Unleash the Power of your DNA!
How clinical pharmacogenomics can improve medication use

Hyun Kim, PharmD
Fellow, Clinical Pharmacogenomics Service
Boston Children’s Hospital and MCPHS University

Statement of disclosure

• I have no conflicts of interest
Learning objectives

1. Describe pertinent genetics, informatics, and pharmacy practice terminology and concepts critical to understanding pharmacogenomic information

2. Identify the medications and associated genes that are discussed in currently available clinical guidelines

3. Interpret appropriate clinical guidelines when given a patient’s genetic information in order to make reasonable therapeutic recommendations

4. Develop a list of logistical, clinical, and administrative considerations for establishing a clinical pharmacogenomics service
Overview

• Rationale
  • Why do we need it?
  • How does it affect what we are already doing?

• Genetics/pharmacogenomics terminology and concepts
  • What is it?
  • What do I need to know about it?
  • How does it work?

The rationale for pharmacogenomics

• Medicine favors a “one size fits all” approach

• Medicine is reactionary and treatment-focused
The role of pharmacogenomics

- Preemptive identification of genetic factors associated with drug response*
- Recommendations for drug selection/dose changes*

*D in certain clinical situations!

Differential responses to medications

- Harmful
  - Effective
- Safe
  - Effective

- Harmful
  - Not effective
- Safe
  - Not effective
What is pharmacogenomics?

- Pharmacogenomics (PGx) = pharmacy practice + genetics/genomics

- Also includes
  - Informatics
  - Medical ethics
  - Public health
  - Regulatory affairs
Genetics terminology

- **Genes**: sections of DNA that encode proteins
- **Genome**: the entire collection of DNA assembled into 23 chromosome pairs
- **Variant**: an alternative version of a region in the genome that varies between individuals
- **Single nucleotide polymorphism (SNP)**: difference at one single nucleotide in the genome, such as rs45523 (T>C)
- **Phenotype**: the observable characteristics based on the genotype of an individual

Star allele nomenclature

- **Allele**
- **Genotype**
  - rs1 G>A = GA
  - rs2 A>C = AC
  - rs3 T>G = TT
- **Haplotype**
  - GAT = *1
  - GCT = *2
  - ACT = *3
  - ACG = *4
- **Diplotype**
  - *1/*3
DNA $\rightarrow$ Genes $\rightarrow$ Proteins $\rightarrow$ Pharmacy?

- Why do we care about DNA in pharmacy practice?
  - Genetic polymorphisms affect the structure and function of proteins, which affect drug kinetics and action
- Pharmacogenomic protein effects may be:
  - Pharmacodynamic
  - Pharmacokinetic
  - Immunologic

Pharmacodynamics PGx

- “What the drug does to the body”
- Genes that code for drug targets
  - Such as serotonin receptors, opioid receptors, VKORC1, HER2
- Influence efficacy and safety by defining the mechanism of action and pharmacology of drugs

Pharmacokinetics PGx

• “What the body does to the drug”

• Genes that code for ADME enzymes
  • Such as CYPs, UGTs, transporters

• Influence efficacy and safety by defining the ADME parameters of a drug

• Phenotypes of interest
  • Increased/decreased function
  • Increased/decreased rate of metabolism

Pharmacokinetics PGx, cont.

Serum Drug Concentration vs. Time

- Poor metabolizer
- Intermediate metabolizer
- Normal metabolizer
- Rapid metabolizer
- Ultrarapid metabolizer

Toxicity

Therapeutic Window

Not effective
**Immunologic PGx**

- Genetically-mediated drug hypersensitivity reactions by genes that code for molecules that present the drugs as antigens

- Influence safety by increasing the risk of hypersensitivity reactions in carriers of certain HLA variants

---

**Learning objectives**

1. Describe pertinent genetics, informatics, and pharmacy practice terminology and concepts critical to understanding pharmacogenomic information

