Improving Medication Use With Pharmacogenomic (PGx) Data: Practical Considerations for Pharmacists

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**Samuel G. Johnson, PharmD, BCPS, FCCP** and APhA’s editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives

1. Compare and contrast available pharmacogenomic testing options
2. Identify reliable pharmacogenomics patient care resources
3. Apply pharmacogenomic information to a patient case scenario
Which is the largest barrier to investing in pharmacogenomics?

A. Cost/Reimbursement for Testing
B. Limited Evidence for Clinical Utility
C. Limited Access to Expertise
D. Uncertainty About Benefits
Which of these is not a reliable resource for pharmacogenomic information?

A. CPIC Guidelines
B. NIH-NHGRI web resources
C. FDA-approved drug labels
D. For-profit, commercial laboratory websites
Self Assessment - Patient case

- 69 yom with recent percutaneous intervention (2 drug-eluting stents placed in proximal left anterior descending coronary artery)
- No history of TIA or CVA
- Now receiving clopidogrel 75 mg/d and ASA 325 mg/d
- CYP2C19 genotype obtained two days ago, results now available (*1/*2, or intermediate metabolizer for CYP2C19)
Which antiplatelet therapy regimen would be the best long-term option for this patient?

A. Clopidogrel
B. Prasugrel
C. Ticagrelor
D. Dipyridamole/ASA
PGx: Path Toward Better Care

• Why? Treating medical conditions often stochastic
• Take a given population with the same diagnosis... 40% have a genetic profile predicting favorable response to drugs “A” or “B”
• 50% have a genetic profile predicting favorable response to drugs “C” or “D”
• And... 10% might have genetic profile indicating toxicity to usual doses of drugs A, B, C, or D... necessitating lower doses or alternative drugs

Trends Mol Med. 2002 PMID: 12067617
Variability in drug response

- Genetics
- Liver function
- Renal function
- Co-morbidities
- Drug interactions
- Foods
- Environmental Factors (e.g. smoking)
- Disease phenotype
- Age
Putting the Pieces Together!

- Goal: Use all available patient data to better understand variability in drug response in order to optimize health care.
Select targeted oncology therapeutics with required or recommended CDx label

Note: * EU approval. FDA NDA (2004) was withdrawn in 2011 and Iressa is currently only approved in Europe for EGFR+ NSCLC patients
** While Tarceva had already been launched, it was approved for first-line treatment for EGFR+ NSCLC patients in 2013

Source: FDA, company websites, L.E.K. analysis of therapeutic drug launches

"It is far more important to know what person the disease has than what disease the person has."
— Hippocrates c. 400 B.C.
Early adopters
Available testing methods

- Single gene tests ($)
- Array-based tests ($)
- Whole genome sequencing & Next-generation sequencing ($$$$)
- Whole exome sequencing ($$$$)

Considerations
- Cost vs. cost-effectiveness
- Analytic validity
- Clinical utility
- Turnaround time
- Software/IT requirements
Laboratory certifications

**CLIA**
- Clinical Laboratory Improvement Amendments
- Created by federal mandate
- Sets standards and issues certificates for clinical testing

**CAP**
- College of American Pathologists
- Best practices for clinical testing and accreditation
- Inspections performed by practicing lab professionals
## Current testing approaches

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Scale</th>
<th>Approach</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted</td>
<td>Single or few genes, genotypes or haplotypes</td>
<td>Intensive evaluation of genotype-phenotype relationships</td>
<td>PK (ADME), PD</td>
</tr>
<tr>
<td>Focused</td>
<td>Dozens to hundreds of genes, genotypes or haplotypes</td>
<td>Evaluation of multiple alleles in a battery of genes related to a specific pathway</td>
<td>HLA genotyping for drug hypersensitivity reactions (e.g. abacavir)</td>
</tr>
<tr>
<td>Exploratory</td>
<td>Genome-wide</td>
<td>Broad screening</td>
<td>GWAS for less common ADRs (e.g. statin-induced myopathy)</td>
</tr>
</tbody>
</table>

Toxicol Lett. 2009. PMID: 19022363
‘Just-in-time’ vs. ‘just-in-case’

‘Just-in-time’ = reactive
- Ordered once treatment in place
- Time-consuming
- Single-gene tests expensive relative to potential benefit of a single therapeutic decision

‘Just-in-case’ = proactive
- Genetic results ‘re-used’
- Results may have use as more drugs are prescribed and as evidence grows
- Decreased relative expense
- Needs advanced CDS to provide relevant info
Personal Genome Service™

Get to know your DNA. All it takes is a little bit of spit.

