INDIVIDUALIZED PATIENT THERAPY: IS IT MORE THAN A BUZZWORD?

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.
Accreditation

- The University of Florida College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Objectives

1. Describe the benefits and limitations of available pharmacogenetic tests
2. Compare and contrast currently available pharmacogenetic tests
3. Identify evidence sources to assist with interpreting pharmacogenetic test results and implementing clinical recommendations into practice
4. Summarize strategies for incorporating pharmacogenetic testing into pharmacy practice
“I want the country that eliminated polio and mapped the human genome to lead a new era of medicine – one that delivers the right treatment at the right time.”
Current Medical Practice

Cancer patients with e.g. colon cancer

Medicine of the present: one treatment fits all

Therapy

Effect No effect Adverse effects

One size does not fit all: Relative efficacy of drug and disease, according to Spear et al.

Source: Hua L.
Adverse Drug Events

2007 – 2009: pts ≥ 65 years
99,628 annual hospitalizations
166,174 annual ED visits

![Graph showing adverse drug events](image)

**Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.**

Factors That Influence Drug Response

Genetics

Pharmacogenomics (PGx)

Image accessed from: http://mytorontocanadambastudentexperience.blogspot.com/2012/10/personalized-medicine-or-p4-medicine.html
PGx Is Not A New Concept

1866 Gregor Mendel establishes the rules of heredity

1900 W. Bateson introduces the term “genetics”

1953 – 1954 Bonicke and Reif →isoniazid acetylation

1959 Vogel coins the term “pharmacogenetics”

1967 Sjoqvist et al. Genetics influence TCA metabolism

1990 Heim and Meyer publish 1st allele-specific PGx test for CYP2D6

1994 Goldstein et al. CYP2C19 cloning and characterization

1997 Pharmacogenomics appears 1st in literature

2000 PharmGKB is constructed through NIH PGRN

2007 FDA includes PGx info in drug labeling

The Human Genome Project

- 13 year international project completed in 2003
- Coordinated by US Department of Energy and the NIH
- Project goals:
  - Identify all genes in human DNA
  - Determine the sequences of the 3 billion chemical base pairs
  - Store the information in databases
  - Improve tools for data analysis
  - Transfer related technologies to the private sector
  - Address the ethical, and social issues that may arise

The New Era of Medical Practice

- Personalized Medicine
  - “Emerging practice of medicine that uses an individual’s genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease” - National Human Genome Research Institute

- Also known as:
  - Individualized medicine
  - Precision medicine

PHARMACOGENOMICS OF DRUG METABOLIZING ENZYMES
Pharmacogenomics of Drug Metabolizing Enzymes

Diagram showing various drug metabolizing enzymes and their substrates. The enzymes include CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4/3A5. The substrates include Aminopyrine, Carbamazepine, Chloroquine, Cyclophosphamide, and other drugs.
Single nucleotide polymorphism (SNP)

Allele = one variant of a gene

- Allele for purple flowers
- Locus for flower-color gene
- Homologous pair of chromosomes
- Allele for white flowers
# Star-allele Nomenclature

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>CYP2D6_ex9</th>
<th>-1584C&gt;G</th>
<th>100C&gt;T</th>
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<tbody>
<tr>
<td>*1/*1</td>
<td>Hs00010001_Cn</td>
<td>C_32407252_30</td>
<td>C_11484460_40</td>
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<tr>
<td>2</td>
<td>G/G</td>
<td>G/G</td>
<td>G/G</td>
</tr>
<tr>
<td>*1/*1x2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>G/G</td>
<td>G/G</td>
<td>G/G</td>
</tr>
<tr>
<td>*1/*2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>G/G</td>
<td>G/G</td>
<td>G/G</td>
</tr>
</tbody>
</table>
*1 allele

Homologous pair of chromosomes

*3 allele
IMPLEMENTATION EXAMPLE: CYP2C19-CLOPIDOGREL
CYP2C19 Genotype and Clopidogrel

