Personalized Medicine:
Pharmacogenetics From Bench to Bedside and Beyond

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Objectives

1. Understand current drug prescription practice and outcomes
2. Discuss examples of genetic variants and their influence on drug therapy
3. Describe the role of genetics in drug response and potential to tailor drug therapy.
4. Understand barriers to implementing a genotype-guided drug therapy
5. Develop a drug selection strategy according to patient demographics, clinical factors, and genotype

How do we prescribe medications?

One size does not fit all!

Many patients do not benefit from the first drug they are offered in treatment. For example, 38% of depression patients, 50% of arthritis patients, 40% of asthma patients, and 43% of diabetic patients will not respond to initial tx.

Is variability in response common?

Disclosure: Conflict of Interest

Pharmacogenomic Resource to Improve Medication Effectiveness (PRIME)
Sponsor: GEF-HSF grant
UAB Personalized Medicine Program

Supported in part by grants from the National Heart Lung and Blood Institute
National Institute of Neurological Disorders and Stroke
Is variability in a serious problem?

A woman was brought to the emergency department with a mild rash which progressed to Stevens Johnson Syndrome.

A 45-year-old man was brought to the emergency department by his friends because of a 1-day history of a severe headache and "bizarre behavior." A computed tomography (CT) scan of his brain revealed acute intracranial hemorrhage with cerebral edema, evidence of midline shift, and increased intracranial pressure.

Why do individuals respond differently?

Realize that people are different

• Variability in genes:
  - Drug metabolism genotype
  - Drug transporter genotype
  - Drug receptor genotype
  - Interactions

• Variability in environment:
  - Medications, Diet, Alcohol
  - Exercise

Definitions

• Pharmacogenetics: Effect of genetic variation in response to a drug in terms of therapeutic and adverse effects.
  - Primary candidate genes of interest include those encoding for drug receptors, metabolizing enzymes, and transporters.
• Pharmacogenomics more broadly involves genome wide analysis of the genetic determinants of drug efficacy and toxicity.
• Personalized Medicine Tailoring treatment for an individual patient based on their genetic makeup and other individual characteristics including clinical, demographics, lifestyles, behavior, and environment to guide disease prediction, prognosis and treatment.

Thiopurine methyltransferase: TMPT

Thiopurine drugs are used to treat patients with neoplasia and autoimmune disease as well as transplant recipients. These agents are metabolized, in part, by 5-methylation catalyzed by thiopurine methyltransferase (TPMT).

Patients with inherited very low levels of TPMT activity are at greatly increased risk for thiopurine-induced toxicity such as myelosuppression when treated with standard doses of these drugs, while subjects with very high activity may be undertreated Long-term results of TPMT activity monitoring in azathioprine-treated renal allograft recipients.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm183178.htm

Genotype-phenotype concordance

Figure 3. Thiopurine S-methyltransferase (TPMT) activity in patients with different TPMT genotypes determined by mutation-specific polymerase chain reaction methods.


Dosing 6MP with pharmacogenetics

Patients who are homozygous for TPMT deficiency mutants should receive 10% of the standard dose.

Mercaptopurine Label update 2003

TPMT testing

Genotypic and phenotypic testing of TPMT status are available. Genotypic testing can determine the allelic pattern of a patient. Currently, 3 alleles: TPMT2, TPMT7/A, and TPMT7/C, account for about 90% of individuals with reduced levels of TPMT activity. Alkaline homogenate from these alleles is TPMT deficient and base-phenotyped for the allele. Phenotyping determines the level of thiopurine methylation (TPMT) activity in erythrocytes and can be informative. Calcium must be used with phenotyping since calcium-phosphate co-crystallized can influence measurement of TPMT activity in blood, and recent blood concentrations will represent a patient’s usual TPMT activity.