Here's what you do:

1. Order a kit from our online store.
2. Register your kit, spit into the tube, and send it to the lab.
3. Our CLIA-certified lab analyzes your DNA in 6-8 weeks.
4. Log in and start exploring your genome.

Implementation of a pharmacogenomics service in a community pharmacy

Stefanie P. Ferreri; Angelo J. Greco; Natasha M. Michaels; Shanna K. O’Connor; Rebecca W. Chater; Anthony J. Viera; Hawazin Faruki; Howard L. McLeod; Mary W. Roederer

Conclusion: A pharmacogenomics service can be an extension of medication therapy management services in a community pharmacy. Prescribers are receptive to having community pharmacists conduct pharmacogenomics testing, but reimbursement is a challenge.
Advancing pharmacogenomic testing: (CPIC)

• International consortium of pharmacogenetics researchers, clinicians, clinical laboratory personnel, FDA, NIH, & observers

• Goals:
  • Mitigate knowledge barriers
  • Systematic review of evidence for clinical utility for genotype-guided therapy
  • Specific recommendations about how to adjust drug therapy based on genotype
  • No recommendations about WHETHER to test but only how to use genetic information that is already available
  • Presume increasing availability of genetic information via preemptive (‘just-in-case’) genotyping
Pharmacogenomic information can be used to:

- Select/avoid therapy based on predicted efficacy
  - Clopidogrel, codeine

- Guide drug dosing
  - Azathioprine, 6-MP, thioguanine, warfarin, TCAs

- Avoid serious adverse drug reactions
  - Simvastatin, abacavir, allopurinol, carbamazepine

Pharmacogenomics 2013. PMID: 23651030
CPIC Guidelines

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing

JA Johnson¹, J Gong², M Whirl-Carrillo³, BF Gage⁴, SA Scott⁵, CM Stein⁶, JL Anderson⁷, SE Kimme⁸⁻⁹, MTM Lee¹⁰, M Pirruccio¹¹, M Wandelius¹², TE Klein¹³ and RB Altman¹⁴⁻¹⁵

Clinical Pharmacogenetics Implementation Consortium Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype

KR Crews¹, A Gaedigk², HM Dunnberger³, TE Klein⁴, DD Sherr⁴⁻⁵, JT Callaghan⁷⁻⁸, ED Kharasch⁹ and TC Skaar⁷

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy

SA Scott¹, K Sangkuhl², EE Gardner³, CM Stein⁴⁻⁵, J-S Hulot⁶⁻⁷, JA Johnson⁸⁻⁹⁻¹⁰, DM Roden¹¹⁻¹², TE Klein¹³ and AR Shuldiner¹³⁻¹⁴

The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for SLCO1B1 and Simvastatin-Induced Myopathy

RA Wilke¹⁻², LB Ramsey³, SG Johnson¹⁻², WD Maxwell³, HI McLeod⁴, D Voora⁵, RM Krusz⁶, DM Roden¹¹⁻¹², Q Feng¹⁻², RM Cooper-DelHoff¹⁹, J Gong¹¹, TE Klein¹³⁻¹⁴, M Wandelius¹² and M Niemi¹⁴

