Pharmacogenomics

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The content of my material/presentation in this CME activity will include discussion of unapproved or investigational uses of products or devices as indicated:

- Genetic testing is a new concept and many package inserts do not discuss when or how to test patients prior to using a drug. Therefore much of this presentation is based on where medicine is in regard to adopting genetic testing in relation to prescribing habits of clinicians.

Learning Objectives
1. Evaluate the availability, efficacy, and utility of pharmacogenomics testing.
2. Develop plans to incorporate appropriate pharmacogenomics testing, as indicated by FDA drug labels.
3. Counsel patients regarding legal or ethical issues associated with pharmacogenetic testing.
4. Evaluate barriers to routine use of pharmacogenetics in a clinical setting

Audience Engagement System

Step 1
- Introduction
- Objectives
- Participant Engagement

Step 2
- Pharmacogenomics Overview
- Benefits of Pharmacogenomics
- Challenges in Implementation

Step 3
- Case Studies
- Interactive Quiz
- Summary

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Brown earned his doctoral degree from Campbell University School of Pharmacy, Buies Creek, North Carolina, and completed his residency training at the Medical College of Virginia, Richmond. He is currently a fellow at the ASHP’s Distinguished Service Award in ambulatory care. He has received the Golden Apple Teacher of the Year Award multiple times and was awarded the William L. Kelly Safety Leadership Award by the Ohio Hospital Association. Brown has authored several articles and presentations on the topic of pharmacogenetics and is a frequent speaker at national conferences. He is the co-editor of two books designed to help others build their practice model in an ambulatory care setting, as well as co-creator of an outpatient intervention tracking application called PACT. He is also a monthly show host called "Brown’s Pharmacy Update," which dives deep into current topics in the pharmacy profession. Brown is a former president of the Ohio Society of Health-System Pharmacists (OSHP) and served on the board of directors for Ambulatory Care Practitioners of the ASHP. He remains active in the organization’s board of directors.
Precision Medicine

• President Obama launched a Precision Medicine Initiative in 2014
  – Goal was to access personalized information to keep each patient healthier
  – Current model uses biological and socio-economic factors
  – Concept of genetic influence has added a whole new dimension to the term “personalized medicine”

Promises of Personalized Medicine

• Genomics can help identify at an individual level:
  – Disease Susceptibility
  – Disease Course
  – Optimal Treatment
  – Disease Prevention

Definition of Terminology

• Gene: DNA unit information encoding an inherited trait
• Allele: the alleles of a gene are the two or more alternative DNA sequences that affect the function of a gene product
• Genotype: the allele combinations that cause a particular trait or disorder
• Phenotype: the visible expression of the gene
• Polymorphism: a gene that has two or more sequence variations (alleles), if present at a frequency of 1% or more in a population then the gene is polymorphic.
• Genetic variations: single-base differences, deletions, duplications, and other insertions.

Definition of Terminology

• Two terms are being used to define the ability of genetic testing to choose the correct dose of the correct drug for the correct patient:
  – Pharmacogenomics:
    • How the ENTIRE genome can influence the response to drugs
  – Pharmacogenetics:
    • Subcategory of genomics where a specific genetic variation (one gene) is inherited through the germline or acquired thus effecting drug metabolism and disposition

The Goal of Pharmacogenomics

Patients with same diagnostics

Pharmacological responses

GCCCACCTC
GCCCACCTC
GCCCACCTC

Normal responders, No severe Toxicity
Non-responders
Toxic responders

AES POLL QUESTION

Which of the following ways can PGx help improve patient safety?

A. Prevention of adverse drug reaction
B. Increase patient adherence
C. Allow selection of optimal therapy
D. All of the above
Does PGx testing improve safety?

- Shifts emphasis in medicine from reaction to prevention
- Allows selection of optimal therapy and reduce trial-and-error prescribing
- Makes prescribing safer by avoiding adverse drug reactions
- Increases patient adherence to treatment

Pharmacogenomics

- Pharmacokinetics
  - Drug metabolism variability
- Pharmacodynamics
  - Reduction in binding of drug to receptor
- Idiosyncratic Reactions
  - Hypersensitivity to certain drug
- Disease Pathogenesis
  - Drug targets for specific cancers

Pharmacokinetics (PK)

- Occurs in CYP450
- 60 different CYP genes (and counting) which code for various CYP isoenzymes
- 18 families have been identified so far
- Most involved in drug metabolism are polymorphic
  - Alters metabolism of certain drugs
  - Variability in ethnic groups
  - 2D6 is functionally absent in 7% of Caucasians and African-Americans but not in Asians

CYP3A4

- Responsible for the metabolism of approximately 50% of drugs
- An example is CYP3A4*22 (c.522-191C->T)
  - Affects hepatic expression of CYP3A4 and response to statin drugs
  - Reduced CYP3A4 activity leads to better response to statins
  - In 235 pts on stable doses for lipid control, carriers of the T allele required lower statin doses for optimal control than did non-T carriers
- Seen in 5-8% of Caucasians and 4.3% in AA and Chinese
- FDA does not recommend testing before starting statins

Pharmacokinetics

- CYP3A4
  - most important (50%)
  - inducible
- CYP2D6
  - next in line (20%)
  - not inducible
- CYP2C9 and 2C19
  - next (15%)
  - inducible

AES POLL QUESTION

Which antiplatelet medication undergoes metabolism via 2C19?

