Nature vs. Nurture...vs. Machine?

A Brief Introduction to Clinical Pharmacogenetics
Ben Kong, PharmD, BCPS
Oregon Health & Science University

Disclosure
I have no actual or potential conflict of interest in relation to this program.

The Precision Medicine Initiative
Learning Objectives

1. Interpret pharmacogenetics results.
2. Discuss the importance of incorporating pharmacogenomics results into patient care.
3. Explain common barriers to the implementation of pharmacogenetics into practice.
4. Develop a list of pharmacogenomic resources.

Pre-Test Assessment #1
Which of the following is the correct interpretation for the *1/*1 genotype?
- A. Normal Metabolizer
- B. Ultra-rapid Metabolizer
- C. Poor Metabolizer
- D. Intermediate Metabolizer

Pre-Test Assessment #2
The incorporation of pharmacogenetics into patient care will result in which of the following?
- A. Improve drug efficacy and therapeutic effects.
- B. Decrease the risk of side-effects and life-threatening outcomes.
- C. Increase the cost of health-care and to the patient.
- D. Answer (A) and (B)
Pre-Test Assessment #3

Which of the following are potential obstacle(s) to the implementation process?

A. Unfamiliarity of topic.
B. Long turn-around time of the pharmacogenetics results.
C. There are not enough healthcare professionals trained in genetics.
D. All of the above.

Pre-Test Assessment #4

Your patient, AB, presents with signs and symptoms of gout and hands you a pharmacogenetics report. It reveals that they are a carrier of the HLA-B genotype.

Which resource(s) below would NOT be appropriate for review?

A. Food and Drug Administration (FDA)
B. Clinical Pharmacogenetics Consortium Implementation (CPIC) guidelines
C. American College of Rheumatology
D. Pinterest©

State of the Union 2015

Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as quick as taking our temperature?

- President Obama, January 30, 2015
Why pharmacogenetics/genomics (PGx)?

- Goal is to reduce adverse drug events (ADE) and improve patient outcomes
  - 750,000 ED visits and 120,000 hospitalizations
  - $3.5 billion is spent on ADE
  - 40% of costs of ambulatory ADE’s are preventable
- Improved adherence
- Companion Testing
  - As a requirement to initiate treatment
  - As a screening tool prior to initiating treatment
- Salving drugs with high toxicity profile
- Drug Development and Clinical trial design

Paradigm Shift in Medicine

Intuition Medicine → Evidence-Based Medicine → Precision Medicine

Symptoms → Pattern → Algorithm

Side-effect ➔ Moderate effect ➔ Adverse Effect
Matching the genotype with a phenotype is important for consistency.

Genotype nomenclature

- **Basic genotype nomenclature**
  - Gene Position: Allele/Allele
    - CYP2C9 144 R/R: rs1799853 R/R
    - CYP2C9 144 R/C: rs1799853 R/C
    - CYP2C9 144 C/C: rs1799853 C/C
### Pharmacogenetic Results

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>*1/*2</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*2</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*3/*3</td>
<td>Non-Expressor (aka normal metabolizer)</td>
</tr>
<tr>
<td>DPYD</td>
<td>*1/*1</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>T/T</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>TPMT</td>
<td>*3B/*3C</td>
<td>Poor metabolizer(?)</td>
</tr>
<tr>
<td>VKORC1</td>
<td>A/A</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

**Word of Caution**

Genotype nomenclature can look exactly the same **BUT** have different functional effects based on the specific protein encoded.

### Current PGx Labeling in FDA Package Insert

![Current PGx Labeling in FDA Package Insert](image-url)
Quick DNA Statistics

- 46 chromosomes
- 3,000,000,000 (billion) base pairs
- 20,000-25,000 protein coding genes
- SNPs are the most common form of mutation

Two individual’s DNA is 99.9% similar. Only 0.1% is unique!

Adapted from NIH NHGRI

Methods of Variant Interrogation

- Chip/Panel
  - A collection of predetermined variant SNPs
  - May miss rare variants
- Next Generation Sequencing
  - Whole Genome Sequence (WGS)
  - Whole Exome Sequence (WES)
  - Information overload

Adapted from ImageSource.com

Cost of DNA Sequencing

- Average cost of sequencing a genome for NHGRI-funded sequencing technology projects over time. This graph captures the dramatic decline in sequencing costs through April 2013, and the cost has continued to drop.

http://www.genome.gov/27014390
Clinical application
TPMT and Thiopurines
Next Example: CYP2C19 and Antiplatelets

THIOPURINES
(azathioprine, mercaptopurine, thioguanine)

Mechanism of Action

AZA = azathioprine
MP = mercaptopurine
TG = thioguanine
TGN = thioguanine monophosphate
TPMT = thiopurine methyltransferase
TPMT Variant Alleles

