Genetics 101 for Healthcare Providers

Key Principles in Pharmacogenomics

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Learning Objectives

At the conclusion of this presentation, you should be able to:

• Describe the basic principles and concepts in pharmacogenomics.

• Discuss the relevance of pharmacogenomics in medicine today.

• Discuss drivers and barriers of clinical implementation of pharmacogenomics.
Background / Introduction
Medical Practice Status Quo

• After diagnosis, patients are prescribed therapy with no reference to the patient’s genetic information.

• Known as
  – “Trial and error”
  – “One size fits all”
US Prescription Medication Use

119 MILLION

- Estimated number of Americans over the age of 12 who take prescription medications.
- 45% of the US population.
One size does not fit all: Relative efficacy of drug and disease, according to Spear et al.

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Relative efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (all types)</td>
<td>25%</td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>30%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>47%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>51%</td>
</tr>
<tr>
<td>Asthma</td>
<td>57%</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>60%</td>
</tr>
<tr>
<td>Depression (SSRIs)</td>
<td>62%</td>
</tr>
</tbody>
</table>
Did You Know?

2.2 MILLION
Serious adverse drug reactions (ADRs) per year

4TH
Leading cause of death
Ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths.

100,000
Deaths due to ADRs per year

$136 BILLION
Costs of ADRs per year

More than 50% ARE PREVENTABLE!
Factors that Influence Medication Response

Genetics

Personalized Medicine and Pharmacogenomics
Pharmacogenetics vs. Pharmacogenomics

• Pharmacogenetics (PGt):
  – Study of the relationship between variations in a single gene and variability in drug disposition, response and toxicity.

• Pharmacogenomics (PGx):
  – Study of the relationship between variations in large collection of genes (up to whole genome) and variability in drug disposition, response and toxicity.

Single Nucleotide Polymorphisms

- Single base pair change in the DNA sequence
- Most common polymorphism
- Once in every 300 nucleotides on average
- More than 10 million SNPs in the human genome
PGx FACT:

Actionable pharmacogenetic variants are *commonly-expressed* in the general population.
Prevalence of Actionable PGx Variants

• Actionable pharmacogenetic variants were identified in:

  – 91% of the genotyped patients and in 96% of African American patients in the 10K PREDICT cohort.

  – 96.19% of the 5000 sequenced cohort in eMERGE-PGx

  – 99% of 1013 subjects in the RIGHT Protocol.

  – Estimated that 99% of veterans who use the Veteran Health Administration in a cross-sectional study
    ▪ Chanfreau-Coffinier et al. JAMA Netw Open. 2019;2(6):e195345
Pharmacogenomics ($\text{PG}_x$)

Image accessed from: http://mytorontocanadambastudentexperience.blogspot.com/2012/10/personalized-medicine-or-p4-medicine.html
Evolution of Pharmacogenomics

- **1930s** – early observations of unusual drug reactions.
- **1959** – Sir Friedrich Vogel coined the term “pharmacogenetics”.
- **1962** – first textbook on this discipline.
- **2000s** – introduction of the term “pharmacogenomics”.

The Human Genome Project

- 13 year international project completed in 2003
- Coordinated by US Department of Energy and the NIH.
- **$2.7 billion** in FY 1991 dollars
- Project goals:
  - Identify all genes in human DNA
  - Determine the sequences of the 3 billion chemical base pairs
  - Store the information in databases
  - Improve tools for data analysis
  - Transfer related technologies to the private sector
  - Address the ethical, and social issues that may arise.
The New Era of Medical Practice

• Personalized Medicine
  – Emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. National Human Genome Research Institute
  
• First coined in April 1999
  – Robert Langreth and Michael Waldholz in WSJ, later in The Oncologist

• Also known as:
  – Individualized medicine
  – Precision medicine

Number of articles per year that included the term “personalized medicine”


