PharmGenEd™
Principles and Concepts of Pharmacogenomics

Learning Objectives
• Upon completion of this program, participants will be able to:
  – Describe and define basic pharmacogenomic nomenclature and principles
  – Describe polymorphism types and their impact on pharmacokinetics (PK) and pharmacodynamics (PD)
  – Understand the ethical, legal, social issues (ELSI) & economic issues related to pharmacogenomic testing
  – Identify resources for obtaining current and updated pharmacogenomic information

Definitions
• Pharmacogenetics
  – “the study of genetic causes of individual variations in drug response” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)
• Pharmacogenomics
  – “more broadly involves genome-wide analysis of the genetic determinants of drug efficacy and toxicity” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)
• The terms are used interchangeably. For the purposes of this presentation we will use the term pharmacogenomics (PGx)
Translating Pharmacogenomics into Practice

Current Drug Therapy

- Drug response rate
  - 30-60% response rate of drug therapies for Alzheimer’s, depression, rheumatoid arthritis, hypertension, osteoporosis (Physician’s Desk Reference 2007)

- Adverse drug reactions (ADRs)
  - ↑ Morbidity and Mortality
    - Up to 100,000 people/year die of ADRs in the U.S. (Lazarou 1998)
  - ↑ Cost

Pharmacogenomics Impacts Pharmacokinetics and Pharmacodynamics

- Variations in a gene may impact either pharmacokinetics or pharmacodynamics
  - Pharmacokinetics = process by which a drug is absorbed, distributed, metabolized, and eliminated
  - Pharmacodynamics = action or effect of a drug on the body

- These impact efficacy and toxicity

Value of Pharmacogenomics

- Personalize medicine using genotyping technologies
- Optimize drug therapy
  - May maximize drug effectiveness
  - May minimize drug toxicity
  - May minimize pharmacokinetic and pharmacodynamic variability of drug therapy
  - May avoid unnecessary treatment

- Optimize drug development
Challenges of Pharmacogenomic Testing

- **Access**
  - Availability of test
  - Providers
  - Insurance coverage

- **Feasibility**
  - Turnaround time
  - Sensitivity/specificity of tests
  - Efficiency

- **Cost**
  - Genetic test
  - Disease management
  - Counseling

- **Limited evidence**
  - Few quality studies
  - Prospective vs retrospective studies
  - Predictive value
  - Analytical and clinical validity
  - Phenotyping of clinical presentation
  - Clinical utility of testing
  - Efficacy
  - Expertise
  - Cost-effectiveness

Patient/Provider Concerns

- **Patients have high expectations**
  - They expect healthcare providers to explain and interpret pharmacogenomic test results

- **Providers lack evidence-based resources**
  - Reluctant to order pharmacogenomic tests due to limited information about clinical utility
  - There are logistical challenges to testing
  - Health informatics tools (Electronic Medical Records, Computerized Provider Order Entry) do not have pharmacogenomic information at the point of care

Patient/Provider Concerns

- **Patients and providers have concerns about privacy issues** (Rogausch 2006, Fargher 2007)
  - Genetic testing policies vary from state to state

- **Current healthcare professionals need education** (Frueh 2004)

- **Future healthcare providers need education**
  - Pharmacogenomics curricula have increased in pharmacy schools (Murphy 2010)
  - Pharmacogenomics is not adequately taught in medical schools (Gurwitz 2005)

Competency in Pharmacogenomics

- **General competency domains include**
  - Genetic basis of disease
  - Impact of genetic variations on drug metabolism
  - Drug discovery
  - Drug disposition and targets
  - Ethical applications, social & economic implications

- **Open-access, comprehensive web-based tutorials are recommended** (Gurwitz 2005)
Practice Gap

- The field of pharmacogenomics is growing rapidly, with many new discoveries coming to light
- It is critical for clinicians to...
  - Appropriately interpret emerging data on pharmacogenomic tests
  - Become familiar with resources applicable to their practice