Common meds with uncommon side effects

• Statins reduce the incidence of heart attacks, strokes, and revascularization procedures by 1/5 for each reduction of 40 mg/dL in LDL cholesterol level
• Rarely, can cause muscle pain or weakness in association with elevated creatine kinase levels (i.e., myopathy), and occasionally, this leads to muscle breakdown and myoglobin release (i.e., rhabdomyolysis), with a risk of renal failure and death
• Incidence of myopathy is ~ 1 case per 10,000 patients per year with standard doses of statins
• Mechanisms by which statins cause myopathy remain unknown but appear to be related to statin concentrations in the blood


Marker for Statin induced myopathy

• 85 subjects with myopathy and 90 controls, all of whom were taking 80 mg of simvastatin daily as part of a trial involving 12,000 participants. Replication was tested in a trial of 40 mg of simvastatin daily involving 20,000 participants.
• The prevalence of the rs4149056 C allele in the population was 15%. OR=4.3, 95%CI 2.6 to 7.2 per copy of the C allele, and 16.9 (95% CI, 4.7 to 62.1) in CC as compared with TT homozygotes. More than 60% of these myopathy cases could be attributed to the C variant.


SLCO1B1 Variants and Statin-Induced Myopathy — A Genome wide Study

SLCO1B1 encodes the organic anion–transporting polypeptide OATP1B1, which mediates the hepatic uptake of various drugs, including most statins and statin acids.
Maximum statins doses: SLOCO1B1

- Statin therapy should be started with the starting dose recommended by the manufacturer or half of the recommended maximum dose, whichever is lower.
- The dose should be titrated up to the minimum effective dose or the suggested maximum dose on the basis of lipid response and tolerability, and the statin should be changed or discontinued as necessary.
- Other factors known to affect statin pharmacokinetics or myopathy risk should be taken into account when selecting a statin and its dose for an individual patient (interacting drugs, concomitant diseases, age, etc.).
- Based on US Food and Drug Administration-approved maximum doses; lower maximum doses may apply in some countries.

A marker for Stevens-Johnson syndrome

<table>
<thead>
<tr>
<th>HLA genotypes</th>
<th>Frequency of HLA alleles in patients with Stevens-Johnson syndrome</th>
</tr>
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<tbody>
<tr>
<td>HLA-B*1502</td>
<td>DLBCL                  CTLA4                  TACI</td>
</tr>
<tr>
<td>B*1502</td>
<td>44 (15.2%)             33 (11.8%)             49 (16.9%)</td>
</tr>
<tr>
<td>B*0702</td>
<td>24 (8.2%)              17 (5.8%)              29 (10.2%)</td>
</tr>
<tr>
<td>B*0701</td>
<td>13 (4.4%)              11 (3.8%)              13 (4.5%)</td>
</tr>
<tr>
<td>B<em>0702</em>0010</td>
<td>7 (2.4%)               6 (2.1%)               9 (3.1%)</td>
</tr>
<tr>
<td>B*3501</td>
<td>6 (2.0%)               5 (1.7%)               8 (2.7%)</td>
</tr>
<tr>
<td>B<em>3501</em>0010</td>
<td>5 (1.7%)               4 (1.4%)               7 (2.4%)</td>
</tr>
<tr>
<td>B*5701</td>
<td>4 (1.3%)               3 (1.1%)               5 (1.7%)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>CBZ-SJS/CBZ-tolerant: 2.504 (95% CI, 126–49.522); ( P = 3.13 \times 10^{-7} )</td>
</tr>
<tr>
<td></td>
<td>CBZ-SJS/normal: 0.895 (95% CI, 50–15.869); ( P = 1.38 \times 10^{-21} )</td>
</tr>
</tbody>
</table>

Ethnicity or Prevalence of HLA-B*1502

Prevent carbamazepine-induced SJS–TEN using HLA-B*1502 screening

| SJS–TEN did not develop in any of the HLA-B*1502-negative subjects receiving carbamazepine (mild transient rash in 4.3% and widespread rash in 0.1%). The estimated historical incidence of carbamazepine-induced SJS–TEN (0.3%) would translate into approximately 10 cases among study subjects (P<0.001). |

Prevent carbamazepine-induced SJS–TEN

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<th>HLA-B*1502 screening Prevents SJS</th>
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Variability in outcomes among patients undergoing PCI

Variability in Clopidogrel effects
- 96 pts- elective PCI, Rx: aspirin (125 mg) + Clopidogrel (300 mg load then 75 mg daily)
- Platelet aggregation (baseline-post-tx. <10%; 0,2h, 24h, 5 days, and 30 days)
- Resistance 63% pts at 2h, 31% pts at 24h, 31% pts at 5 days and 15% pts at 30 days