## CPIC vs. EGAPP

<table>
<thead>
<tr>
<th>CPIC</th>
<th>EGAPP</th>
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<tbody>
<tr>
<td>- Partnership between NIH-PGRN and PharmGKB</td>
<td>- Partnership between independent experts and CDC</td>
</tr>
<tr>
<td>- Recommendations for altering drug therapy based on genotype</td>
<td>- Recommendations for or against genotyping based on evidence</td>
</tr>
<tr>
<td>- Updated biennially</td>
<td>- Not routinely updated</td>
</tr>
</tbody>
</table>
CPIC Informatics:
Supporting Guideline Implementation

Guideline Development

CPIC
Coordinate Refinements

Guideline Adoption

Implementers
Feedback

CPIC Informatics
Creation and Maintenance of Translation Tables
- Human-readable
- Semi-structured text
- Formal knowledge representation

Genotype
Phenotype
Recommendation

Overall, a tremendous opportunity to align/meld just-in-time education for front-line clinicians.

Pharmacist Competency Map. Genetics and Genomics Competency Center. Available at: http://g-2-c-2.org/competency/pharmacist
Bioethical considerations

- May be different depending on type of testing:
  - Tumor testing (somatic variants)
  - Germline testing (inherited variants)
  - Variants associated with inherited disease risk (e.g., ApoE variants) vs. variants associated only with response to drug therapy (e.g., CYP2C19)
- Multiple stakeholders
  - Health systems, providers, patients
- Ethical dilemmas (separate from legal or regulatory issues)
  - Duty to warn, risk for unmasking non-paternity, weighing clinical utility against personal utility (e.g. 23andMe)
Legal and regulatory factors

• Federal Law = Genetic Information Nondiscrimination Act (GINA) passed 2008
  • Protects Americans from discrimination based on genetic information for employment and health insurance
  • Still has gaps → life-insurance and disability insurance

• State statutes also apply (Most mirror GINA)

## CPIC recommendations

<table>
<thead>
<tr>
<th>Phenotype (genotype)</th>
<th>Implications for clopidogrel</th>
<th>Therapeutic recommendations</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)</td>
<td>Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation</td>
<td>Clopidogrel: label-recommended dosage and administration</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer (*1/*2, *1/*3, *2/*17)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer (*2/*2, *2/*3, *3/*3)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Strong</td>
</tr>
</tbody>
</table>

*aSee Supplementary Materials and Methods (Strength of Therapeutic Recommendations) online.* †The CYP2C19*17 allele may be associated with increased bleeding risks (ref. 15). ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.
Clinical recommendations...

CYP2C19 Genotyping

Ultra-rapid and Extensive Metabolizer
*1/*1
*1/*17
*17/*17

Intermediate Metabolizer
*1/*2

Poor Metabolizer
*2/*2

Normal or increased antiplatelet effect

ACS (Strong)
IS\(^a\) (Weak)

Clopidogrel

Reduced antiplatelet effect; increased risk for adverse cardiac outcomes

ACS (Moderate)
IS\(^a\) (Weak)

Prasugrel OR Ticagrelor\(^b\)
Dipyridamole AND ASA

Significantly reduced antiplatelet effect; increased risk for adverse cardiac outcomes

ACS (Strong)
IS\(^a\) (Weak)

Prasugrel OR Ticagrelor\(^b\)
Dipyridamole AND ASA


\(^a\) ASA

\(^b\) Dipyridamole

Derived from Clin Pharmacol Ther. 2013. PMID: 23698643
Implications for pharmacy profession

**Pharmacists**
- Little question that genomic medicine is part of the future
- Pharmacists should be positioned as the most knowledgeable member of team in pharmacogenomics
- Opportunities/roles for pharmacists are many

**Pharmacy education**
- Must include solid understanding of basic concepts in genetics, genomics, molecular biology
- Clinical implications of genomics and pharmacogenomics
- Ethical, legal and social implications of genomic information
Summary

- Pharmacogenomics isn’t science fiction!
- Clinical implementation is evolving
- Help is available! See CPIC! Use CPIC! Join CPIC!

Bottom line: Pharmacists should take ownership of PGx along with PK, PD, in the context of medication management services
Which is the largest barrier to investing in pharmacogenomics?