Molecular Biology 101

• What are alleles?
  - Different versions (alternate sequences) of a gene at a particular location on a chromosome
  - Alleles include the wild-type (usual) sequence, mutations, and polymorphisms of a given gene
  - Within a gene, variations of an individual nucleotide can be considered alleles

• Humans are diploid organisms
  - Humans normally have 2 copies of every chromosome; thus we have 2 copies of each gene
  - One allele is from your biological mother
  - One allele is from your biological father
Molecular Biology 101

• What is a polymorphism?
  – A variation in DNA sequence
  • If present in >1% of the population, it is known as a polymorphism
  • If present in <1% of the population, it is known as a mutation
  – Types of polymorphisms
  • Single nucleotide polymorphism (SNP, pronounced ‘snip’)
  • Other types of polymorphisms involve changes in more than one nucleotide

• What is a haplotype?
  – A set of alleles at multiple, neighboring positions that coexist on the same chromosome
  – These alleles may be in separate locations within a single gene or among different genes
  – Neighboring alleles (located near one another) are physically tethered and usually inherited as a set, i.e. their linkage on the chromosome prevents their separation during inheritance
  – One individual inherits two copies of a haplotype

Pharmacogenomic Nomenclature

Where discoveries are delivered.
Pre-Test Question:
An example of a SNP is VKORC1 1173 C>T. Based on the nomenclature of this SNP, what is the gene of interest?

A. 1173  
B. VKORC1  
C. Thymine (T)  
D. Cytosine (C)

Pharmacogenomic Nomenclature

The following slides will describe:

– SNP nomenclature  
– Reference SNP (rs) nomenclature  
– “Star” nomenclature  
– Genotype nomenclature  
– Haplotype nomenclature

SNP Nomenclature

• Examples
  – VKORC1 1173 C >T  
  – ABCB1 3435 C >T

• Explanation
  – The first few letters/numbers (e.g. VKORC1, ABCB1) identify the gene
  – The numbers following the gene (e.g. 1173, 3435) indicate the nucleotide position in the gene
  – The first letter (e.g. C) represents the original (or wild-type) nucleotide
  – The second letter (e.g. T) represents the change in the nucleotide sequence (i.e. the SNP)

Reference SNP (rs) Nomenclature

• The “rs” naming system is used by the SNP database (dbSNP)
  – dbSNP is the central database for all genetic variation information
  – Recommended by Human Genome Variation Society as the standard nomenclature for SNPs
  – As each new polymorphism is identified, the information is submitted by researchers to the SNP database. The sequence data are curated and an “rs” number is created
“Star” Nomenclature

- Example 1: CYP2C19*1 and CYP2C19*2
  - CYP2C19 function varies based on the allele
    - *1 allele → normal (wild-type) enzyme activity
    - *2 allele → no enzyme activity
- Example 2: CYP2C9*1 and CYP2C9*2
  - CYP2C9 function varies based on the allele
    - *1 allele → normal (wild-type) enzyme activity
    - *2 allele → decreased enzyme activity
- Key point: Identical allele names may indicate different functional outcomes, depending on the specific gene/protein

Genotype Nomenclature

- Genotype refers to the two alleles inherited for a specific gene
- Example:
  - A person may carry two copies of the *2 allele for CYP2C19
  - Genotype = CYP2C19 *2/*2
- Genotypes may impact drug metabolism
  - CYP2C19 *1/*1 → normal (wild-type) enzyme activity
  - CYP2C19 *1/*2 or *1/*3 → reduced enzyme activity
  - CYP2C19 *2/*2, *2/*3, or *3/*3 → no enzyme activity

Haplotype Nomenclature

- Haplotype refers to a combination of alleles or a set of SNPs found on the same chromosome
- Example: VKORC1 gene
  - There are SNPs in at least 10 separate positions throughout the gene that may have functional effects
  - A haplotype name is used to simultaneously describe each set of linked SNPs in an individual
    - Haplotype A = a set of SNPs at 10 different positions along one chromosome
    - Haplotype B = a different set of SNPs at the same 10 positions on another chromosome

Post-Test Question:
An example of a SNP is VKORC1 1173 C>T. Based on the nomenclature of this SNP, what is the gene of interest?

