Bringing Pharmacogenomics into Clinical Practice: The Why, When and How

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6/22/2017
How often do you apply pharmacogenomics in your area of practice?

A. Frequently
B. Sometimes
C. Rarely
D. Never
How comfortable are you with applying pharmacogenomic results in clinical decision making?

A. Very
B. Somewhat
C. Not comfortable at all
Today's Objectives

• Describe the science of pharmacogenomics and how it applies to clinical practice
• Identify genetic variant effects as pharmacokinetic, pharmacodynamics or immunologic
• Recognize therapeutic modification based on published guidelines and available pharmacogenomics results
• Express methods for incorporating pharmacogenomics into clinical practice and describe challenges faced in doing so
What is “Pharmacogenomics” or PGx?

- Study of genetic changes impacting proteins involved in drug metabolism, action and response
  - Personalized medicine
  - Precision medicine
  - Targeted therapy
What is the goal of PGx?

Image: http://www.pharmainfo.net/reviews/role-pharmacogenomics-drug-development
What is the goal of PGx?

• Benefits of clinical implementation:
  – Reduction of adverse drug events (ADEs)
    • 2 million per year in the US alone
    • 100,000 deaths
    • 6% of hospital admissions
    • $20.6 billion per year
  – Improved drug efficacy and outcomes
  – Salvaging drugs with high toxicity profiles
  – Improved adherence
Clinical Use of Pharmacogenomics

• Pre-emptive testing not currently in wide use
  – Teaching/university hospitals, cancer centers
  – Limited by time, funding, policy development

• Clinical Pharmacogenomics Implementation Consortium (CPIC)
  – Published Level I evidence dosing guidelines
  – **Key limitation**: Does not address who should be tested
PGx Resources

• Homepage: www.pharmgkb.org
## PGx Resources

- CPIC Guidelines for drug/gene pairs

<table>
<thead>
<tr>
<th>Drug</th>
<th>CPIC Dosing Guideline</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>allopurinol</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>atazanavir</td>
<td>CPIC</td>
<td>10/19/2015</td>
</tr>
<tr>
<td>azathioprine</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>boceprevir</td>
<td>CPIC</td>
<td>06/19/2014</td>
</tr>
<tr>
<td>capecitabine</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>citalopram</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>clomipramine</td>
<td>CPIC</td>
<td>01/16/2013</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>codeine</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>desipramine</td>
<td>CPIC</td>
<td>07/13/2015</td>
</tr>
<tr>
<td>doxepin</td>
<td>CPIC</td>
<td>07/13/2015</td>
</tr>
<tr>
<td>escitalopram</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>fluvoxamine</td>
<td>CPIC</td>
<td>09/18/2015</td>
</tr>
<tr>
<td>imipramine</td>
<td>CPIC</td>
<td>07/13/2015</td>
</tr>
</tbody>
</table>
PGx: Genetic Testing & Results

- Testing options
  - Next Generation Sequencing
  - Targeted sequencing of regions of interest
  - SNP-based panels

- Variant forms
  - IN/DELs
  - SNPs
  - Duplication

- Defining variants
  - RS ID
  - Star alleles haplotypes
    - Associated protein expression/enzyme activity level
PGx at BCH

- Clinical Pharmacogenomics Services
  - Inpatient service & outpatient clinic
    - Referrals from providers at BCH and neighboring institutions
    - Adult and pediatric patients with history of adverse drug events or non-response
  - 2 appointment structure
    - Visit 1: patient PMH, review of testing information and limitations
    - Visit 2: result return
- InforMED Kids Research Study
PGx at BCH

• SNP based panel
  – Affymetrix DMET Plus: 225 genes
  – Pros:
    • Detect major common variants
    • Limited incidental findings
  – Cons:
    • Miss rare variants
    • Genes of interest possibly unavailable
PGx at BCH

- Return of results to the EHR problem list
- Alerts firing for variants of clinical significance

Patient with TPMT Deficiency

Has a documented problem of TPMT - Thiopurine methyltransferase deficiency. Thiopurine methyltransferase (TPMT) is the enzyme responsible for the metabolism of mercaptopurine. Patients with TPMT - Thiopurine methyltransferase deficiency MAY require REDUCED doses of mercaptopurine.