Genome-wide association
Clopidogrel inhibition of ADP-stimulated platelet aggregation

Clopidogrel - Reduced-Function CYP2C19 and Clinical Outcomes
- Mega et al. [JAMA. 2010;304(16):1821-1830] used consistent end-point definition, investigators from each of the primary studies provided additional data - standardized CV end point (CV death, MI, or stroke)
- Hypothesis: CYP2C19 loss-of-function variant (*2 is the most common) confers an increased risks for major adverse cardiovascular events (MACE)
- Meta-analyses of 9685 patients (91.3% PCI; 54.5% ACS) from 9 trials
- 863 experienced the composite end point of cardiovascular death, myocardial infarction, or stroke; 84 patients had stent thrombosis

<table>
<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Prevalence</th>
<th>Risk for MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>71.5%</td>
<td>Reference</td>
</tr>
<tr>
<td>*1/*2</td>
<td>26.3%</td>
<td>1.55; 95% CI, 1.11-2.17; P=0.01</td>
</tr>
<tr>
<td>*2/*2</td>
<td>2.2%</td>
<td>1.76; 95% CI, 1.24-2.50; P=0.002</td>
</tr>
<tr>
<td>≥ 1 variant</td>
<td>15.7%</td>
<td>1.97; 95% CI, 1.13-3.16; P=0.006</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Prevalence</th>
<th>Risk of stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>71.5%</td>
<td>Reference</td>
</tr>
<tr>
<td>*1/*2</td>
<td>26.3%</td>
<td>2.67; 95% CI, 1.69-4.22; P&lt;0.001</td>
</tr>
<tr>
<td>*2/*2</td>
<td>2.2%</td>
<td>3.97; 95% CI, 1.75-9.02; P&lt;0.001</td>
</tr>
<tr>
<td>≥ 1 variant</td>
<td>2.81%</td>
<td>9.55; 95% CI, 1.81-4.87; P&lt;0.0001</td>
</tr>
</tbody>
</table>
CYP2C19 LoF alleles and outcomes

- Nine systematic review with meta-analysis have been published from 2010 to 2012 ranging from a highly significant effect of the CYP2C19 genotype (RR=1.96; 95% CI = 1.14–3.37), to a modest and non-statistically significant effect (RR of 1.11; 95% CI; 0.89–1.39).

CYP2C19 Genotype (*2 to *8 vs *1 or *17) and Risk of CV Outcomes

Strategies for CYP2C19 intermediate/poor metabolizers

- Prasugrel: Provides greater protection against CV events, but increases bleeding risk compared to clopidogrel.
- Ticagrelor: Undergoes bioconversion into an active metabolite.

Clopidogrel Dose Escalation

- 335 patients with stable CAD on clopidogrel 75 mg daily (ELEVATE-TIMI)
- 4 x 14d treatment period based on CYP2C19. VerifyNow platelet function testing

Summary of Evidence for CYP2C19 guided antiplatelet therapy

- CYP2C19 genotype associated with clinical outcomes, especially stent thrombosis
- Clopidogrel labeling now contains a boxed warning regarding reduced effectiveness in CYP2C19 poor metabolizers.
- CPIC guidelines are available to assist with clinical decisions regarding CYP2C19 genotype.
- Recommend alternative antiplatelet therapy (prasugrel or ticagrelor) in PMs (strong recommendation) and IMs (moderate recommendation) in ACS/high risk PCI patients.
Challenges and Opportunities

- Limited of evidence of efficacy
- Lack on knowledge of harms
- Lack of genotyping capability
- Lack of guidelines on geno-therapy
- Lack of provider education
- Lack of institutional support
- Lack of reimbursement
- Legal/ethical issues

UAB Personalized Medicine Institute

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PMI- Strategic Initiatives

1. Fuel discovery through research: Conduct and support innovative and collaborative research in basic, clinical, population, and translational science focused on identifying the genetic basis of disease and drug response. Specifically where UAB has unique populations such as cancer, cardiovascular, cerebrovascular, endocrine and immunologic disorders, and transplantation.
   - Identify and respond to research opportunities
   - Biobank (information and biologic samples)

2. Improve patient care through implementation: Deliver personalized health care
   - Facilitate diagnosis/prognosis of disease (include genetic markers)
   - Integrating genetic information along with clinical and demographic information to guide selection of medications and their doses.
   - Identify drug/disease targets for which genomics can potentially improve patient outcomes

3. Educate and engage stakeholders: Develop an innovative curriculum to educate current and future practitioners, payors and the community at large in the field of genomics, pharmacogenomics and personalized medicine.