A. 1173  
B. VKORC1  
C. Thymine (T)  
D. Cytosine (C)
Polymorphism Types

• Single nucleotide polymorphism (SNP)
• Variable number tandem repeat
• Gene deletion
• Copy number variant

Single Nucleotide Polymorphism (SNP)

• A single base substitution
• Several million SNPs have been identified, and novel SNPs continue to be discovered
• Some SNPs lie outside the protein-coding regions of genes
• Other SNPs lie within coding regions of genes
  - These may or may not alter protein synthesis
    • Synonymous polymorphism
    • Non-synonymous polymorphism
    • Premature stop codon

Pre-Test Question:
A polymorphism has been found in the gene for a drug-metabolizing enzyme. A nucleotide change occurs, yet the encoded amino acid is unchanged. What type of SNP is this?

A. Gene deletion
B. Synonymous
C. Non-synonymous
D. Premature stop codon
**Synonymous SNP: ABCB1 and P-glycoprotein**

- The gene **ABCB1** encodes P-glycoprotein
- **ABCB1 3435C>T allele (rs1045642)**
  - Nucleotide change occurs (C > T), yet the resultant amino acid (isoleucine) is unchanged

<table>
<thead>
<tr>
<th>Reference or ‘wild type’ nucleotide sequence</th>
<th>Corresponding amino acid sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTG TCA CAG GAA GAG</td>
<td>Val Ser Gln Glu Glu</td>
</tr>
</tbody>
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**ABCB1 3435C>T polymorphism – nucleotide sequence**

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<td>GTG TCA CAG GAA GAG ATC</td>
<td>Val Ser Gln Glu Glu Ile</td>
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</table>

- Function effect: Conflicting data on whether there is an effect on P-glycoprotein expression or function (Kimchi-Sarfaty 2007, Leschziner 2007, Fung 2009, PharmGKB)
- Affected drugs: efavirenz, cyclosporine

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**Non-Synonymous SNP: TPMT**

- The gene **TPMT** encodes thiopurine methyltransferase
- **TPMT*3A haplotype** (Tai 1996, Weinshilboum 2001)
  - **TPMT 615 G > A** results in an amino acid change (alanine > threonine)
  - **TPMT 874 A > G** results in an amino acid change (tyrosine > cysteine)

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<tbody>
<tr>
<td>GCA TTA AAG</td>
<td>Ala Leu Lys Leu</td>
</tr>
</tbody>
</table>

**TPMT*3A polymorphism – nucleotide sequence**

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<th>Corresponding amino acid sequence</th>
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</thead>
<tbody>
<tr>
<td>ACA TTA AAG</td>
<td>Thr Leu Lys Leu</td>
</tr>
</tbody>
</table>

- Functional effect: Decreased TPMT enzyme activity
- Affected drugs: azathioprine, 6-mercaptopurine

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**Post-Test Question:**
A polymorphism has been found in the gene for a drug-metabolizing enzyme. A nucleotide change occurs, yet the encoded amino acid is unchanged. What type of SNP is this?

A. Gene deletion
B. Synonymous
C. Non-synonymous
D. Premature stop codon
**Patient Case #1**

- 7-year old Caucasian child diagnosed with acute lymphoblastic leukemia. Patient has finished remission induction and will begin intensification chemotherapy that will include 6-mercaptopurine (6-MP)
- Allergies: no known drug allergies
- Questions:
  - Should a genetic screening test be done before starting 6-MP?
  - What will be the empiric 6-MP starting dose?

