Pharmacogenomics and Clinical Application

Cynthia A. Prows, MSN, CNS, FAAN
Clinical Nurse Specialist, Genetics
Children’s Hospital Medical Center
Cincinnati, OH, USA

Objectives

• Describe the multifactorial aspects of drug response
• Discuss the purpose and limitations of using pharmacogenomics in clinical practice
• Discuss nurses’ genetics / genomics competencies as they relate to pharmacogenomics
BRIEF Overview of Terms & Concepts

Genetic Terms

- **Allele**: One version of a gene at a given location (locus) along a chromosome
  - The most common version of a gene in a population is called the **wild type allele**

- **Genotype**: Single or pair of alleles at a specific locus of a chromosome
  - BRCA1 (del185AG)
  - CYP2D6*5 / CYP2D6*17

- **Phenotype**: Measurable or observable expression of the genotype

Few More Definitions

- **Pharmacogenetics**: study of genetic causes of individual variations in drug response determined by **single genes**
- **Pharmacogenomics**: study of variability in drug response determined by **multiple genes**
- **Personalized Medicine**: using patient-specific genetic and clinical information to select a treatment for that individual
Categories of Drug Response

- Measureable response
  - Laboratory values
- Observable clinical outcomes
  - Efficacy: desired (therapeutic) response from medication
  - Toxicity: undesired responses from medication; side effects, adverse drug reactions
    - Adverse Drug Reaction (ADR): any noxious or unintended action / reaction to a drug administered in standard doses

Adverse Drug Reactions

- In hospitalized patients¹-⁴
  - Incidence: 28% overall, 17% children, 7% serious
  - 50% no preventable cause
  - ADR-related morbidity/mortality³,⁵
    - Over 100,000 deaths/year in U.S. (4⁴th-6⁶th leading cause of death)
    - $177 billion (>10% of total health care spending)
    - Approximately equal to the cost of medications

References:

Modern Pharmacology:
Science of Drugs and their Actions

Pharmacokinetics
- What the body does to the drug
  - PK
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

Pharmacodynamics
- What the drug does to the body
  - PD
  - Receptor binding
  - Post-receptor effects
  - Chemical interactions

Factors Contributing to Clinical Response

Clinical Response – Efficacy / ADRs

Pharmacokinetics
- Age
- Gender
- Infection
- Hepatic function
- Drugs

Pharmacodynamics
- Renal function
- Alcohol
- Exercise
- Herbs
- Diet
- Genetics
- Pregnancy
- Smoking
- Occupational Exposure

Type of Drug Response Genes

- Genes that produce proteins involved in drug absorption, distribution, metabolism, elimination (Pharmacokinetics)
  - Clinically available pharmacogenetic tests primarily analyze genes that produce drug metabolizing enzymes (DME)
Type of Drug Response Genes

- Genes that produce proteins which influence how the drug affects the body (Pharmacodynamics)
  - Cell surface drug receptors (site of drug action)
  - Transporters and ion channels
  - Immune molecules

Genotype: single locus or multiple loci

FDA Adding Genetics Information to Some Drug Labels

- If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug (- 21 CFR 201.57)
Genetics Information in Drug Labels

- PG info in ~10% of labels for FDA-approved medications
- Genomic biomarkers can be important in
  - Identifying responders and non-responders
  - Adjusting doses to optimize efficacy and safety
- Genomic biomarkers classified on the basis of their use
  - Clinical response and differentiation
  - Risk identification
  - Dose selection guidance
  - Susceptibility, resistance and differential disease diagnosis
  - Polymorphic drug targets

Sample of FDA Approved Drug Labels Containing Genomic Biomarkers Information

<table>
<thead>
<tr>
<th>Genomic Biomarkers</th>
<th>Drug</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Her2/neu over-expression</td>
<td>Herceptin (Trastuzumab)</td>
<td>Required</td>
</tr>
<tr>
<td>CYP2C9 variants</td>
<td>Coumadin (Warfarin)</td>
<td>Recommended</td>
</tr>
<tr>
<td>Vitamin K epoxide reductase (VKORC1) variants</td>
<td>Coumadin (Warfarin)</td>
<td>Recommended</td>
</tr>
<tr>
<td>CYP2D6 variants</td>
<td>Straterra (Atomoxetine) Ability (Aripiprazole) Risperdal (Risperidone)</td>
<td>Information</td>
</tr>
</tbody>
</table>

