New Approach to Medicine: Personalized Medicine/Pharmacogenetics/Pharmacogenomics

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Required Disclosure

• The presenter for this activity has been required to disclose all relationships with any proprietary entity producing health care goods or services, with the exemption of non-profit or government organizations and non-health care related companies.

• No significant financial relationships with commercial entities were disclosed by any of the speakers.
1. Pharmacogenetics has potential to? (Select all that apply)

a. Improve patient outcome
b. Decrease risks of adverse events
c. Promote use of targeted cost-effective therapy for patient care
2. Genomic medicine can help with which of the following? (Select all that apply)

a. Disease risk stratification
b. Disease diagnosis
c. Disease prognosis
d. Selecting optimal therapy
e. Disease monitoring
3. Analytic validity is defined as?

a. Accuracy with which a specific characteristic is identified in the laboratory test
b. Accuracy with which a genetic test identifies a specific clinical condition
c. Risk and benefits that result from genetic test use
4. Which of the following is true about reactive pharmacogenetic tests?

a. They are ordered when the new medication is prescribed

b. Obtained for future use when needed in the clinical setting

c. Also called prospective testing
5. The Genetic Information Nondiscrimination Act of 2008 protects from discrimination based on genetic information in?

a. Health insurance only
b. Employment only
c. Health insurance and employment
d. Neither health insurance nor employment
Objectives

- At the completion of this activity, the participants will be able to:
  - List indications for use of pharmacogenetics and pharmacogenomics
  - Describe major methods for evaluating evidence for application of pharmacogenetics and pharmacogenomics in the clinical practice
  - Evaluate strengths of pharmacogenomics data
  - Apply pharmacogenomics data for different disease states
Objective: List indications for use of pharmacogenetics and pharmacogenomics
Personalized Medicine, Pharmacogenetics, and Pharmacogenomics

- **Personalized/precision medicine**: right treatment to the right person at right dose with maximizing efficacy and minimizing toxicity
- **Pharmacogenetics**: the study of variability in drug response due to genetics; relation to genes which determine drug metabolism
- **Pharmacogenomics**: broad term which includes all genes in the genome that may determine drug response
Pharmacogenetics/Pharmacogenomics

- Pharmacogenetics/pharmacogenomics can target genes that are involved in drug:
  - Metabolism (pharmacokinetic/pharmacodynamics)
  - Binding and/or interfering with different cellular process
Pharmacogenetics in Clinical Settings

- Pharmacogenetics uses genetic information to improve clinical outcomes of pharmacotherapy

- Pharmacogenetics has potential to:
  - Improve patient outcomes
  - Decrease risks of adverse event
  - Promote use of targeted cost-effective therapy for patient care

Genomic Medicine

- According to the National Human Genome Research Institute, genomic medicine is defined as:
  “Emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic of therapeutic decision-making) and the health outcomes and policy implications of that clinical use”

National Human Genome Research Institute at: www.genome.gov/27527652/genomic-medicine-and-health-care/
Genomic Medicine Definitions

- Genomic medicine: individual patient’s genotypic information in his or her clinical care
- Includes both Mendelian and multigenic complexes diseases
- Currently genomic focuses more on single Mendelian variants with large effect
- Expected that genomics soon should change to using at the same time numerous variants

Genomic Medicine Projects Currently In Implementation

- Some examples of genomic medicine projects which are currently being implemented in clinical practice include:
  - Tumor-based genotype-driven treatment
  - Risk/susceptibility testing in relatives of patients with mutation-bearing cancer
    - E.g. BRCA1 and BRCA2 mutations
  - CYP2C19 and antiplatelet therapy

Genomic Medicine

- Genomic Medicine can help:
  - Disease Risk Stratification
  - Disease Diagnosis
  - Disease Prognosis
  - Selecting Optimal Therapy
  - Disease Monitoring