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**Systematic Approach to Understanding Polymorphisms**

- **Identify the polymorphism and what it may affect**
  - TPMT*3A → decreased TPMT enzyme activity
- **Who is impacted?**
  - 1-10% in Caucasian populations
- **Relevance to a drug?**
  - Increased 6-mercaptopurine (6-MP) concentrations
  - Increased toxicity risk (myelosuppression)
  - 6-MP dose reduction is needed
- **Relevance to a disease?**
  - No difference in overall survival in individuals who have the TPMT*3A polymorphism

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**Systematic Approach to Understanding Polymorphisms**

- **Identify the polymorphism and what it may affect**
  - Enzyme, transporter, receptor
  - It may or may not have functional effect
- **Who is impacted?**
  - Individual and population variation may exist
- **Relevance to a drug?**
  - May affect drug PK or PD, influencing dosing, efficacy, or toxicity
  - May have no effect on a drug
- **Relevance to a disease?**
  - May increase or decrease disease susceptibility or disease condition
  - May be useful as a screening or diagnostic tool

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**Patient Case #1 Summary**

- Patient was screened for the TPMT polymorphism before starting intensification chemotherapy
  - Patient's genotype was TPMT*3A/*3A
- Patient’s genotype increases risk of myelosuppression upon starting 6-MP
- To decrease this risk, 6-MP starting dose reductions are recommended (Purinethol® Prescribing Information)
**Pre-Test Question:**
If drug X is predominantly metabolized by the CYP2C19 enzyme, which CYP2C19 genotype may result in the lowest amount of metabolite Y in the blood?

A. CYP2C19 *1/*1  
B. CYP2C19 *1/*2  
C. CYP2C19 *1/*3  
D. CYP2C19 *3/*3

**CYP2C19 Genotype and Omeprazole Pharmacokinetics**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CYP2C19 activity</th>
<th>Omeprazole Exposure (Mean + SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 *1/*1</td>
<td>normal</td>
<td>384 ± 64</td>
</tr>
<tr>
<td>CYP2C19 *1/*2</td>
<td>reduced</td>
<td>1002 ± 532</td>
</tr>
<tr>
<td>CYP2C19 *1/*3</td>
<td>absent</td>
<td>5590 ± 294</td>
</tr>
</tbody>
</table>

**Premature Stop Codon SNP: CYP2C19**

- **CYP2C19 encodes a cytochrome P450 enzyme**
- **CYP2C19*3 allele** (Demorais 1994)
  - The nucleotide change (G >A), replaces reference sequence (encoding the amino acid tryptophan) with a stop codon, resulting in termination of protein synthesis
  
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  CYP2C19*3 polymorphism – nucleotide sequence
  
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- Functional effect: CYP2C19*3 abolishes enzyme activity  
- Affected drugs: proton pump inhibitors (omeprazole, lansoprazole)

**CYP2C19 Genotype, Omeprazole Therapy, & H. pylori Cure Rates**

- Drug X (omeprazole) → CYP2C19 → Metabolite Y

(Furuta 1999)

**H. pylori cure rates (%)**

- p < 0.05 for A vs B, and A vs C (Adapted from Furuta 1998)
Patient Case #2

- 35 year old Asian female complains of dyspepsia & epigastric pain. Denies nausea and vomiting and blood in stools. Urea breath test is positive. She is diagnosed with *H. pylori* peptic ulcer disease

- **Past Medical History:**
  - No other significant past medical history
  - No known drug allergies

- **Medications:** Begins 10-day course of omeprazole, amoxicillin, and clarithromycin

- **Questions:**
  - What is the primary enzyme responsible for omeprazole metabolism?
  - Does a polymorphism exist for this enzyme?
  - What is the anticipated effect on omeprazole pharmacokinetics and the *H. pylori* cure rate?

Systematic Approach to Understanding Polymorphisms

- **Identify the polymorphism and what it may affect**
  - CYP2C19*3 allele ➔ no CYP2C19 enzyme activity

- **Who is impacted?**
  - Frequency of the CYP2C19*3 allele higher in Asian populations

- **Relevance to a drug?**
  - The CYP2C19*3 allele leads to higher omeprazole plasma concentrations, compared to the wild-type CYP2C19*1 allele

- **Relevance to a disease?**
  - *H. pylori* cure rates in patients taking omeprazole vary based on CYP2C19 genotype

Patient Case #2 Summary

- Patient purchased a commercially available genotyping kit
  - Patient’s genotype was CYP2C19*3/*3

- **H. pylori** cure rate is anticipated to be 100% in patients with the CYP2C19*3/*3 genotype (Furuta 1998)

- Patient completed 10 day course of omeprazole, amoxicillin, and clarithromycin
  - Symptoms of dyspepsia and epigastric pain resolved
  - Patient was *H. pylori* negative and considered cured

Post-Test Question:
If drug X is predominantly metabolized by the CYP2C19 enzyme, which CYP2C19 genotype would be predicted to result in the lowest amount of metabolite Y in the blood?

