Pharmacogenomics: What is your patient telling you?

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Disclosure

- The speakers do not have any conflicts of interest to disclose.
- The views shared during this presentation are our own and do not represent the National Institutes of Health, the Department of Health and Human Services, or the federal government.

Learning Objectives

By the end of this session, the participant will be able to:

1. Define pharmacogenomics, pharmacogenetics, and metabolizer phenotypes.
2. Describe how the cytochrome P450 genes affect the selection of medications for common primary care visits (i.e. hypertension, diabetes, depression, upper respiratory tract infections, and back pain).
3. Identify at least five credible genetic/genomic resources for patients and/or nurse practitioners.

National Institutes of Health

Genetics Versus Genomics

- **Genetics:** study of heredity
  - Investigates the functions and composition of a single gene
- **Genomics**: study of genes and their functions, and related techniques
  - Addresses all genes and their inter relationships in order to identify their combined influence on the growth and development of an organism
- Pharmacogenetics versus pharmacogenomics

World Health Organization: https://www.who.int/genomics/geneticsVSgenomics/en/

Defining Pharmacogenomics

- Study of how genetic factors influence individual variability of drug response and toxicity
- Investigation of how genetics influences a patient's response to pharmacotherapies
- Targeting the right drug, for the right person, at the right dose
- Cornerstone of personalized medicine

Lea, 2012
Atkinson, 2012

Defining Pharmacogenomics

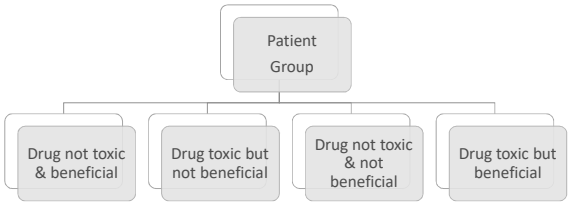
Three broad classes of genes investigating genetic human variation:

- **Drug-metabolizing pharmacogenetics**
  - Genes that code for enzymes involved in drug metabolism
- **Drug-transporter pharmacogenetics**
  - Genes that code for membrane transporters moving drugs into or out of cells
- **Drug-target pharmacogenetics**
  - Genes that code for the direct target of the drug or code for other proteins associated with the pathway of the drug

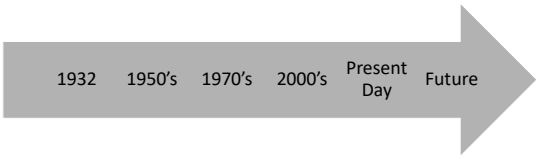
Lea, 2012
Atkinson, 2012

Defining Pharmacogenomics

Study of variations of single genes influencing specific drug metabolism and/or receptors which influence individual variability in drug response of toxicity



History of Pharmacogenomics



Gene Testing Versus Pharmacogenomic Testing

- Gene Testing
  - Screening for genetics diseases or conditions
  - Assessing carrier status
  - Testing for genetic diseases in adults before they cause symptoms
  - Making a diagnosis in someone who has disease symptoms
  - Determining the type or dose of medication that is best for a certain person
- Pharmacogenomic Testing
  - Determine if the medication will be effective for person
  - Best dosage
  - Predict serious side effects from the medication

Application to Nurse Practitioners

2011 Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees

- Professional practice
  - Risk assessment and interpretation
  - Genetic education, counseling, testing, and results interpretation
  - Clinical management
  - Ethical, legal, and social implications (ELSI)
- Professional responsibilities
  - Professional role
  - Leadership
  - Research

Greco et al., 2012

Application to Nurse Practitioners

Genetic education, counseling, testing, and results interpretation:

- Provide genetic/genomic education and counseling appropriate to practice setting
- Select appropriate genetic/genomic tests and/or studies
- Communicate results of genetic/genomic screening and/or testing at a level that clients can understand

Greco et al., 2012

Technologic Advances

- Human Genome Project 2001-2003
- International Hapmap Project - 2003
- 1000 Genomes Project - 2010
- ENCODE - 2012
- All of Us - 2017

Technologic Advances

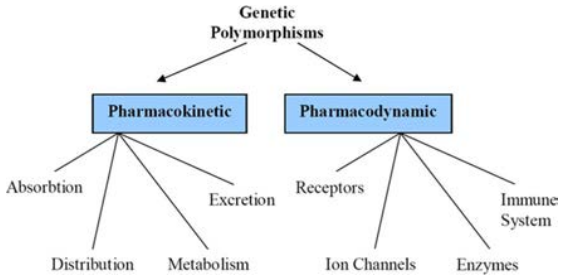
- Genome Wide Association Studies (GWAS)
- Next Generation Sequencer (NGS)
- DMET analyzer