BRCA1 and BRCA2 Gene Mutations:
- One of the best known and most widely discussed genetics test ever
- Overall, women have 12% lifetime risk of developing breast cancer
- Women with BRCA1 mutation have increased risk of developing breast cancer
- Women with BRCA2 mutation have increased risk of developing breast cancer

Disease Risk Stratification

National Cancer Institute at: www.cancer.gov/about-cancer/causes-prevention/genetics/brc...
Disease Risk Stratification

- BRCA1 and BRCA2 Gene Mutations:
  - Overall about 1.3% women will develop ovarian cancer
  - Estimated that 44% of women with BRCA1 mutation will develop ovarian cancer
  - Estimated that 17% of women with BRCA2 mutation will develop ovarian cancer

National Cancer Institute at: www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet
Disease Risk Stratification

- BRCA1 and BRCA2 Gene Mutations:
  - Men with BRCA1 and BRCA2 mutations also have an increased risk of breast cancer
  - Men with BRCA1 and BRCA2 mutations also have an increased risk of prostate cancer

National Cancer Institute at: www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet
Disease Diagnosis

- Diagnostic testing: using test to confirm the presence or absence of a disease

- Before the era of genomic medicine diagnosis was usually based on:
  - Patient’s age
  - Clinical features
  - Laboratory test
  - Imaging studies
Disease Prognosis

- DNA Single-Gene Tests:
  - RAS regulates cell growth and regulation
  - RAS has three isoforms with KRAS most commonly mutated
  - KRAS mutated in 30%-50% of colon cancers and is associated with:
    - Shorter survival
    - More aggressive tumors
DNA Single-Gene Tests:

- Ability to define distinct subgroups within a disease improves ability to use targeted therapies
- Example includes Cystic Fibrosis (CF):
  - CFTR gene gives instructions for making a protein called the cystic fibrosis transmembrane conductance regulator
  - Cystic fibrosis transmembrane conductance regulator functions as a channel across the membrane of cells which produce mucus, sweat, saliva, etc.

Selecting Optimal Therapy

- DNA Single-Gene Tests:
  - Example includes Cystic Fibrosis (CF):
    - Mutations in CFTR gene (e.g. E56K, P67L, G551D, and some others) → Impaired chloride channel function
    - Novel small molecule, ivacaftor improves function of specific mutations in CFTR and patient outcome
Disease Monitoring

- The risk of rejection with transplant:
  - Highest in the early period immediately after transplant
  - Declines over time
  - Never goes away

- With cardiac and renal transplant need to do invasive biopsies to identify graft dysfunction
Disease Monitoring

- Potentially available less invasive procedure, RNA profiling of:
  - Peripheral blood for cardiac transplant
  - Urine in kidney transplant

- RNA profiling technique allows to identify a key set of transcripts to detect rejection of transplanted grafts

Objective: Describe major methods for evaluating evidence for application of pharmacogenetics and pharmacogenomics in the clinical practice
Evidence Supporting Clinical Implementation of Pharmacogenomics

- Criteria for evaluating genetic and genomic tests include:
  - Analytical validity
  - Clinical validity
  - Clinical utility

Analytical Validity

“Analytic validity: accuracy with which a particular genetic characteristic can be identified in a laboratory test” (Burke W et. al., 2002)

Can use different protocols to test most genetic characteristics of clinical interest

There can be different technical issues when evaluating analytic validity such as:
  - Specific technical requirements for chosen assay
  - The reliability of assay
  - How much reliability varies from laboratory to laboratory
Analytical Validity

• Two different types of genetic tests:
  • **In-house**: test by clinical laboratory (e.g. laboratory-developed or home-grown)
  • **Manufacturer-developed**: *in vitro* diagnostic test for a specific drug that is critical for safe and effective use of that drug (e.g. companion diagnostic tests)
Analytical Validity

- The Clinical Laboratory Improvement Amendments (CLIA) governs quality standards for laboratory-developed tests.