- A. CYP2C19 *1/*1
- B. CYP2C19 *1/*2
- C. CYP2C19 *1/*3
- D. CYP2C19 *3/*3
Variable Number Tandem Repeat: UGT1A1

- **UGT1A1** encodes UDP-glucuronyl transferase 1A1
- **UGT1A1*28** allele
  - Insertion of one additional T, followed by one additional A
  - Copies of the “T-A” dinucleotide repeat increase from 6 to 7, in the promoter region of the gene (not the coding region) (Hall 1999)
  - Functional effect: decreased UGT1A1 transcription & enzyme (glucuronidation) activity
  - Affected drug: irinotecan (metabolized by UGT1A1)

Gene Deletions and Copy Number Variants - CYP2D6

- **CYP2D6** encodes a cytochrome P450 enzyme
- Deletions and duplications of **CYP2D6** alter the number of copies of the gene, and the resulting activity of the CYP2D6 enzyme
- **CYP2D6** polymorphisms have as much as a 200-fold effect on drug metabolism
- **CYP2D6** polymorphisms affect pharmacokinetic variability among patients:
  - Ultra-rapid metabolizers
  - Extensive metabolizers
  - Intermediate metabolizers
  - Poor metabolizers

Metabolizer Variability, Resulting from CYP2D6 Genotypes

- **CYP2D6*5** allele (Gaedigk 1991)
  - The entire gene (thousands of nucleotides) is deleted
  - Functional effect: Loss of function of CYP2D6 enzyme
  - Affected drugs: selective serotonin reuptake inhibitors (SSRIs), tamoxifen, codeine, β-blockers
Copy Number Variant: CYP2D6

- **CYP2D6*2XN allele** (Dahl 1995)
  - Extra copies of the CYP2D6 gene are present on a single chromosome (N = 2, 3, 4, 5, 13)
  - Functional effect: increased amount of CYP2D6 enzyme
  - Contributes to an ultra-rapid metabolizer phenotype
- Affected drugs: SSRIs, tamoxifen, codeine, β-blockers

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Ethical, Legal, Social Issues (ELSI) & Economics

Ethical Issues

- Loss of privacy
- Whom do we test?
  - Genetic profiling
  - Discrimination/stigmatization
- Distributive justice
  - Equitable distribution of benefits to patient populations
- Prevention strategies (public health at large)
  - Genotypic versus phenotypic prevention
- Clinical decisions
  - Should the test be ordered?
  - What should be done with test result?

Legal Issues

- **Case Study**
  - In 2001, the Equal Employment Opportunity Commission (EEOC) filed suit against the Burlington Northern Santa Fe (BNSF) Railroad for secretly testing its employees for predisposition to a rare genetic condition (carpal tunnel syndrome).
  - Genetic testing for other medical predispositions (e.g., diabetes, alcoholism) was also performed.
  - BNSF employees were not informed of the genetic testing and were threatened with possible termination if they did not comply.
  - EEOC argued that the tests were unlawful under the Americans with Disabilities Act because the tests were not job-related.
  - BNSF settled lawsuit with EEOC and stopped testing in 2002.
Legal Issues

• Legislation
  – The Genetic Information Nondiscrimination Act (GINA) of 2008 protects Americans from discrimination regarding health insurance and employment, based on genetic information

• Questions to consider
  – If testing is recommended, are clinicians liable if they do not offer or order the test?
  – If an adverse drug reaction occurs, who is responsible?