Future Pharmacogenomic Tests

- Analytic validity
- Clinical validity
- Clinical utility
- Personal utility

Pharmacokinetics

- Polymorphisms in genes encoding drug metabolism and drug transporter affect drug availability
- How the body processes the medication

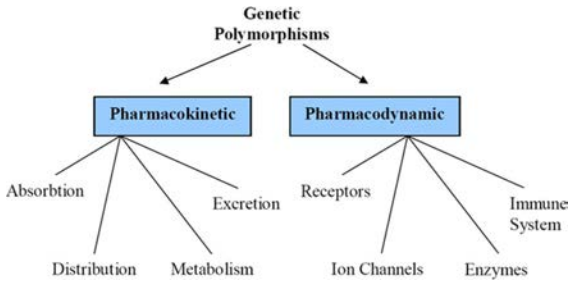


Pharmacokinetics

- Phase I metabolism (modification)
- Phase II metabolism
- CYP isoenzymes and drug metabolism

Pharmacodynamics

- Polymorphisms in gene coding drug target proteins, such as receptors, enzymes and intracellular signaling proteins affect a patient's sensitivity to a drug
- How the medication affects the body

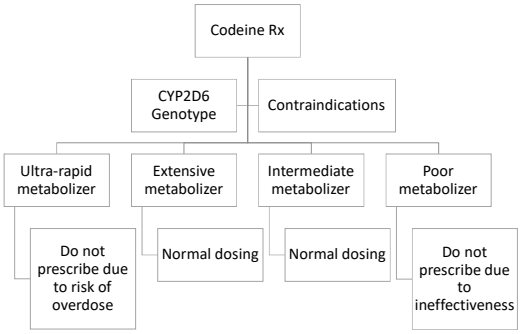


Drug Metabolism Phenotypes

- Ultra-rapid metabolizer
- Extensive metabolizer
- Intermediate metabolizer
- Poor metabolizer
- Indeterminate

Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines: https://cpicpgx.org/content/guideline/publication/SSRI/2015/25974703.pdf

Phenotypes and Codeine



FDA Codeine Sulfate Tablets Highlights of Prescribing Information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022402s012lbl.pdf
PharmGKB Recommended Dosing of Codeine by CYP2D6 Phenotype: https://www.pharmgkb.org/chemical/PA449088/guidelineAnnotation/PA166104996

CYP Isoenzymes and Drug Metabolism

- Cytochrome P450's (CYP's) family of oxidative enzymes
- 58 different human CYP genes which encode for various CYP isoenzymes
- Hepatic and small intestine CYP's
  - CYP2C9
  - CYP2C19
  - CYP2D6
  - CYP3A4
  - CYP1A2
- Detoxify medications
- Produce ROS (reactive oxygen species)

Veith et al., 2018

Gene-Drug Relationships

Prescription	Genes
Warfarin	CYP2C9 and VKORC1
Plavix	CYP2C19
Tamoxifen	CYP2D6, CYPD6, CYP2C9, CYP1A2, SLC6A4, HTR2A/C
Antipsychotics	DRD3, CYP2D6, CYP2C19, CYP1A2
Attention Deficit Disorder treatments	D4D4
Carbamazepine	HLA-B*1502
Abacavir	HLA-B*5701
Opioids	OPRM1
Statins	SLCO1B1
Childhood leukemia and some autoimmune disorders	TMPT

MedlinePlus: https://medlineplus.gov/lab-tests/pharmacogenetic-tests/

Gene-Drug Relationships

- About 200 therapeutic products with pharmacogenomics information found in the drug labeling
- Describe:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype-specific dosing
  - Mechanism of drug action
  - Polymorphic drug target and disposition genes
  - Trial design features

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Gene-Drug Relationships

- Cardio-renal
- Metabolic
- Transplant
- Oncology
- Antiviral
- Pain
- Hematology
- Psychopharm
- Neuropharm

Treatment Response Factors

- Age
- Disease severity
- Co-morbid conditions
- Concomitant medications
- Medication adherence
- Genotype
- Ethnicity
- Gender
- Pregnancy

Lea, 2012

Epigenetic Influences

- Health status
- Diet
- Seasonal links
- Disease exposure
- Toxic exposures
- Health insurance
- Exercise
- Medications
- Psychological state

Kanherkar et al., 2014

Clinical Guidelines

- Pharmacogenomics Research Network (PGRN)
- PharmGKB database
- Clinical Pharmacogenetics Implementation Consortium (CPIC)

Clinical Application

Patient considerations

- Pregnancy
- Pediatrics
- Older adults

Clinical Application

- Personnel health history
- Family health history including a three-generation pedigree
- Ask if pharmacogenomics testing was performed
- Monitor and document response to medications
- Communicate medication response to other team members
  - Specialists (cardiology, endocrinology, etc.)
  - Pharmacist
- Patient education