- CLIA regulations classifies laboratory testing based on the complexity of the tests as either:
  - Waived or
  - Non-waived → Molecular genetic testing is high-complexity

- Genetic test will not be used if it does not meet acceptable standards for analytic validity.
Clinical Validity

“Clinical validity: accuracy with which a genetic test identifies a particular clinical condition” (Holtzman NA, Watson MA, 1999)

Clinical validity is described by:

• Sensitivity
• Specificity
• Positive predictive value
• Negative predictive value
Clinical Validity

- Sensitivity: among people with a particular condition the proportion who have positive test
- Specificity: among people who do not have condition the proportion who have negative test
- Positive predictive value
- Negative predictive value
Clinical Validity

• Positive predictive value: among people with positive test the proportion who have the condition

• Negative predictive value: among people with negative test the proportion who have the condition

Burke W. Curr Protoc Hum Genet. 81:9.15.1-9.15.8
Clinical Utility

• “Clinical utility: refers to the likelihood that the test will lead to an improved health outcome” (Burke et.al. 2002)

• The most important factors in determining clinical utility include:
  • If the test or subsequent interventions lead to improved health outcomes in people with positive test result
  • What risks happen as a result of testing
Clinical Utility

- To completely measure clinical utility need to include:
  - Medical outcomes
  - Social outcomes
  - Subsequent interventions for peoples with positive and negative test results
Objective: Evaluate strengths of pharmacogenomics data
Drug-Gene Association

- Evaluation of drug-gene association should include:
  - Genetic variants of interest
  - Evidence to support clinical utility
  - Evidence-based guidelines (e.g. Clinical Pharmacogenetic Implementation Consortium guidelines with clear recommendation)

Pharmacogenetic Test Ordering and Laboratory Processing

- Pharmacogenetic testing can be performed:
  - Reactively (at point-of-care):
    - At the point of care to guide drug therapy or
  - Pre-emptively (prospective):
    - Obtained for future use when needed in clinical setting
Point-of-Care vs. Preemptive/Prospective Pharmacogenomic Testing

- **Reactive/Point-of-Care Pharmacogenomic Testing:**
  - Ordered when new medication is prescribed
  - Pharmacogenomic test can be ordered for the specific gene or genes that are involved in drug metabolism, transport and/or target
  - Delay in therapy until results are back
    - Would still need interim medication

Haga SB and Moaddeb J. Pharmacogenet Genomics 2014. 24(3): 139-145
Point-of-Care vs. Preemptive/Prospective Pharmacogenomic Testing

- **Preemptive/Prospective Pharmacogenomic Testing:**
  - Involves analysis of a panel of genes with known associations to drug outcome
  - Some populations may specifically benefit from pre-emptive testing such as populations with:
    - Chronic conditions
    - Risk factors for chronic conditions
  - Preemptive pharmacogenomic tests results available whenever treatment is needed
Challenges Associated with Producing Evidence

- Growing list of drugs that have some reference to pharmacogenomic testing included in the drugs labeling
  - Germline mutations (e.g. CYP metabolizing enzyme gene variations)
  - Somatic mutations (e.g. KRAS expression in colorectal cancer)
- Some drugs are co-developed with pharmacogenetic tests
Challenges Associated with Producing Evidence

- Most labels refer to reported pharmacogenetic associations (e.g. altered drug metabolism or drug-gene interactions).