HER2: Somatic Cell PG

- **HER2**: human epidermal growth factor receptor 2 gene (**ERBB2**)
  - Overexpressed in 18% to 30% of breast cancer (source dependent)
- Trastuzumab (Herceptin), a monoclonal antibody, specifically targets HER2 receptors

ASCO/CAP Guidelines 2007

- HER2 positive disease if
  - Protein expression positive
  - or HER2 gene amplification positive
    - Genetic but not inherited
    - Testing tumor cells


Nurse’s Role

A. Before administering first dose of Herceptin, determine if HER2 testing was done
B. Assess client’s knowledge & perceptions about HER2 testing
C. Assess client’s knowledge of and response to HER2 test results
D. Explain / clarify purpose, limitations of HER2 testing
E. All of the above

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Warfarin
- One of the most commonly prescribed drugs in the U.S.A
- Narrow therapeutic range
  - Above = risk of hemorrhage
  - Below = risk of thrombosis
- Optimal dose difficult to predict

Warfarin Narrow Therapeutic Range
- Therapeutic target International Normalized Ratio (INR) usually 2 – 3
- INR > 4.5 = 5 fold increase risk of intracranial hemorrhage
- INR < 2.0 = 17 fold increased risk of stroke due to thrombosis

Reynolds, KK, et al. 2007, Personalized Medicine
Ansell JE, 2003, Semin Vasc Med

Variability in Warfarin Maintenance Dose Requirement

Reynolds, KK et al. 2007 Personalized Medicine
Warfarin Package Insert PG Information

- “Must be individualized for each patient according to the particular patient’s PT/INR response to the drug”
- Recommended starting dose = 2 to 5 mg per day with dosage adjustments based on the result of PT/INR. “The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes…”

Package Insert Recommendation – Role of Prescribing APN?

A. Order CYP2C9 and VKORC1 genetic testing prior to initiation dose
B. Order CYP2C9 and VKORC1 genetic testing if difficulty achieving INRs in therapeutic range
C. Use CYP2C9 and VKORC1 test results instead of age, weight, gender & race information to determine initiation dose
D. Determine if client has had testing for CYP2C9 or VKORC1 or both in the past
E. Order CYP2C9 and VKORC1 genetic test even if previously done as this information changes over time
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PG Limitations

- Only common alleles known to affect protein function and drug response are tested
  - Alleles “not found” ≠ “normal”
  - Drug response result of multi-gene, multi-environmental and behavioral factors
Centers for Medicare and Medicaid Services Response to Warfarin Pharmacogenetic Test, May 4, 2009

...good evidence that:

tests accurately identify persons who have variant CYP2C9 and VKORC1 alleles... persons who have these variant alleles have heightened warfarin responsiveness....

do not conclusively establish an actual benefit or risk to a beneficiary's health outcome.

PG testing... covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin and only then in the context of a prospective, randomized, controlled clinical study... [in which] the frequency and severity of the following outcomes [are measured]:

- major hemorrhage, minor hemorrhage, thromboembolism related to the primary indication for anticoagulation, other thromboembolic event, mortality


Why PG Testing in Psychiatry?

• Significant variability in clinical response^1-4
  • 30%-75% of patients experience efficacy
  • 65%-75% encounter adverse events


Proportion of Pharmaceuticals Metabolized by Individual Cytochrome P450 Enzymes

Shimada et al, 1994
Why PG Testing in Psychiatry?

- CYP2D6, CYP2C19-metabolized psychotropics include
  - Antidepressants
  - Antipsychotics
  - Psychostimulants
- Approximately 50% of psychiatric and psychogeriatric patients use at least one drug metabolized by CYP2D6.
- Serum concentrations of CYP2C19- and CYP2D6-dependent antidepressants influenced by predicted phenotype

Kootstra-Ros JE et al., J Clin Pharmacol 2006;46:1320-7
van der Weide J et al., Ther Drug Monit 2005;27:478-83

CYP2D6

- Influenced by inherited variations
- Influenced by concurrent medications
- At least 70 variant alleles that affect function
- Four phenotypic groups
  - Poor metabolizer
  - Intermediate metabolizer
  - Extensive metabolizer
  - Ultra rapid metabolizer
- Polymorphism frequencies differ among populations