Programs at Your Institution

- How are pharmacogenomic test results communicated to you?
- Who are your resources?
  - Genetic counselors
  - Pharmacists
  - Physicians
  - Researchers

Ethical Considerations

- Health inequalities
  - Within the United States
  - Between countries
- Cost of new technology and the cost-benefit ratio
- Incidental findings
- Reassessment of previous findings
- Sample sizes
- Pediatric testing for adult onset diseases

Clinical Resources for Nurse Practitioners

- Genetics Home Reference
  https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics
- Genetics/Genomics Competency Center for Education
  https://www.genomicseducation.net/
- Genetic Testing Registry
  https://www.ncbi.nlm.nih.gov/gtr/

Clinical Resources for Nurse Practitioners

- ClinGen
  - Dedicated to building an authoritative central resource that define the clinical relevance of genes and variants for use in precision medicine and research
- Implementing Genomics in Practice – IGNITE
  - Consortium created to enhance the use of genomic medicine by supporting the development of methods for incorporating genomic information into clinical care
- eMERGE and DIGITizE
  - Combining biorepositories with Electronic Health Record for genomic medicine implementation research
- Food and Drug Administration (FDA)
  - Precision medicine and pharmacogenetic associations

Online Resources for Patients

- National Institutes of Health
  - https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx
- National Human Genome Research Institute
  - https://www.genome.gov/FAQ/Pharmacogenomics
- Centers for Disease Control and Prevention
  - https://www.cdc.gov/genomics/about/precision_med.htm
- Genetics Home Reference
  - https://ghr.nlm.nih.gov/primer/genomicresearch/pharmacogenomics
- Genetic Alliance
  - http://www.geneticalliance.org/

Challenges

- Slow to change decision making in relation to prescribing
  - Independently replicate
  - Variability in phenotype definition
  - Rare phenotype, lack of sample sets
- FDA has over 200 drug labels that refer to pharmacogenetic biomarkers
  - Support therapeutic management recommendations
  - Drug safety or efficacy
- Still need to consider the individual's age, weight, health status, and other medications (Rx and OTC)

Case Study #1

- Dwayne is a 55 year old African American male with a past medical history of type 2 diabetes mellitus and hypertension.
- Medications: metformin, hydrochlorothiazide, diltiazem
- He is married, no children, works full-time as a computer programmer, and routinely cycles for 60 minutes/day 5 times a week.
- Presents today for a follow-up discussion regarding lab work from his annual physical.
- You as the nurse practitioner are going to start him on a statin.

Case Study #1

- Dwayne tells you that he just got his genetic tests done from a direct-to-consumer (DTC) site
- What questions should you ask Dwayne about his genetic test results?
  - Where did he have the tests performed?
  - Request to see the tests results and scan/enter them into your electronic medical record.
  - Are these test results valid?
  - Were they performed in a CLIA-certified lab?
  - Would you prescribe a statin based on DTC results?

Simvastatin

Allele	Phenotype
AA	May have a better response (as measured by higher reductions in total cholesterol) compared to patient with the CC genotype
AC	May have a better response (as measured by higher reductions in total cholesterol) compared to patient with the CC genotype
AT	May have a better response (as measured by higher reductions in total cholesterol) compared to patient with the CC genotype
CC	May have a reduced response (as measured by lower reductions in total cholesterol) compared with other patients
TT	May have a better response (as measured by higher reductions in total cholesterol) compared to patient with the CC genotype

**Studies were conducted with in people of European biogeographical group

PharmGKB: https://www.pharmgkb.org/gene/PA267/clinicalAnnotation/1150414901

Simvastatin

- **Clinical Pharmacogenetics Implementation Consortium (CPIC**) – 2014 update recommending the starting dose at 40 mg QD, testing (if available and should be a priority), and based on results, switching to an alternative
- **FDA** added warnings to simvastatin product label to direct providers away from initiating at the 80mg dose
- **Royal Dutch Pharmacists Association** – testing and then choosing an alternative medication such as rosuvastatin or pravastatin.
- **French National Network of Pharmacogenetics** - recommends testing for rs4149056 before starting treatment or early after treatment onset

Case Study - alternative

- Li is a 62-year old Chinese American female presenting for unipolar major depression
- Medications: tamoxifen
- PMH: ductal carcinoma in situ (DCIS) diagnosed in August 2019
- Your treatment recommendation includes an antidepressant and psychotherapy
- What category of antidepressant would you consider starting Li on?

Summary

- Pharmacogenomic testing is only indicated if a person is going to take, or is taking, a medication that has an accepted pharmacogentic test associated with it
- Safe prescribing and medication metabolism phenotypes:
  - Ultra-rapid metabolizer
  - Extensive metabolizer
  - Intermediate metabolizer
  - Poor metabolizer
- Investigate your local pharmacogenomic resources

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- http://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomics-biomarkers-drug-labeling

For Questions Following the Presentation

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