- Most labels do not specifically recommend testing before prescribing a drug or provide any recommendation how prescribing should be modified.
Synthesizing Evidence-Based Guidelines

- Very important to develop clinical practice guidelines for pharmacogenomics

- Major pharmacogenomics guidelines:
  - The Clinical Pharmacogenetic Implementation Consortium (CPIC), established 2009

Clinical Pharmacogenetics Implementation Consortium Guidelines at: www.cpicpgx.org/guidelines/
Evidence-Based Guidelines

- The Clinical Pharmacogenetic Implementation Consortium (CPIC):
  - Formed by joint effort between the Pharmacogenomics Knowledge Base (PharmGKB) and the National Institute of Health (NIH)-funded Pharmacogenomics Research Network
  - Created to develop guidelines that would enable translation of clinically relevant pharmacogenetic test results into accountable therapeutic recommendation
  - Provide guidance to clinicians how available genetic test results should be used to improve drug therapy

Clinical Pharmacogenetics Implementation Consortium: https://cpicpgx.org/
Evidence-Based Guidelines: Evaluating Strengths of Pharmacogenomics Data

The Clinical Pharmacogenetic Implementation Consortium (CPIC):

- Genes-Drugs: CPIC assigns CPIC levels to genes/drugs with:
  - PharmGKB Clinical Annotation Levels of Evidence
  - PharmGKB PGx level for FDA-approved drug labels
  - Based on nomination to CPIC for consideration

Clinical Pharmacogenetics Implementation Consortium: https://cpicpgx.org/genes-drugs/
### Evidence-Based Guidelines: Evaluating Strengths of Pharmacogenomics Data

**PharmGKB Clinical Annotation Levels of Evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Gene/drug pairs have sufficient evidence for at least one prescribing action to be recommended</td>
</tr>
<tr>
<td>1B</td>
<td>Gene/drug pairs have sufficient evidence for at least one prescribing action to be recommended</td>
</tr>
<tr>
<td>2A</td>
<td>Gene/drug pairs have sufficient evidence for at least one prescribing action to be recommended</td>
</tr>
<tr>
<td>2B</td>
<td>Gene/drug pairs have sufficient evidence for at least one prescribing action to be recommended</td>
</tr>
<tr>
<td>3</td>
<td>Not considered to have adequate evidence or actionability to have prescribing recommendations</td>
</tr>
<tr>
<td>4</td>
<td>Not considered to have adequate evidence or actionability to have prescribing recommendations</td>
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</tbody>
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Clinical Pharmacogenetics Implementation Consortium: [https://www.pharmgkb.org/page/clinAnnLevels](https://www.pharmgkb.org/page/clinAnnLevels)
Evidence-Based Guidelines: Evaluating Strengths of Pharmacogenomics Data

- PharmGKB PGx level for FDA-approved drug labels of:
  - Genetic testing required
  - Genetic testing recommended
  - Actionable
  - Informative

- Based on nomination to CPIC for consideration

Clinical Pharmacogenetics Implementation Consortium Guidelines at: www.cpicpgx.org/guidelines/
Clinical Practice Dissemination

- Guidelines need to be disseminated at:
  - Peer reviewed journals
  - Web sites
  - National guidelines site
Main Characteristics of Clinical Pharmacogenetics Services

- Selecting gene-drug pairs for implementation
- Institutional oversight of pharmacogenetic evidence analysis and application to patient care
- Clinical support for health care providers
- Standardized laboratory ordering and interpretation procedures
- Involvement of informational technology
- Education of different health care professionals
- Quality improvement and economic evaluations

Administrative and Stakeholder Engagement

- Need to obtain support from institutional leadership

- Generally should obtain support from:
  - Administration
  - Medicine
  - Pharmacy
  - Laboratory
  - Health informational technology (IT)

Major Barriers to the Clinical Implementation of Pharmacogenetics

- Informational technology
- Scientific
- Education
- Ethical, legal, social and regulation issues
- Reimbursement

Barriers to the Clinical Implementation of Pharmacogenomic Testing

Some of potential barriers to the clinical implementation of pharmacogenomic testing include:

- Test-related barriers
- Knowledge barriers
- Evidence barriers

Challenges In Implementation of Genomics in Clinical Practice

- Many challenges in implementation of genomics in clinical practice:
  - Limited evidence
  - Conflicting interpretation of benefit and value
  - Limited access to genomic medicine expertise and testing
  - Lack of standards for genomic applications
  - Lack of research funding and reimbursement