Please page the Pharmacogenomics Service (pager #7454) if further information is required.

Alert Action
- [ ] Cancel order
- [ ] Acknowledge and override
- [ ] Modify

[Ok]
PGx: Protein Effects

• Pharmacokinetic (PK)
  – ADME
    • Drug metabolism: CYP enzymes, TPMT, NAT2
    • Drug transport: SLCO1B1, ABCG2

• Pharmacodynamic (PD)
  – Drug targets: VKORC1, HER2, CFTR

• Immunologic
  – Drug allergies: HLAs
### PGx: PK

![Diagram showing enzyme expression and drug response](http://www.gbhealthwatch.com/Trait-Beta-Blocker-Response.php)

<table>
<thead>
<tr>
<th>Enzyme Expression</th>
<th>[Parent Drug]</th>
<th>Active Parent Drug</th>
<th>Pro-drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PGx: PK of Codeine

• Which certain children are affected?
PGx: PK of Codeine

- Metabolism
  - Pro-drug
  - Primary pathway: CYP2D6

Image: http://www.pharmgkb.org
### PGx: PK of Codeine

- **CPIC Guidelines for Codeine Dosing**

<table>
<thead>
<tr>
<th>CYP2D9 Genotype</th>
<th>CYP2D6 Metabolizer Phenotype</th>
<th>CPIC Codeine Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene Duplication (*1/*1XN)</td>
<td>Ultra-rapid</td>
<td><strong>Avoid due to toxicity</strong></td>
</tr>
<tr>
<td>Homozygous Wild-Type (*1/*1)</td>
<td>Normal/Extensive</td>
<td>Standard dosing</td>
</tr>
<tr>
<td>Heterozygous (*1/*2, *1/*3)</td>
<td>Intermediate</td>
<td>Standard dosing</td>
</tr>
<tr>
<td>Homozygous Variant (*2/*2, *2,*3, *3/*3)</td>
<td>Poor</td>
<td><strong>Avoid due to lack of efficacy</strong></td>
</tr>
</tbody>
</table>

Boston Children’s Hospital
PGx: Phenytoin Case

• 10 yo male admitted for status epilepticus, treated with:
  – IV Fosphenytoin 18 mg PE/kg (500 mg PE) on presentation
  – Single maintenance dose of 140 mg PE (5 mg PE/kg) five hours later on day 1 of the hospitalization

• PMH:
  – Congenital hydrocephalus
  – VP shunt
  – Refractory epilepsy secondary to an in utero right MCA stroke
PGx: Phenytoin Case

• On day 5 of his hospitalization
  – Extremely lethargic
  – Free Phenytoin level is high (Ref: 0.4 – 1.4 mcg/mL)
    • Day 2: 3 mcg/mL
    • Day 5: 1.4 mcg/mL

• No clinically relevant drug-drug interactions and his albumin is normal.

• What is a possible pharmacogenomic reason for the toxicity TB is experiencing?
PGx: Phenytoin Case

• Fosphenytoin/Phenytoin toxicities
  – Chronic effects associated with long-term use:
    • Hepatotoxicity
    • Osteoporosis
    • Megaloblastic anemia
    • Gingival hyperplasia
    • Hirsutism
    • Peripheral neuropathy
  – Acute effects with toxic plasma concentrations
    • CNS effects (dizziness, confusion, drowsiness, and ataxia)
    • GI upset and nausea
  – Immunologic reactions:
    • Severe cutaneous reactions (SJS, TEN)
PGx: Phenytoin Case