A. Aspirin
B. Ticagrelor (Brilinta)
C. Prasugrel (Effient)
D. Clopidogrel (Plavix)
CYP2C19

• Controversial example
• Thought that decreased function CYP2C19 may impact CV effect of Clopidogrel
• FDA released statement on genetic testing available
  – Did NOT recommend it
• Subsequent meta-analysis showed the impact was minimal and CYP2C19 was not relevant in choosing an anti-platelet medication

CYP2D6

• One of most well studied subfamilies with over 90 known variants
• Responsible for metabolism of:
  – Codeine
  – Metoprolol
  – Simvastatin
  – Tamoxifen
• No recommendation for routine genetic testing prior to using any of these products

Thiopurine S-Methyltransferase (TPMT)

• Not CYP but another type of PK genetic variant
• Responsible for metabolism of Azathioprine and 6-Mercaptopurine
• If low or absent TPMT activity then dose reductions of up to 90% may been needed due to leukopenia
• Prospective testing allows for dosing changes to decrease the chance of leukopenia while not affecting efficacy
• FDA does not specifically recommend but guidelines do especially if evidence of severe toxicity

Pharmacodynamics (PD)

• Effect of a drug at its therapeutic target and at other nontarget sites
• May achieve concentrations but the response is different than expected
• PD changes can impact the drug target itself or one of the components through the pathway
• Not as straightforward as PK with differences being difficult to detect and identify with testing

AES POLL QUESTION

CHEST guidelines recommend routine PGx testing prior to initiating warfarin.

A. True
B. False

Warfarin

• Genetic variant called VKORC1 polymorphism has impact on Vitamin K oxide reductase complex
  – VKORC1 converts Vitamin K-epoxide to Vitamin K
  – This is the rate limiting step in recycling Vitamin K
  – Also the target of warfarin
• Changes the enzyme’s response to warfarin
• Stratifies doses of warfarin to reach target INR based on how quickly Vitamin K is recycled
Warfarin

- Also has PK issues with CYP2C9
- Very common in Caucasians less so in Asians and AA
- Variant shows reduced activity of the enzyme
  - Slower warfarin metabolism
  - Lower mean doses of warfarin
  - Longer times to stabilize INR
  - Higher risk of bleeding events
- Genetic testing is available but not recommended
- PI does reflect dosing recommendations if warranted by genetics

Idiosyncratic Reactions

- Adverse drug reaction that cannot be anticipated based on known drug target
- Examples
  - Abacavir
    - Hypersensitivity reaction if + for HLA-B*5701
    - Testing must be done prior to using antiviral
  - Aromatase Inhibitors
    - Musculoskeletal side effects have been seen if + for TDL1A
  - Carbamazepine
    - Stevens Johnson if + for HLAB*1502 (Asians) or A*3101 (Europeans)
    - Recommend testing in Asians

Disease Pathogenesis

- Actually identifying the genetic mutation and “correcting” with targeted drug therapy
- Cystic Fibrosis is caused by mutations in the CFTR gene
  - G551D mutation is present in 5% of CF patients
  - Interferes with activation of CFTR chloride channel
- Ivacaftor is an oral CFTR modulator that is specific for the G551D mutation
  - This drug restores function in patients with this mutation
- All patients should be tested for G551D mutation

Challenges with PGx Testing

Who’s in Charge?

- FDA mandates manufacturers to update PIs for specific PGx testing
  - https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
- FDA has mandated changes to 41 drug labels
  - Only 3 require testing prior to initiation of therapy
  - The updates are in a variety of sections within PI
    - Many chemotherapy agents require genetic testing to determine first line tx (i.e. Breast Cancer)
  - Three categories
    - Mandatory for drug use
    - Important for drug use
    - Purely informational

- Individual treatment guidelines may or may not support the use of PGx testing
  - CHEST guidelines recommend against for warfarin
  - HIV guidelines recommend for Abacavir
- No standardized approach in translating PGx testing into clinical practice
Barriers Converting to Clinical Practice

- Limitations in the design of published PGx studies
- Regulatory and ethical concerns
  - Potential for delay in therapy awaiting genotyping results
- Lack of cost-effectiveness analysis
- Lack of number of tests
- Lack of guidelines for test implementation
- Lack of education on the benefits of testing

AES POLL QUESTION
Which of the following hinders the use of RCTs in testing validity of PGx testing?