Metabolic Fate of Drugs

Metabolism Phenotypes

- Poor metabolizer (PM) (5 – 10%)
  - Active drug
    - Higher levels of drug in the blood (accumulation)
    - Respond to lower doses of these medications
    - Increased risk for side effects/ADRs at usual or higher doses
  - Pro-drug
    - Lack of therapeutic response (not converted to active form)
- Intermediate metabolizer (IM) (~38%)
  - Active drug
    - May require lower than normal doses but can generally tolerate normal doses
- Extensive metabolizer (EM) (~50%)
  - Majority of the population (‘wild type’)
  - Respond to standard drug dosing
- Ultra-rapid metabolizer (UM) (1 – 4%)
  - Active drug
    - Lower levels of drug in the blood (rapidly converted to inactive metabolites)
    - Require higher doses of these drugs for response
    - Less likely to incur side effects at usual doses
  - Pro-drug
    - Increased risk of toxicity (rapid conversion to active form)
Dose Adjustment Based on CYP2D6 Status


Which Clinical Outcomes Matter?

Psychotropics and DME Phenotype

- Concentrations outside therapeutic range associated with CYP2C19 PM and CYP2D6 PM and UM phenotypes
- Antipsychotic metabolic ratios correlated with CYP2D6, CYP2C19 genotypes

Kootstra-Ros JE et al., J Clin Pharmacol 2006;46:1320-7
van der Weide J et al., Ther Drug Monit 2005;27:478-83
### Clinical Outcomes in Psychiatry Associated with DME Phenotype

- **Trends toward**
  - More ADRs in CYP2D6 PMs
  - Longer hospitalizations in CYP2D6 PMs
  - Increased health care costs in CYP2D6 PMs and UMs

- **More ADRs in CYP2D6 PMs**
- **Longer hospitalizations in CYP2D6 PMs**
- **Increased health care costs in CYP2D6 PMs and UMs**

- **Trend toward longer hospital stays for CYP2D6, CYP2C19 IMs and PMs**

- **More frequent need to switch antidepressants and change dosing regimen for 2D6 IMs, PMs**

- **More likely to be prescribed drugs to treat parkinsonian side effects**
  - 2D6 PMs on antipsychotics metabolized by CYP2D6

- **Retrospective review of 279 CCHMC psychiatry inpatients**
  - In patients taking CYP2D6 and/or CYP2C19-metabolized psychotropics
    - Increased use of behavioral interventions CYP2D6 PMs to UMs
    - Increased number of ADRs in CYP2C19 PMs
    - Trend toward increasing number of ADRs from CYP2D6 UMs to CYP2D6 PMs

Prows, et al (in press) *Journal of Pediatric and Adolescent Psychopharmacology*
### PG Information in Select Psychotropic Package Inserts

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
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<tbody>
<tr>
<td>[Table of Substrates]</td>
<td>[Table of Inhibitors]</td>
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</table>
Atomoxetine Label and CYP2D6

- Label information
  - CYP2D6 PMs have a 10 fold higher AUC and a 5 fold higher peak concentration to a given dose compared with EMs... Laboratory tests are available to identify CYP2D6 PMs... The higher blood levels in PMs lead to a higher rate of some adverse effects.

- Drug – drug interactions
  - CYP2D6 inhibitors result in increased atomoxetine steady-state plasma concentrations similar to those observed in PMs

- Dosing
  - Suggested dose adjustments if using a strong CYP2D6 inhibitor (no recommendations based on being a CYP2D6 PM)

More Side Effects / Better Efficacy?

- Michelson et al (2007) demonstrated:
  - Atomoxetine more effective (P = 0.002) in CYP2D6 PMs than CYP2D6 EMs
  - CYP2D6 EMs more likely to discontinue therapy due to lack of efficacy than CYP2D6 PMs
  - A trend for more discontinuations due to ADRs in PMs when compared to EMs (P=0.063)


Aripiprazole (Abilify)

- CYP2D6 PMs have about an 80% increase in aripiprazole exposure than CYP2D6 EMs
- The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs
- PMs typically need 30-40% lower doses to achieve a similar steady-state serum concentration as EMs.
- Strong CYP3A4 (eg. ketoconazole) or CYP2D6 (eg. fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one half when used concomitantly except when used as adjunctive treatment with antidepressants
- CYP3A4 inducers (eg. carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly

http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021436s21,021713s16,021729s8,021866s8lbl.pdf
Risperidone