- Fosphenytoin/Phenytoin metabolism
  - Fosphenytoin → Phenytoin via plasma esterases
  - Phenytoin 90% metabolized by CYP2C9
    - *2, *3 common loss of function alleles
  - Non-linear saturatable kinetics

Image: http://www.pharmgkb.org
PGx: Phenytoin Case

Phenytoin/Dilantin, Free

mcg/mL

TOXIC

THERAPEUTIC

Generalized Normal Low

Generalized Normal High

1/13/13
12/14/13
12/15/13
12/16/13
12/17/13
12/18/13
12/19/13
12/20/13
12/21/13

Boston Children’s Hospital
### PGx: Phenytoin Case

- Phenytoin Dosing Based on Genotype

<table>
<thead>
<tr>
<th>CYP2C9 Metabolizer Status</th>
<th>Sample Genotype(s)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive Metabolizer</td>
<td>*1/*1</td>
<td>Initiate therapy with recommended maintenance dose.</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>*1/*2, *1/*3</td>
<td>Consider <strong>25% reduction of recommended starting maintenance dose</strong> and adjust according to therapeutic drug monitoring and response.</td>
</tr>
<tr>
<td>Poor Metabolizer</td>
<td>*2/*2, *3/*3, *2/*3</td>
<td>Consider <strong>50% reduction of recommended starting maintenance dose</strong> and adjust according to therapeutic drug monitoring and response.</td>
</tr>
</tbody>
</table>
PGx : TPMT

Image: http://www.rxresource.org/prescription-information/Azathioprine-Mylan-Pharmaceuticals-Inc.html
PGx: TPMT

• Detoxifying pathway
  – Decreased TPMT activity \(\rightarrow\) accumulation of toxic metabolites
  \(\rightarrow\) myelosuppression and neutropenia
  – Prevalence of variants:
    • \(~89\%\) of the population *1/*1
    • \(~11\%\) heterozygous
    • \(~0.3\%\) homozygous variant
## PGx: TPMT

<table>
<thead>
<tr>
<th>Phenotype (Genotype)</th>
<th>Examples of diplotypes</th>
<th>Implications for azathioprine pharmacologic measures</th>
<th>Dosing recommendations for azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous wild-type or normal, high activity</td>
<td>*1/*1</td>
<td>Lower concentrations of TGN metabolites</td>
<td>Start with <strong>normal starting dose</strong> (e.g., 2-3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines.</td>
</tr>
<tr>
<td>Heterozygote or intermediate activity</td>
<td>*1/*2, *1/*3A, *1/*3B, *1/*3C,</td>
<td>Moderate to high concentrations of TGN metabolites</td>
<td>If disease treatment normally starts at the &quot;full dose&quot;, <strong>consider starting at 30-70%</strong> of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance.</td>
</tr>
<tr>
<td>Homozygous variant or low activity</td>
<td>*3A/*3A, *2/*3A, *3C/*3A, *3C/*4,</td>
<td>Extremely high concentrations of TGN metabolites; fatal toxicity possible</td>
<td>Consider alternative agents or drastically reduced doses (<strong>reduce daily dose by 10-fold</strong> and dose thrice weekly instead of daily).</td>
</tr>
</tbody>
</table>

Image: [http://www.pharmgkb.org](http://www.pharmgkb.org)
**PGx: TPMT**

- Defining Star Alleles

<table>
<thead>
<tr>
<th>TPMT</th>
<th>TAG(S)</th>
<th>rs1800462</th>
<th>rs1142345</th>
<th>rs1800460</th>
<th>rs1800584</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td></td>
<td>C</td>
<td>T</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>*2</td>
<td></td>
<td>G</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3A</td>
<td></td>
<td></td>
<td>C</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>*3B</td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>*3C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
</tr>
</tbody>
</table>
PGx: Star Alleles Defined