2. Identify the medications and associated genes that are discussed in currently available clinical guidelines

3. Interpret appropriate clinical guidelines when given a patient’s genetic information in order to make reasonable therapeutic recommendations

4. Develop a list of logistical, clinical, and administrative considerations for establishing a clinical pharmacogenomics service

---

PGx resources - CPIC

- copicpgx.org
- Clinical Pharmacogenomics Implementation Consortium
  - Multi-institutional, multi-national collaborative group
  - Critically evaluate scientific evidence for drug-gene associations
  - Construct clinical guidelines with recommendations
- 20 clinical guidelines currently available
  - 12 genes+4 HLA variants
  - 37 drugs

CPIC drug-gene pairs

- Tricyclic antidepressants-CYP2C19+CYP2D6
  - Amitriptyline
  - Desipramine (CYP2D6 only)
  - Imipramine
  - Trimipramine
  - Doxepin
  - Nortriptyline (CYP2D6 only)
  - Clomipramine
- SSRIs-CYP2C19/CYP2D6
  - Citalopram (CYP2C19)
  - Escitalopram (CYP2C19)
  - Fluvoxamine (CYP2D6)
  - Paroxetine (CYP2D6)
  - Sertraline (CYP2C19)
- 5-HT₃R antagonists-CYP2D6
  - Ondansetron
  - Tropisetron
### CPIC drug-gene pairs, cont.

<table>
<thead>
<tr>
<th>Fluoropyrimidines-DPYD</th>
<th>Thiopurines-TPMT</th>
<th>Interferons-IFNL3</th>
<th>Voriconazole-CYP2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>Azathioprine</td>
<td>Peginterferon-alfa-2a</td>
<td>Phenytoin-CYP2C9+HLA-B*15:02</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Mercaptopurine</td>
<td>Peginterferon-alfa-2b</td>
<td>Carbamazepine-HLA-A<em>31:01/HLA-B</em>15:02</td>
</tr>
<tr>
<td></td>
<td>Thioguanine</td>
<td>Ribavirin</td>
<td>Oxicarbazepine-HLA-B*15:02</td>
</tr>
<tr>
<td>Fluorouracine</td>
<td></td>
<td></td>
<td>Abacavir-HLA-B*57:01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Allopurinol-HLA-B*58:01</td>
</tr>
<tr>
<td>Thiopurines-TPMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thioguanine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferons-IFNL3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon-alfa-2a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peginterferon-alfa-2b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CPIC drug-gene pairs, cont.**

- Warfarin-CYP2C9+VKORC1+CYP4F2
- Clopidogrel-CYP2C19
- Simvastatin-SLC01B1
- Tamoxifen-CYP2D6
- Codeine-CYP2D6
- Tacrolimus-CYP3A5***

- Voriconazole-CYP2C19
- Atazanavir-UGT1A1
- Ivacaftor-CFTR
- Rasburicase-G6PD
- Phenytoin-CYP2C9+HLA-B*15:02
- Carbamazepine-HLA-A*31:01/HLA-B*15:02
- Oxicarbazepine-HLA-B*15:02
- Abacavir-HLA-B*57:01
- Allopurinol-HLA-B*58:01
PGx resources - PharmGKB

- pharmgkb.org
- Pharmacogenomics Knowledgebase
  - Comprehensive repository of all sorts of PGx information
    - 641 drugs
    - 100 dosing guidelines
    - 498 drug labels
    - 65 VIP summaries (Very Important Pharmacogene)
    - 130 pathway diagrams
    - 3,753 clinical annotations (clinical evidence)
    - 20,017 variant annotations (scientific evidence)
PharmGKB: How to get to CPIC guidelines

![PharmGKB: How to get to CPIC guidelines](image1.png)

PharmGKB: How to get to CPIC guidelines

![PharmGKB: How to get to CPIC guidelines](image2.png)
Learning objectives

1. Describe pertinent genetics, informatics, and pharmacy practice terminology and concepts critical to understanding pharmacogenomic information