Pharmacogenomic Resource to improve Medication Effectiveness: Genotype-guided antiplatelet therapy

- Aim 1: Build genotyping capability within the Molecular Diagnostic laboratory within UAB hospital that can perform candidate gene assessment within the timeline conducive to the delivery of care.
  - We selected implementation of CYP2C19 genotype-guided antiplatelet therapy as there is sufficient evidence of justify its use in clinical practice and a patient volume (~100 PCI/year) at UAB to support assessment of outcomes.

- Aim 2: Build clinical decision making algorithms (CDMAs) within our EMR (CERNER: IMPACT) and enable automated integration of patient-specific clinical, demographic and genetic information into these CDMAs to guide drug therapy.
  - We will develop clinical decision support based on for published guidelines.

- Aim 3: Generate evidence of capability by demonstrating feasibility of genotype-guided drug therapy and measure outcomes to demonstrate impact (effectiveness, cost-effectiveness) on clinically meaningful outcomes.
  - We will assess effect of CYP2C19 genotype-intervention on outcomes (30 day readmissions, major adverse cardiovascular events, stent thrombosis, bleeding).
  - We will also assess process outcomes (e.g. assay validation, turnaround time for genotype results, adoption of testing and recommendations, etc.)

UAB BioBank

- The University of Alabama at Birmingham Health System (UABHS) provides an ideal setting to identify and address challenges in the delivery of genomic medicine and provide information on clinical validity and utility in racial minorities

- Racially and socio-economically representative population: The UAB hospital (UABH; ~45,000 admissions/year; 45% men and 37-46% African Americans) and associated the outpatient clinics (~1.4 million visits/year; 51% men, 40% African American) have extensive experience in the care of patients

<table>
<thead>
<tr>
<th>Population reflects socio-demographic</th>
<th>West</th>
<th>South</th>
<th>North</th>
<th>Mountain</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race: African Americans</td>
<td>65.2%</td>
<td>63.3%</td>
<td>62.4%</td>
<td>61.8%</td>
<td>62.7%</td>
</tr>
<tr>
<td>European American</td>
<td>56.1%</td>
<td>54.7%</td>
<td>55.2%</td>
<td>54.9%</td>
<td>57.9%</td>
</tr>
<tr>
<td>Income &lt;$15k</td>
<td>62.0%</td>
<td>61.6%</td>
<td>60.6%</td>
<td>60.4%</td>
<td>61.3%</td>
</tr>
<tr>
<td>Income $15K – $30K</td>
<td>36.5%</td>
<td>36.6%</td>
<td>37.3%</td>
<td>37.3%</td>
<td>36.2%</td>
</tr>
<tr>
<td>Income $30K – $50K</td>
<td>34.3%</td>
<td>32.4%</td>
<td>33.5%</td>
<td>33.7%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Income $50K +</td>
<td>27.5%</td>
<td>26.9%</td>
<td>26.6%</td>
<td>26.4%</td>
<td>27.6%</td>
</tr>
</tbody>
</table>

Pharmacy and Therapeutics Committee: Platelet aggregation inhibitor guidelines

- CYP2C19*3 genotype results

- Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)
Pharmacogenomic Resource to Improve Medication Effectiveness
Genotype Guided Antiplatelet Therapy (PRIME-GGAT) (Funded by HSF-GEF)

Outcomes Evaluated
- 30 day mortality
- Major Adverse Cardiac Events
- Major Bleeding
- Stent Thrombosis

Research Coordinator
- Obtains consent for 1 year follow-up
- DNA sample for PCI/ACS patients

Premier Science Session AHA: 15 Nov 2016
Prospective Clinical Implementation of CYP2C19
Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes

Putting personalized medicine to the test

Thank you