• Which of the following star alleles corresponds with the genetic results described below:
  – rs1800462 (C > G) C
  – rs1142345 (T > C) C
  – rs1800460 (C > T) C
  – rs1800584 (C > T) C
PGx: Pediatric PK

### PGx: PK Summary

<table>
<thead>
<tr>
<th>Gene/Enzyme</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>PPIs, TCAs, SSRIs, Clopidogrel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Phenytoin, Celecoxib, Sulfonylureas, Warfarin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>SSRIs, TCAs, Codeine, Ondansetron, Tramadol, Oxycodone</td>
</tr>
<tr>
<td>TPMT</td>
<td>6-mercaptopurine, Azathioprine</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>NAT2</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>Statins</td>
</tr>
<tr>
<td>DPYD</td>
<td>5-Fluorouracil</td>
</tr>
</tbody>
</table>
PGx: PD

• Drug target variation: shape, amount
• May determine drug efficacy (i.e. Herceptin)

PGx: Warfarin

• Review: warfarin MOA
  – Reduced Vit K required for coagulation factors II, VII, IX, and X and Protein C & S
  – VKORC1 reduces Vit K
  – Warfarin inhibits subunit 1 of VKORC1
  – S-warfarin = active isomer

• Highly variable dosing & narrow therapeutic index
  – Age, height, weight
  – Race
  – Enzyme inducers & inducers
  – Drug-food interactions
PGx: Warfarin

• Gene(s) of interest?

Image: http://pharmrev.aspetjournals.org/content/63/2/437/F3.expansion.html
PGx: Warfarin

• **CYP2C9**: primary metabolic pathway of S-warfarin

<table>
<thead>
<tr>
<th>CYP2C9 Allele</th>
<th>Metabolism Reduction</th>
<th>Implication at Standard Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>*2</td>
<td>30-40%</td>
<td>↑ [S-warfarin] Over-anticoagulation</td>
</tr>
<tr>
<td>*3</td>
<td>80-90%</td>
<td>↑ INR &amp; risk of bleeding</td>
</tr>
</tbody>
</table>

• **VKORC1**: S-warfarin drug target
  – Common variant (−1639G>A, rs9923231)
    • −1639A: less VKORC1 expressed
PGx: Warfarin

• Warfarin starting dose by genotype

<table>
<thead>
<tr>
<th>VKORC1 Genotype (-1639G&gt;A, rs9923231)</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7</td>
</tr>
<tr>
<td>GA</td>
<td>5-7</td>
</tr>
<tr>
<td>AA</td>
<td>3-4</td>
</tr>
</tbody>
</table>

• Algorithms available: [www.warfarindosing.org](http://www.warfarindosing.org)
  – NOTE: NOT applicable for patients under 18 years old
PGx: Immunologic HLA

- HLA variants $\rightarrow$ recognition of drugs as foreign $\rightarrow$ increased risk of cutaneous reactions (SJS, TEN)

http://www.pharmacologyweekly.com/content/images/newsletterimages/p geneticsv1i3.gif
PGx: HLA

• HLA Class I complex on all nucleated cells

• Complex components
  – Heavy $\alpha$ chain w/ peptide binding cleft
  – Light $\beta$2-macroglobulin chain
  – Antigenic peptide
    • Self-peptides
    • Foreign peptides (drug, virus, tumor antigen, etc.)

• Foreign peptides $\rightarrow$ T-cell immune response
CarBAMazepine *(Lexi-Drugs)*

**ALERT: US Boxed Warning**

- Serious dermatologic reactions and HLA-B*1502 allele:

  Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome, have been reported during treatment with carbamazepine. These syndromes may be accompanied by mucous membrane ulcers, fever, or painful rash. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly white populations, but the risk in some Asian countries is estimated to be approximately 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing Stevens-Johnson syndrome/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Screen patients with ancestry in genetically at-risk populations for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Do not treat patients testing positive for the allele with carbamazepine unless the benefit clearly outweighs the risk. Discontinue carbamazepine if the patient is suspected of having a serious dermatologic reaction.
**PGx: HLA**