2. Identify the medications and associated genes that are discussed in currently available clinical guidelines

3. Interpret appropriate clinical guidelines when given a patient’s genetic information in order to make reasonable therapeutic recommendations

4. Develop a list of logistical, clinical, and administrative considerations for establishing a clinical pharmacogenomics service

Patient case: TR

• TR is a 19 year old male with ulcerative colitis that has proven refractory to first and second-line options
• Recently started on mercaptopurine 50 mg once daily with plans to go up to 100 mg once daily
• TR’s weight is 70 kg

• TR is brought to the ED 5 days after therapy initiation with complaints of lethargy, fever, and malaise
• Labs show WBC=750 cells/microliter
• The ED resident turns to you, the ED clinical pharmacist, if this caused by the mercaptopurine
Patient case: TR

• What pharmacogenomic factors might explain TR’s condition?

Patient case: TR

• Your research seems to suggest you need to get the patient’s TPMT genotype
• Good thing your superpower is to invent technology in the blink of an eye!
• Using your newly crafted STAT-TPMT-genotyper, you determine TR’s genotype to be *1/*3A
• You have no idea what this means so you decide to consult your friend who happens to be a pharmacogenomics fellow at a nearby pediatrics hospital to see how you should proceed
• He just sends you a cryptic email that just says “CPIC guideline” and this algorithm...
Patient case: TR

- What type of metabolizer phenotype does this genotype correspond to?
- Based on this information, what should you do?

Before final dose recommendation is made REVIEW:
1. Drug-drug interactions
2. Renal dysfunction
3. Hepatic dysfunction

Patient case: TR

- You tell the ED resident what you found and write up your pharmacist’s clinical intervention so that the treating gastroenterologist knows that the patient would need a lower maintenance dose of mercaptopurine (and perhaps close monitoring of neutropenia)
- You are hailed as a hero and the pharmacy leadership throw a party in your honor as you are the PGx-pert for your hospital!
Learning objectives

1. Describe pertinent genetics, informatics, and pharmacy practice terminology and concepts critical to understanding pharmacogenomic information

2. Identify the medications and associated genes that are discussed in currently available clinical guidelines

3. Interpret appropriate clinical guidelines when given a patient’s genetic information in order to make reasonable therapeutic recommendations

4. Develop a list of logistical, clinical, and administrative considerations for establishing a clinical pharmacogenomics service

Where is PGx being implemented?

BIC Healthcare
Boston Children’s Hospital
Children’s Hospital Minnesota
Cincinnati Children’s Hospital
Clearview Cancer Institute
Cleveland Clinic
Geisinger Health System
Icahn School of Medicine at Mount Sinai
Indiana University
Levine Cancer Center
Mayo Clinic
Medical College of Wisconsin
Mission Health
Moffitt Cancer Center
NorthShore University HealthSystem
Northwestern Medicine
Stanford University
St. Jude Children’s Research Hospital
University of Colorado
University of Chicago
University of Florida
University of North Carolina
University of Pennsylvania
University of Pittsburgh
University of South Florida
Vanderbilt University
Washington University in St. Louis
Clinical Pharmacogenomics Service (CPS)

Shannon Manzi PharmD, BCPPS, FPPAG
- Co-director

Hyun Kim PharmD
- Fellow

Jonathan Picker MBChB, PhD
- Co-director
- Geneticist

PGx at Boston Children’s Hospital

• Who do we see?
  • ANYONE with a history of ADRs or non-response to medications
  • Any age (not just pediatrics)
  • Any diagnosis
  • Any hospital or institution (not just BCH)
  • Any state or country

• Where do we see them?
  • Weekly outpatient clinic
  • Inpatient consults
CPS logistics

- Before first visit
  - Complete chart review
- First visit
  - Medication reconciliation
  - Complete past medication history
  - Discuss genetic testing logistics
  - Obtain consent
- After first visit
  - Obtain blood draw
  - Send out blood draw to lab
  - Complete clinical note
- Before second visit
  - Review PGx results
  - Construct results summary
  - Review PGx evidence
- Second visit
  - Medication reconciliation
  - Discuss results
- After second visit
  - Enter variants into problem list
  - Complete clinical note
  - Work with providers