- At least 11 variant alleles associated with decreased activity:
- Wild-type – TPMT *1
- Loss of function alleles
  • TPMT*2 – rare
  • TPMT*3A – common in white Europeans
  • TPMT*3C – common in Asians and Africans

Dose & Adverse Effects

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>2-3 mg/kg/day</td>
<td>Common: Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serious: pancreatitis, leukopenia, macrocytic anemia,</td>
</tr>
<tr>
<td>(AZA) pro-drug</td>
<td></td>
<td>neutropenia, anemia, neutropenia, thymolysis, lymphoma</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>1-1.5 mg/kg/day</td>
<td>Common: Nausea and vomiting</td>
</tr>
<tr>
<td>(MP)</td>
<td></td>
<td>Serious: neutropenia, myelosuppression, leukopenia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lymphoma, T-cell lymphoma</td>
</tr>
<tr>
<td>Thioguanine</td>
<td>60 mg/m2/day</td>
<td>Common: Nausea, loss of appetite, stomatitis, vomiting</td>
</tr>
<tr>
<td>(TG)</td>
<td></td>
<td>Serious: myelosuppression, neutropenia, lethargy,</td>
</tr>
<tr>
<td></td>
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<td>lymphoma, anemia, neutropenia, myelosuppression</td>
</tr>
</tbody>
</table>
### CPIC Guidelines

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>AZA</th>
<th>6-MP</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, high activity</td>
<td>Start with normal dose of 2 mg/kg/day</td>
<td>Allow two weeks to reach steady state</td>
<td>Start with normal dose of 1.5 mg/kg/day</td>
</tr>
<tr>
<td>Intermediate activity</td>
<td>Reduce dose by 30-50%</td>
<td>Adjust based on degree of myelosuppression</td>
<td>Reduce dose by 30-50%</td>
</tr>
<tr>
<td>Low activity</td>
<td>Reduce daily dose 10X and frequency to thrice weekly (from 5X weekly)</td>
<td>4-6 weeks to reach steady state for each adjustment</td>
<td>Reduce daily dose 10X and frequency to thrice weekly (from 5X weekly)</td>
</tr>
</tbody>
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### Patient Case

A provider ordered both TPMT genotype and phenotype for a 46 yo newly diagnosed Crohn's patient. They are looking to start the patient on azathioprine.

**What dose should the patient be started on based on the lab results?**

- A. Normal dose
- B. Intermediate dose
- C. Deficient dose
- D. Either A or B

### Clinical application

CYP2C19 and Antiplatelets
Plavix does not have its anti-platelet effects until it is metabolized into its active form by the liver enzyme CYP2C19. It is estimated that 2-14% of the U.S. population are poor metabolizers.

Metabolic pathway – Clopidogrel & Prasugrel

CYP2C19 Polymorphisms

• Highly polymorphic
  • At least 35 variants

• Pertinent medications affected by CYP2C19
  • Clopidogrel
  • PPIs
  • Some antidepressants
  • Voriconazole
CYP2C19 Polymorphisms

- Allelic frequency of the *2 (loss-of-function)
  - 25-35% in Asians
  - 11-15% in African-Americans
  - 61% in Oceanians

- Allelic frequency of the *3 (loss-of-function)
  - 3-9% in Asians
  - 0.5% in Caucasians

- Allelic frequency of the *17 (gain-of-function)
  - 14-21% in Caucasians
  - 18% in Africans
  - 3-6% in Asians

CPIC Guideline: Clopidogrel and CYP2C19

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<tr>
<th>Genotype</th>
<th>Example of Phenotype</th>
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<td>Wild</td>
<td>No significant loss of function</td>
<td>No significant drug-drug interactions</td>
<td>No significant drug-drug interactions</td>
<td>Strong</td>
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<tr>
<td>*2/2</td>
<td>Significant loss of function</td>
<td>No significant drug-drug interactions</td>
<td>No significant drug-drug interactions</td>
<td>Strong</td>
</tr>
<tr>
<td>*2/3</td>
<td>Significant loss of function</td>
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<td>*2/17</td>
<td>Significant gain of function</td>
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Patient case

Past Medical History
- Diabetes
- Hypertension
- GERD/heartburn
- Depression
- Coronary artery disease s/p previous stent

Which option could be considered to optimize drug therapy?