• Resources
  – National Human Genome Research Institute
    www.genome.gov/24519851
  – University of Michigan Center for Public Health and Community Genomics
    http://www.sph.umich.edu/genomics/

Social Issues

• Health disparities
  – Access to pharmacogenomic tests
  – Limitation of race-based therapeutics

• Employment
• Insurance
  – Loss of coverage
  – Increase in premiums
  – Life, disability and long-term care insurance
  – Unfair risk assessment for coverage

• Societal benefits and burdens
• Mandatory versus voluntary screening

Economics & Cost Implications for Public Health

• Implementation of pharmacogenomic (PGx) tests will require
  – Evidence-based rationales demonstrating cost-effectiveness (Vegter 2008)
  – Payers agreeing to cover costs (Williams 2007)

• Cost of PGx tests is unlikely to disrupt the current public health system
  – Gradual and incremental progression
  – Our system has flexibility to adapt (Garrison 2008)

Roles for Healthcare Professionals
Potential Roles for Healthcare Professionals

- **Become an informational resource by:**
  - Identifying published literature and online resources
  - Maintaining up-to-date knowledge
  - Interpreting test results (potential outcomes and adverse reactions)

- **Educate:**
  - Healthcare professionals
  - Patients (genetic counseling)

- **Collaborate with:**
  - Researchers
  - Clinicians
  - Educators

Patient Counseling

- Information about pharmacogenomics tests
- Assessment of risk in absence of genetic testing
- Cost associated with testing and counseling
- Technical accuracy of test
- Interpretation of positive, negative and inconclusive results
- Psychological impact of test results
- Confidentiality issues and risks of potential discrimination
- Sharing genetic test results with at-risk relatives

Implications for Clinical Practice

- It is unclear how standard of care will be developed
  - Mandate testing
  - Restrict testing
  - Offer testing & let the patient decide

- Role of epigenomics should be considered
  - Influence of environment on gene expression

- Cost and coverage
- Informed consent and patient counseling
- Confidentiality and privacy

Pharmacogenomic Resources

Where discoveries are delivered...
Centers for Disease Control and Prevention (CDC)

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) launched in 2004
  - EGAPP Working Group (2005)
  - Independent, multi-disciplinary panel reviews available evidence on genetic tests, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios (http://www.egappreviews.org/about.htm)

- GAPP Translation Programs
  - Currently there are 5 translation programs (Michigan Department of Community Health, Oregon Department of Human Resources, Sepulveda Research Corporation, University of California at San Diego, University of Washington)

Food and Drug Administration (FDA)

- Examples of topic areas for required or voluntary submissions to FDA
  (Attachment to Guidance on Pharmacogenomic Data Submissions 2005)
  - Metabolizing Enzymes, Transporters, Receptors, Clinical Outcomes: Efficacy and Safety, Nonclinical Safety

- Of 1,200 drug labels reviewed from 1945-2005
  - 121 labels contained pharmacogenomic information (Frueh 2008)
  - 69 of these referred to human genomic biomarkers

- Currently, FDA lists 155 approved drugs with valid genomic biomarkers described their labels (Table of valid genomic biomarkers in the context of approved drug labels 2014)

Information and Resource Databases

- Definitions, Terminology, Nomenclature
  - National Human Genome Research Institute (NHGRI) http://www.genome.gov/10002096

- Molecular Biology and SNP concepts

Information and Resource Databases

- Information for Health Care Professionals
  - PharmGKB http://www.pharmgkb.org/
  - FDA: Valid Pharmacogenomic Biomarkers http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
  - National Coalition for Health Professional Education in Genetics http://www.nchpeg.org
Information and Resource Databases (cont.)

- **Information for Patients** (Public policy, Ethical issues, Genetic testing)
  - CDC National Office of Public Health Genomics
    http://www.cdc.gov/genomics/resources/e.htm#Ethical
  - University of Michigan Center for Public Health and Community Genomics
    http://www.sph.umich.edu/genomics
  - National Human Genome Research Institute
    http://www.genome.gov/policyethics
  - Genetic Alliance http://www.geneticalliance.org

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References
The references for this module are posted on the PharmGenEd website at: https://pharmacogenomics.ucsd.edu/

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The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.

Thank you!