- Severe Cutaneous Adverse Reactions (SCARs)
  - Maculopapular rash
  - Stevens Johnson Syndrome (SJS)
  - Toxic Epidermal Necrosis (TEN)
- Onset: delayed
- Mortality (> 30% w/ TEN)
- Treatment:
  - Typically requires hospitalization, ICU
  - D/C precipitating medication
  - Fluids, steroids, antihistamines, analgesics, antibiotics, etc.
PGx: HLA

• DNA test for allele carrier status
• Strong ethnic associations (see following slide)
• Result reported:
  – Positive: present on one or both gene copies
  – Negative: not present on either gene copy
## PGx: HLA Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Allele</th>
<th>Race/Ethnicities of High Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B*57:01</td>
<td>European: 6-7% South West Asian: 20%</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B*58:01</td>
<td>Han Chinese: 6-8% Korean: 12%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*15:02</td>
<td>Han Chinese, Taiwanese: 10% Populations from Hong Kong, Thailand, Malaysia, Vietnam, Philippines, India and Indonesia: &gt;5%</td>
</tr>
<tr>
<td></td>
<td>HLA-A*31:01</td>
<td>Northern European: 2-5% Japanese: 9%</td>
</tr>
<tr>
<td>Fosphenytoin/Phenytoin</td>
<td>HLA-B*15:02</td>
<td>See Above</td>
</tr>
</tbody>
</table>
PGx: HLA

• CPIC recommendations vary by drug
  – Who to test?
    • Abacavir: all patients
    • Fosphenytoin/Phenytoin, carbamazepine: certain Asian ethnicities
  – If positive related allele variant known?
    • Drug is contraindicated if positive
    • In case of Fosphenytoin/Phenytoin: if patient has taken drug > 3 months previously without incident, may reinitiate
PGx: What’s next?

- Educating pharmacists and prescribers
- Incorporation into RCT criteria
- Incidental findings
- Discovery of novel drug-gene associations and the development of corresponding guidelines
- Insurance coverage for testing
- Implementation of pre-emptive testing protocols
PGx: Assessment Question 1

• Which of the following statements is true of HLA associated CPIC recommendations?

  A. Universal testing of all patients is recommended prior to initiating abacavir therapy.
  B. Variants associated with cutaneous reactions and carbamazepine are most prevalent in European populations.
  C. A patient who has taken phenytoin for at least 1 month without incident may reinitiate therapy regardless of HLA variant status.
  D. Cutaneous reactions associated with HLA variants typically happen immediately following the first medication dose.
PGx: Assessment Question 2

Which of the following drugs and genes provide an example of pharmacogenetics testing for pharmacodynamic protein effects?

I. Herceptin & HER2/neu
II. Ivacaftor & CFTR mutations
III. Warfarin & VKORC1 rs9923231

A. I only
B. I & II
C. II & III
D. I, II, & III
A provider orders a warfarin PGx panel for a patient CT prior to initiating therapy. The results come back as follows: CYP2C9 *2/*3, VKORC1 rs9923231 AA. How will CT’s variants affect the recommended starting dose for warfarin versus a patient who is wild-type for CYP2C9 and VKORC1 rs9923231? Assume ALL other clinical factors (height, weight, age, diet, smoking status, etc.) between the patients are equal.

A. CT’s CYP2C9 genotype is associated with a required increase in starting dose, but the VKORC1 rs9923231 genotype suggests a decrease may be necessary.
B. CT’s CYP2C9 genotype is associated with a required decrease in starting dose, but the VKORC1 rs9923231 genotype suggests an increase may be necessary.
C. Both CT’s CYP2C9 and VKORC1 rs9923231 genotypes are associated with a required increase in starting dose.
D. Both CT’s CYP2C9 and VKORC1 rs9923231 genotypes are associated with a required decrease in starting dose.
Questions?
References

References