A. Everyone is genetically equal
B. Number Needed to Treat (NNT)
C. No interest by the government
D. All the above

Study Design Limitations

- Many trials are underpowered for genetic association
  - Sample sizes are inadequate
  - Expensive and difficult to recruit NNT to see power
- Heterogeneity is lacking secondary to comparison of phenotypes vs. genotypes
- Identified variables within a trial may not be translatable to clinical practice
  - TPMT is only seen in 1 in 300
  - Gene found only shows a minor improvement if targeted with therapy

Regulatory and Ethical Concerns

- Only about 10% of labels include pharmacogenetic information
- No strict regulation of genotyping tests
- No guarantee drug industry is using genotyping and if so in what phase of the new drug development
- If genetic “issues” are discovered will this stigmatize individuals
  - Will testing delay treatment
  - Increase complications
- Genetic Information Nondiscrimination Act of 2008

Lack of Cost-Effectiveness

- Need high prevalence of the genetic variant
- Good correlation between phenotype and genotype
- Appropriate testing criteria
- Disease associated with morbidity and mortality if left untreated
- Significant reduction in ADRs if testing done
  - CYP2CP and VKORC1 testing prior to warfarin use??
- Good news is the price of PGx tests is becoming more affordable

Lack of Tests and Guideline Adoption

- Industry still growing with new testing being investigated
- Testing does not always impact a large population
- Limited tests that have impact on clinical outcomes
- Lack of clear, peer-reviewed EBM guidelines that show test results used in prescribing specific medications
- Lag in implementation of guidelines
  - Disease state specific
  - Governing bodies do not universally accept pharmacogenetic testing
Provider Education

- Survey of Primary Care Physicians, Cardiologists, and Psychiatrists
  - 12.6% very familiar
  - 11% had formal training
  - 37% agreed there is impact on drug therapy
- Professional Schools are updating curricula
- Professional organizations are playing catch up to educate healthcare practitioners
- Preparing HC workers to assist patients
  - Increasing knowledge of utilization
  - Addressing fear of discrimination

How Will We Know When Its Right?

Burden of Proof

- Goal is to create tests that are cost-effective and clinically useful
- Reminder that RCTs are not always amenable to pharmacogenomics
  - Safety concerns
  - NNT to power the study
- Trial design of PGx testing is being driven by several factors
  - Knowledge about potential genetic effects
  - Where should testing be done in clinical development process
  - Viewpoint of experts on what type of trial is needed

Clinical Utility

- PGx tests need evidence of clinical utility
  - Easy Access and quick results
  - Minimize complications
  - Improve health outcomes
- Studies are needed that:
  - Use genomic tests in a practical manner
  - Compare to the current standard of care
  - Measure the impact of tests on important health outcomes
  - Demonstrate effective action or other measurable benefit from the test
- How to design the studies is case-by-case challenge

ACCE Model

- Series of 44 questions that are useful to define scope of a review and appraise studies of PGx tests
- ACCE
  - Analytic validity: technical accuracy and reliability
  - Clinical validity: ability to detect or predict an outcome, disorder or phenotype
  - Clinical utility: whether use of the test to direct clinical management improves patient outcomes
  - Ethical, legal, and Social implications

ACCE model

- Endorsed by the CDC-sponsored EGAPP initiative
  - Evaluation of Genomic Applications in Practice and Prevention
  - EGAPP extended and refined the ACCE
- Added a multidisciplinary Working Group
  - Employs rigorous process to develop EBM reviews
  - Makes recommendations for use of PGx in clinical practice
  - Not a government advisory committee and has no regulatory authority
- Three PGx evidence based drug recommendations
  - All 3 say there is insufficient evidence to support or deny use
CPIC

- Clinical Pharmacogenetics Implementation Consortium
- Established by NIH PharmGKB
- Specifically they assist clinicians to understand how PGx tests may improve drug therapy
  - All guidelines have a specific format
  - Grade levels of evidence based on several factors
- Endorse guidelines for 35 drugs
  - Give very specific information on how to use PGx tests in clinical practice
  - Examples include TPMT and CYP2C9 and VKORC1

Evidence vs. Payment

- Lack of consensus in clinical guidelines and limited evidence for clinical utility hinder use in practice
- EBM and cost-effectiveness are the keys to reimbursement and acceptance
- Government insurers and PBM rarely pay for “random” PGx tests unless life saving ie Heme/Onc
- Access may be limited but testing companies work with patients
- Prices Vary

Practice Recommendations

- At this time required testing is for specific circumstances and diseases – not universal in primary care
- Current EBM structure is incompatible with PGx however ACCE/CPIC are standardizing approaches to analyzing literature
- Current Clinical Practice should include:
  - Be aware of a reliable testing company/center
  - Documentation within the medical record should be linked to either diagnosis or medication associated with the test results
  - EMR should prompt when test is standard of care/FDA requirement
  - Patient education materials should be readily available
  - Have an understanding of 3rd party payors and if testing is covered

Questions
Stay Tuned

- https://www.pharmgkb.org/
- https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
- https://www.genome.gov/27530645/faq-about-pharmacogenomics/