A. Continue with clopidogrel 75 mg daily
B. Recommend changing therapy to prasugrel 10 mg daily
C. Recommend changing therapy to ticagrelor 90 mg twice daily
D. Recommend increasing the dose of clopidogrel to 150 mg daily to overcome the intermediate metabolizer genotype
Role of Pharmacist

- Medication use policies and processes
- Literature evaluation and application of evidence-based medicine (EBM)
- Pharmacy informatics
- Direct patient care
- Medication safety
- Research and Ethics

ASHP Statement

ASHP Statement on the Pharmacist’s Role in Clinical Pharmacogenomics

ASHP REPORTS - Pharmacist's role in clinical pharmacogenomics

Position

The American Society of Health-System Pharmacists (ASHP) believes that pharmacogenomic testing can improve medication-related outcomes, reduce adverse drug reactions, and improve the efficacy and safety of medications. ASHP supports the implementation and application of pharmacogenomic testing to optimize patient care and improve therapeutic outcomes. ASHP recommends that pharmacists play a key role in the integration of pharmacogenomics into clinical practice, working collaboratively with other healthcare professionals to ensure that patients receive the most appropriate medications and dosages based on their genetic makeup.

AJHP

American Journal of Health-System Pharmacy

Vol. 64 No. 24 / December 15, 2007

The Role of the Pharmacist in Implementing Pharmacogenomics

The use of pharmacogenomics in clinical practice involves the identification of genetic variations that affect drug response and the development of strategies to optimize medication treatment. Pharmacists play a vital role in this process, as they have a unique understanding of medication use, patient care, and the integration of new technologies.

- Pharmacists can help identify patients who may benefit from pharmacogenomic testing.
- They can provide education on the implications of genetic testing results and the need for individualized medication adjustments.
- Pharmacists can work with healthcare providers to develop and implement personalized treatment plans.
- They can monitor patient outcomes and adjust medications as needed based on pharmacogenomic data.

In conclusion, the role of the pharmacist in implementing pharmacogenomics is crucial for optimizing patient care and improving health outcomes. Through collaboration with other healthcare professionals, pharmacists can actively contribute to the advancement of pharmacogenomic technology and its integration into clinical practice.
Clinical PGx Resources

<table>
<thead>
<tr>
<th>Resource</th>
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<tbody>
<tr>
<td>APhA DrugInfoLine, Pharmacogenomics Corner</td>
<td><a href="http://www.aphadruginfoline.com/pharmacogenomics-corner">http://www.aphadruginfoline.com/pharmacogenomics-corner</a></td>
</tr>
<tr>
<td>School of Pharmacy, University of Florida</td>
<td><a href="https://www.ufl.edu/pharmacy/pharmacogenetics%E6%B7%B1%E6%83%85/uid/158">https://www.ufl.edu/pharmacy/pharmacogenetics深情/uid/158</a></td>
</tr>
<tr>
<td>Clinical Pharmacogenetics Implementation Consortium (CPIC)</td>
<td><a href="https://cpicpgx.org/">https://cpicpgx.org/</a></td>
</tr>
<tr>
<td>American Society of Health-Systems Pharmacists</td>
<td><a href="https://www.ashp.org/pharmacy-practice/pharmacy-topics/emerging-sciences/pharmacogenomics">https://www.ashp.org/pharmacy-practice/pharmacy-topics/emerging-sciences/pharmacogenomics</a></td>
</tr>
<tr>
<td>Genetics/Genomics Competency Center (G2C2)</td>
<td>genomicseducation.net/</td>
</tr>
<tr>
<td>National Human Genome Research Institute</td>
<td><a href="https://www.genome.gov/">https://www.genome.gov/</a></td>
</tr>
<tr>
<td>Pharmacogenomics Knowledgebase (PharmGKB)</td>
<td><a href="https://www.pharmgkb.org/">https://www.pharmgkb.org/</a></td>
</tr>
<tr>
<td>University of Florida SNPits</td>
<td><a href="http://personalizedmedicine.ufhealth.org/tag/snpits/">http://personalizedmedicine.ufhealth.org/tag/snpits/</a></td>
</tr>
<tr>
<td>Warfarin Dosing</td>
<td><a href="http://www.warfarindosing.org/">www.warfarindosing.org/</a></td>
</tr>
</tbody>
</table>

Potential Challenges Opportunities!

- Knowledge
- Resources
- Infrastructure
- Cost/reimbursement
- Portability of lifetime results
- Re-visibility of reporting as science changes
- Application against previous pharmacogenomic results

Future Directions

- Whole Genome Sequencing (WGS)
- Whole Exome Sequencing (WES)
- Proteomics & Metabolomics
- Computer chip implant
- Expansion of biobank repositories
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D. All of the above.
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Take-Home Points

• #1
  • Pharmacogenetics/genomics is not a matter of IF it should be used, but rather WHEN will it be fully incorporated.

• #2
  • Genetics is one piece of Precision Medicine - must take into account the full clinical picture

• #3
  • Implementation takes an interdisciplinary team consisting of pharmacy, informatics, pathology, and the provider.