetine, fluvoxamine
- Antifungals—ketoconazole
- PPI's—lansoprazole, omeprazole
- Antigout agents—probenecid
- Anti-inflammatory drugs—indomethacin

**CYP 2C19 Inducers**
- Anticonvulsants—carbamazepine
- Steroids—prednisone
- Antibacterials—rifampin
CYTOCHROME P450 2D6

Drugs Metabolized by CYP2D6

- Antidepressants—amitriptyline, amphetamine, clomipramine, duloxetine, fluoxetine, mirtazapine, nortriptyline, paroxetine, sertraline, venlafaxine
- Antipsychotic—haloperidol, perospiridone
- Beta Blockers—carvedilol, labetaolol, metoprolol, propranolol
- Anesthetics—lidocaine
- Antiemetics—metoclopramide, ondansetron, promethazine
- Opioids—codeine, oxycodone, methadone

CYP2D6 Inhibitors

- Antidepressants—bupropion, clomipramine, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline
- Antipsychotics—chlorpromazine, perazine, perphenazine, pimozide
- Antihistamines—hydroxyzine, ranitidine, diphenhydramine

CYP2D6 Inducers

- Corticosteroids—dexamethasone
OTHER USEFUL CONSIDERATIONS

**Factor II (Prothrombin)**
- Protein in the blood that is required for the blood to clot
- Circulates in bloodstream in an inactive form until an injury occurs that damages blood vessels

**Factor V Leiden (Thrombophilia)**
- Risk for developing abnormal blood clots
Apolipoprotein E (ApoE)

- Convert fats and cholesterol into forms for cellular transportation
- Assessment of cardiovascular disease risk
- ApoE genotype
  - 4—high risk
  - 2—increased risk
  - 3—normal risk
DRUG METABOLISM GENOTYPING
(METABOLIZER PHENOTYPING)

• Determines how much medication is available to produce the desired therapeutic effect of toxicity
  • Analyzes key genes that determine how well critical drug metabolizing enzymes function in each patient
    • Poor Metabolizer
    • Intermediate Metabolizer
    • Extensive Metabolizer
    • Ultra Rapid Metabolizer
PATIENT REPORT

• Genotyping results for key drug metabolism and pharmacological activity genes governing how patients may respond to each drug indicated to treat diagnosis medical condition

• Reports indicates which medications should be used as directed, used with caution, or avoided based on metabolic screening and phenotype
  • Poor Metabolizer
  • Intermediate Metabolizer
  • Extensive Metabolizer
  • Ultrarapid Metabolizer
POOR METABOLIZER

• Absent or low enzyme levels (increased effectiveness) when active drug metabolism inactivates drug
  • Active drug may accumulate
  • Require lower dose to avoid toxic accumulation
  • Wrong amount of pain medication can results in longer treatments
• Decreased effectiveness when prodrug requires metabolism to convert to active form of drug
  • Inactive prodrug may accumulate
  • May require lower dose to avoid toxic side effects if prodrug causes adverse effects, toxicity, or may require alternate drug
INTERMEDIATE METABOLIZER

- Reduced enzyme levels
  - May require reduced doses
  - May lead to drug-to-drug interactions with concomitant medications
EXTENSIVE METABOLIZER

- Normal enzyme levels
  - Confirms standard dose is appropriate for patient
ULTRA RAPID METABOLIZER

• Increased enzyme levels (decreased effectiveness) when active drug metabolism inactivates drug
  • Any active metabolites using this same enzymatic pathway could also be rapidly inactivated
  • Require higher dose to offset higher rate of metabolism
• Increased effectiveness when prodrug requires metabolism to convert to active form of drug
  • Rapid onset of effect
  • May require lower dose to prevent excessive accumulation of any active metabolite using this same metabolic pathway
ALGORITHMIC SCREENING

• Identifies key metabolic interactions that can alter which medications are optimal for each patient.

• Screen for metabolic interactions caused by concomitant prescription, OTC, & herbal medications that may significantly alter the metabolism of medications.
DEPRESSION & ANXIETY PANEL
EXTENSIVE PANEL
CASE STUDY
TESTING COMPANIES

- AltheaDx/IDgenetix
- PGX Laboratories
- Genelex
- AIBiotech
- PCLS
- ACLS
- Atherotech
- Emgenex
- CompanionDx
- Diatech
- Vantari
- DNAStat
- AssureRx/GeneSight
- Kailos Genetics
THANK YOU

Questions?
TACKLING THE FREQUENTLY ASKED QUESTIONS BY PROVIDERS

• What exactly are the procedures to follow if we want to have someone do the swab testing out of our offices?

• What insurance companies cover this test, and what companies need prior authorization, or won't cover at all?

• Can we ask for specific panels or does the insurance company determine that?
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Skype: malaproject
EVIDENCE BASED RESEARCH REFERENCES

• Cadule, KE., et. al. (2014). Incorporation of pharmacogenomics into routine clinical practice: the clinical pharmacogenetics implementation consortium (CPIC) guideline development process (15).