- Largely dependent on CYP2D6 with minor involvement of CYP3A4/5
- Approximately 7-fold reduced mean total body clearance of risperidone in CYP2D6 PMs
- Lipophilic risperidone crosses blood-brain barrier more efficiently than hydrophilic 9-OH-risperidone in rats
- P-glycoprotein has greater affinity for pumping 9-OH-risperidone out of the brain
- CYP2D6 PMs had over 3-fold higher risk of significant ADRs and 6-fold higher risk of discontinuing due to ADRs than EMs


SSRIs, Genetic Testing: EGAPP

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) report: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors
  - “Insufficient evidence to support a recommendation for or against use of cytochrome P450 (CYP450) testing in adults beginning selective serotonin reuptake inhibitor (SSRI) treatment for non-psychotic depression.”
  - “EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.”
  - “Considering the high prevalence of depressive disorders and the length of time required to determine whether a given antidepressant is successful or not, there may be a perceivable impact at the population level if even a small benefit can be demonstrated at the individual level.”
  - “Recommend prospective studies of CYP450 genotyping in the treatment of non-psychotic depression with selective serotonin reuptake inhibitors (SSRIs) to examine the utility of such genotyping in clinical practice”

Paroxetine & Fluoxetine
- Potent CYP2D6 inhibitors
  - Can cause CYP2D6 EMs to function as PMs
    - Tamoxifen
      - Prodrug - CYP2D6 responsible for metabolic activation of tamoxifen to its most potent anti-tumor metabolite, endoxifen
      - CYP2D6 PMs shown to have greater than threefold increased risk of recurrence
      - The most common side effect = HOT FLASHES
      - Up to 25% women treated with an SSRI to manage the hot flashes

  - CYP2D6 *1/*1 assumed when specific PM associated alleles not found
  - Use of SSRI modifies endoxifen levels
  - Three patients with vt/vt genotype not on SSRI because hot flashes not problematic
    - Still had lowest mean plasma concentrations of endoxifen at 4 months of therapy


SSRIs and Tamoxifen
- Fluoxetine, paroxetine are CYP2D6 enzyme inhibitors
  - Used to treat Tamoxifen related hot flashes
    - IMs, EMs become PMs? (Steams, 2003)
    - Change in phenotype NOT genotype
    - May increase risk for breast cancer recurrence (Goetz, 2007)
  - Citalopram may be safe alternative
    - did not increase breast cancer recurrence (Lash, 2008)

Pharmacogenetics: CCHMC Experience

Cynthia A. Prows, MSN, CNS, FAAN
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Cincinnati, OH, USA

Genetic Pharmacology Service

- Internal start up funding October 2003
  - Intuitive ordering system
  - Clinically useful laboratory reports
  - Consultation services
  - Education
- Service available July 2004

Intuitive Ordering System
Clinically Useful Reports

- Available in 2 business days
  - Blood (4 business days if cheek sample)
- Test performed
- Predicted phenotype (PM, IM, EM, UM)
- General dosing recommendations
  - If backed by evidence
- Key enzyme inhibitors / inducers
- Critical drug – drug interactions
- Test limitations
- Location of supplemental information

CCHMC Genetic Pharmacology Service

- Service available July 2004 and adapted as needed
  - Order by drug rather than gene
  - **Psychiatrists: PG test for panel of psychotropics (January 2005)**
  - Gastroenterology & Oncology: Order TPMT test by gene rather than drug & report genotype
  - Oncology: Tamoxifen PG test
  - Cardiology (most recent): Warfarin test (CYP2C9 + VKORC1)

Psychiatry Use of PG Testing

- Standing order for all new inpatients
  - Can be canceled
- Close consultation with clinical pharmacist assigned to units
  - Pharmacists notifies physician if patient is a poor metabolizer
    - Part of performance improvement initiative
    - Also done for repeat patients
Psychiatry Use of PG Testing

- Results may trigger prescriber to:
  - Switch to a non-CYP2D6 or non-CYP2C19 psychotropic
  - Escalate dosing more rapidly than is usual practice
    - For genotype predicted extensive and ultra rapid metabolizers

GPS Future Directions

- Additional DMEs and specific alleles tested, when identified and found to influence function
- Expand services to include PG testing for candidate genes other than DME
  - Serotonin transporter (5HTTLPR)
  - Dopamine pathway genes
- Gather data on outcomes
- Develop algorithms to aid in drug/dose selection