Clinical Pharmacogenomics Implementation

- Clinical pharmacogenetics implementation can be incorporated into electronic health record (EHR)

- EHR can help health care providers to easily and quickly interpret and act on pharmacogenetic test results

Educational Needs to Support Implementation of Pharmacogenomics

- Need comprehensive and multidisciplinary strategies to educate different health care professionals

- Genetics/Genomics Competency Center (G2C2) established to provide high quality genetics/genomics educational resources for health care educators and practitioners

National Human Genome Research Institute at: www.genomicseducation.net
Educational Needs to Support Implementation of Pharmacogenomics

• Genetics/Genomics Competency Center (G2C2) has competencies map for:
  • Nursing
  • Physician assistant
  • Pharmacist
  • Genetic counselors
  • Physicians

National Human Genome Research Institute at: www.genomicseducation.net
Educational Needs to Support Implementation of Pharmacogenomics

- Genetics/Genomics Competency Center (G2C2) competency map for pharmacists include:
  - Basic genetic concepts
  - Genetic and diseases
  - Pharmacogenetics/pharmacogenomics
  - Ethical, legal and social implications

National Human Genome Research Institute at: www.genomicseducation.net
The Genetic Information Nondiscrimination Act of 2008

- The Genetic Information Nondiscrimination Act (GINA) of 2008 protects from discrimination based on their genetic information in both:
  - Health insurance (Title I) and
  - Employment (Title II)

Informed Consent and Patient-Provider Communication

- **Informed consent**: a process for getting permission before conducting a healthcare intervention on a person

- A health care provider may ask a patient to consent to receive therapy before providing it or a clinical researcher may ask a research participant before enrolling that person into a clinical trial
Informed Consent for Pharmacogenomics

- Different factors should be taken into considerations when designing an informed consent process and consent form such as:
  - Information is personal and unique to each individual
  - If information is going to be stored and used indefinitely
  - Need to inform individuals about susceptibility to a broad range of conditions (some of which are unexpected given personal or family history)
  - If tests carry with them risks that are uncertain or unclear
  - Raise privacy concerns (due to the risk of re-identification)

National Human Genome Research Institute at: https://www.genome.gov/about-genomics/policy-issues/Informed-Consent
FDA Drug Labels and Pharmacogenomics

- Drug labeling may include information on genomic biomarkers which can define:
  - Drug exposure and clinical response variability
  - Risk for adverse events
  - Genotype-specific dosing
  - Mechanisms of drug action
  - Polymorphic drug target and disposition genes
  - Trial design
Objective: Apply pharmacogenomics data for different disease states
Pharmacogenomics Data for Different Disease States

- Psychiatry
- Cardiology
- Neurology
- Infectious diseases
- Hematology/Oncology
- Pulmonology
- Anesthesiology
- Gastroenterology

U.S. Food and Drug Administration at: www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
Pharmacogenomics in Oncology Research

- Oncology has the most success in search for useful biomarkers
- With the success of targeted therapies there is a huge interest in finding more biomarkers to help to identify patients with the greatest likelihood of receiving benefits from a specific therapy
Pharmacogenomics in Oncology Research

- In pharmacogenomics research in oncology very important both:
  - Somatic mutations and
  - Germline mutations
Pharmacogenomics in Oncology Research

- **Somatic mutations**: present in the cancer tissue and can define cancer subtype
  - Can develop medications that target specific receptor expressed on the cancer cell
  - Examples include: Monoclonal antibodies panitumumab and cetuximab directed against the epidermal growth factor receptor (EGRF)

Germline mutations:

- Present in patient’s normal tissues
- Affect pharmacokinetics and pharmacodynamics of a medication
- Example include: Mercaptopurine used for the treatment of acute lymphoblastic leukemia (ALL)
  - Patients with inactive variant of TPMT allele need to have mercaptopurine dose reduced due to the increased toxicity

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