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3. Click “Claim Credit”
4. Click “Enroll Now”
5. Enter attendance code: RPL6LG
6. Complete evaluation
7. Claim credit

Your CPE must be filed by November 5, 2017, at 5 p.m. ET to receive credit.
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>Allele</strong></td>
<td>One of two or more forms of a gene that arise by mutation and found at the same location on a chromosome</td>
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<tr>
<td><strong>Genome</strong></td>
<td>The complete set of genetic material for an individual</td>
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<tr>
<td><strong>GWAS</strong></td>
<td>An approach involving scanning markers across complete genomes to identify variation associated with a particular disease or condition. Especially useful to find genetic variants that contribute to drug response.</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td>The genetic makeup of an organism with reference to a single trait or set of traits</td>
</tr>
<tr>
<td><strong>Genotyping</strong></td>
<td>Testing that reveals specific alleles inherited by an individual</td>
</tr>
<tr>
<td><strong>Haplotype</strong></td>
<td>A combination of alleles that are located closely together on the same chromosome and tend to be inherited together</td>
</tr>
<tr>
<td><strong>Pharmacogenetics</strong></td>
<td>Study of the relationship between single gene variants and variability in drug disposition, response, and toxicity</td>
</tr>
<tr>
<td><strong>Pharmacogenomics</strong></td>
<td>Study of the relationship between variants in a large collection of genes and variability in drug disposition, response, and toxicity</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>Observable characteristics of an individual resulting from the interaction of its genotype with the environment</td>
</tr>
<tr>
<td><strong>Polymorphism</strong></td>
<td>The occurrence of different phenotypes among members of a population of the same species. A single nucleotide polymorphism (SNP) is variation occurring when a single nucleotide in the genome differs between paired chromosomes in an individual.</td>
</tr>
<tr>
<td><strong>Wild-type</strong></td>
<td>A characteristic that refers to the typical form of a trait in a species as it occurs in nature</td>
</tr>
</tbody>
</table>
**Common abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CPIC</td>
<td>Clinical Pharmacogenetics Implementation Consortium</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association study</td>
</tr>
<tr>
<td>SNP</td>
<td>Single nucleotide polymorphism</td>
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<tr>
<td>DMET</td>
<td>Drug metabolizing enzymes and transporters</td>
</tr>
<tr>
<td>PGx</td>
<td>Pharmacogenomics</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>ADRs</td>
<td>Adverse drug reactions</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>EGAPP</td>
<td>Evaluation of Genomic Applications in Practice and Prevention</td>
</tr>
</tbody>
</table>
Historical evolution of PGx: 1950-1970

1953
Bönicke et al describe slow and rapid acetylation of isoniazid

1956
Association of primaquine-induced hemolysis with G6PD deficiency in erythrocytes

1957
Kalow and Staron characterize serum cholinesterase deficiency

1959
Vogel coins the term “pharmacogenetics”

1960
Evans establishes genetic control of isoniazid acetylation

1962
Kalow publishes: “Pharmacogenetics: Heredity And Response to Drugs”

1967
Sjöqvist et al establish that TCA metabolism is under ‘genetic control’

- 1980
  Weinshilboum & Sladek discover TPMT polymorphism

- 1985
  PCR allows exponential amplification of genetic sequences

- 1991
  First issue of *Pharmacogenetics* is published

- 1975
  Smith & Eichelbaum discover debrisoquine/sparteine polymorphism

- 1984
  Kupfer & Wedlund describe polymorphism of mephenytoin hydroxylation

- 1988
  Gonzales & Meyer clone CYP2D6 to characterize debrisoquine genetic defect

Nat Rev Genet. 2004 PMID: 15372089
Historical evolution of PGx: 1992-2003

1997
The term Pharmacogenomics first appears in the literature

1994
Cloning and characterization of CYP2C19, which causes mephenytoin polymorphism

2000
PharmGKB is constructed with support from the NIH PGRN

1999
A nomenclature website for CYP alleles is established

2003
FDA issues draft guidelines for submission of PGx data for NDAs

2003
Human genome sequence nearly completed