Testing logistics

- Tests offered:
  - Affymetrix DMET Plus panel
    - Coverage: 230 genes
    - Turnaround time: 3-4 weeks
  - HLA panel
    - Coverage: 4 HLA genotypes (HLA-A*31:01, HLA-B*15:02, HLA-B*57:01, HLA-B*58:01)
    - Turnaround time: 1-2 weeks
  - CNT (CEP72/NUDT15/TPMT) panel for GI department
  - 5 mL blood draw
  - All tests performed at Medical College of Wisconsin (MCW)/RPRD
Clinical decision support (CDS)

- CYP2C19
- CYP2C9
- CYP2D6
- CYP3A5
- DPYD
- TPMT
- SLCO1B1
- UGT1A1
- VKORC1

9 genes with high level evidence

230 genes on DMET panel

4 genes entered into patient's chart

CDS alerts
OK, so you want to start your own PGx service...

Key considerations

• Knowledge

• Laboratory medicine

• Informatics

• Administrative

• Legal

• Education
Key considerations: Knowledge

• Comprehension of PGx knowledge
  • Basic concepts of genetics
  • Interpretation of genomics data
• Membership to CPIC
  • Monthly conference calls
• Access to PGx databases
  • PharmGKB
  • PharmVar
• Partnerships with newly trained PGx-perts
  • Residencies
  • Fellowships
• Additional training
  • CE programs
  • Certificate programs

Key considerations: Laboratory medicine

• Decide which tests to offer, to whom, and when
  • Patient populations
  • Disease states
  • Volume
  • Preemptive testing?
• Establish relationship with CLIA-certified genetics testing laboratory
  • In-house vs. send-out?
• Establish relationship with hospital/institution laboratory medicine
  • Specimen retrieval logistics
Key considerations: Informatics

- Understand how your EHR platform operates
  - Who manages CDS rules?
  - Who can query CDS data warehouses?
- Information presentation in EHR
  - Raw lab report PDF images
  - “Face up” results (“*1/*3” vs. “see image”)
- Patient portal?
- Secure storage of genetics results
  - How is data transferred from lab to your institution?
Key considerations: Administrative

- Operational logistics
  - Clinic space
  - Staff composition
  - Patient scheduling
  - Medication reconciliation
  - Contact information
  - Marketing
  - SOPs
- Billing processes
  - Understand which insurance companies your institution works with
- Institutional involvement
  - Oversight committee
- Credentialing
  - Who can see patients?
  - Who signs off on notes?
  - Who can orders tests?

Key considerations: Legal

- Understanding laws and regulations surrounding genetic testing
  - Genetic Information Nondiscrimination Act (GINA)- covers employment and health insurance, but not life, long-term care, or disability insurance
- CDTM agreement
  - Scope of practice = physician advocate!
- Incidental findings
  - Consent form
  - Involvement of genetic counselor
- External genetic testing
  - Validity of results/interpretations
Key considerations: Education

- Educate providers
  - Roadshows, grand rounds, department rounds
- Educate pharmacists
  - Create/host CE presentations
  - Modules
- Educate students
  - APPE students
  - Elective courses
- Educate the public
  - Patient advocacy
- Educate yourself
  - Read literature
  - Attend CEs

Learning objectives

✓ Describe pertinent genetics, informatics, and pharmacy practice terminology and concepts critical to understanding pharmacogenomic information

✓ Identify the medications and associated genes that are discussed in currently available clinical guidelines

✓ Interpret appropriate clinical guidelines when given a patient’s genetic information in order to make reasonable therapeutic recommendations

✓ Develop a list of logistical, clinical, and administrative considerations for establishing a clinical pharmacogenomics service
A story about Cameron...

Pharmacogenomics

Thanks!
Questions?