Jørgensen J T The Oncologist 2009;14:557-558
Shifting the Status Quo

PERSONALIZED MEDICINE: Tailored Treatments

MEDICINE OF THE PRESENT
One Treatment Fits All

- Patients with cancer
- Therapy

MEDICINE OF THE FUTURE
More Personalized Diagnostics

- Patients with cancer
- Biomarker Diagnostics (Blood, DNA, urine, and tissue analysis)
- Therapies
- Effect
- Effect
- Effect
Genetics and Pharmacology

Variability in Efficacy / Toxicity

Pharmacokinetics
- Drug Metabolizing enzymes
- Drug Transporter Proteins

Pharmacodynamics
- Drug Target Proteins
Pharmacokinetics Genes of Interest

Evans WE and Relling MV. Science. 1999

Oxidation
Reduction
Hydrolysis

Conjugation
- acetylation
- glucuronidation
- sulfation
- methylation
Cytochrome P450 Enzymes

- Biosynthesis and catabolism of endogenous and exogenous compounds.
- Role in determining intensity and duration of action of medications.
- Over 60 different CYP genes and pseudogenes.
- CYP2C9, CYP2C19 and CYP2D6 carry out ~40% of drug metabolism.

NOMENCLATURE: \textit{CYP2C19} *2

(CYP) (2) (C) (19) *2

Genetic variant (c. 681G>A)
CYP Phenotypes Explained

- CYP2C9*1/*3
  - VKORC1 A/B
  - Intermediate Metabolizer

- CYP2C9*1/*1
  - VKORC1 A/A
  - Intermediate Metabolizer

- CYP2C9*3/*1
  - VKORC1 A/B
  - Poor Metabolizer

- CYP2C9*1/*1
  - VKORC1 A/A
  - Poor Metabolizer

Genotype – Phenotype Relationship

CYP2D6

- Ultrarapid metabolizers
- Extensive metabolizers
- Intermediate metabolizers
- Poor metabolizers

Frequency (Caucasians):
- Ultrarapid: 5–10%
- Extensive: 80–65%
- Intermediate: 10–15%
- Poor: 5–10%

Nortriptyline dose requirement (mg day$^{-1}$)
- >250–500
- 20–50
- 150–100

Meyer UA. Nat Rev Genet. 2004
PGx FACT:

Actionable pharmacogenetic-implicated medications are *commonly prescribed*. 
Prescribing of PGx Meds

• In 2011, 47% of South Korean population was estimated to have been prescribed at least one PGx med as per insurance claims dataset.

• 65% of Vanderbilt cohort (73% EA, 13% AA) were found to have been prescribed at least one of the 56 PGx meds reviewed within 5 years, 12% were prescribed 4 or more meds.

PGx and FDA Approved Medications

FDA-approved medications n = 1200

- 85% with PGx information in drug label
- 15% without PGx information in drug label

Prescriptions in the US n = 4 billion

- 82% for PGx high risk meds
- 18% for other medications

Prescriptions for PGx high risk meds

- 7% affected by actionable pharmacogenes
- 93% not affected

Relling MV, Evans WE. Nature. 2015
Drivers

- Robust genetic association evidence for some examples
- Availability of clinical guidance resources
  - Peer-reviewed clinical guidelines
  - FDA product-label recommendations
  - PharmGKB.org
  - CPICPGx.org

Barriers

- Lack of provider/patient knowledge
- Lack of evidence supporting clinical utility of testing
- Limited insurance coverage and reimbursement of testing.
- Limited infrastructure and resources
CONCLUSION / SUMMARY
Potential Benefits of Pharmacogenomics

- Personalized treatment plans
  - RIGHT medication at the RIGHT dose for the RIGHT patient!
- Cost-Effective
  - Fewer treatment failures
- Better medication response
- Prevents / Minimizes serious adverse effects and minor side effects
Conclusion

• Many commonly prescribed medications have PGx implications.
• Actionable PGx variants are also very common.
• The FDA has PGx information in the drug labels.
• Pharmacogenomics is here to stay!