**Clopidogrel**

- **Esterases**
  - 85%
  - 15%

  - **CYP1A2**
  - **CYP2C19**
  - **CYP2B6**

  - **2-oxo-clopidogrel**

  - **CYP3A**
  - **CYP2B6**
  - **CYP2C9**
  - **CYP2C19**

  - **Inactive metabolite**

**Prasugrel**

- **Esterases**

  - **CYP3A**
  - **CYP2B6**
  - **CYP2C19**
  - **CYP2C9**

  - **Inactive metabolite**

  - **active metabolite**

  - **P2Y12**

  - **Platelet**
CYP2C19 and Clopidogrel Response

- Reduced function genotype associated with:
  - Decreased clopidogrel metabolism
  - Reduced inhibition of platelet aggregation with clopidogrel
- Meta-analysis of 9 trials and 9684 patients:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Ratio (95% CI)</th>
<th>IM vs EM</th>
<th>PM vs EM</th>
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</thead>
<tbody>
<tr>
<td>MACE*</td>
<td>1.5 (1.1-2.1)</td>
<td>1.8 (1.2-2.5)</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>2.7 (1.7-4.2)</td>
<td>4.0 (1.8-9.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Major adverse CV events (CV death, MI, or stroke)

GIANT Trial: *CYP2C19* Genetic Profiling for Thienopyridine Management Post-PCI

- **n=1,445** AMI post-PCI
- **n=327** LOF allele
  - **n=55** no adjustment
  - **n=272** regimen adjusted
- **n=1118** no LOF allele

**Risk for death, MI, stent thrombosis at 1 yr**

- 15.6%
- 3.3%
- 3.0%

Chevalier et al. Presented at the 2013 Transcatheter Cardiovascular Therapeutics Scientific Symposium
FDA-Approved Clopidogrel Labeling

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel bisulfate is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Clopidogrel bisulfate at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel bisulfate at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient’s CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].

CPIC Guidelines for CV Drugs

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy
SA Scott1, K Sungkuh1, EE Gardner1, CM Stein2, J-S Hulot3,7, JA Johnson3,9,10, DM Roden1,11,12, TE Klein7 and AR Shuldiner13,14


Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing
JA Johnson1, L Gong2, M Whirl-Carrillo3, BF Gage4, SA Scott4, CM Stein5, JL Anderson6, SE Kimmel7, MTM Lee8, M Pirmohamed9,10, M Wadelius11, TE Klein12 and RB Altman12,13


The Clinical Pharmacogenomics Implementation Consortium: CPIC Guideline for SLCO1B1 and Simvastatin-Induced Myopathy
RA Wilke1,2, LB Ramsey9, SG Johnson1,4,5, WD Maxwell6, HL McLeod2, J Voor7,9, RM Kraus9, DM Roden1,2, Q Feng3,2, RM Cooper-DeHoff16, L Gong11, TE Klein11,12, M Wadelius13 and M Niemi14

CPIC Guidelines for CYP2C19 and Clopidogrel: 2013 Update

ACS/PCI Patients

CYP2C19 Genotyping

UM (*1/*17 or *17/*17)

EM (*1/*1)

IM (e.g. *1/*2)

PM (e.g. *2/*2)

Clopidogrel at a standard dose

Alternative antiplatelet (Prasugrel or Ticagrelor)

Personalized Medicine Program—Launched June 25, 2012

UF delivers promise of personalized medicine to heart patients

Personalized medicine — a concept in which an understanding of a patient’s genetic makeup is used to enhance treatment — has arrived at UF&Shands, the University of Florida Academic Health...
UF Health PMP

- Establish UF Health as leaders in genetic-guided care
- Develop informatics systems to handle genomic data linked to EMR (lifetime result)
- Define when and how to use genetic data in patient care
- Evaluate impact on patient safety, outcomes and costs of care
Clopidogrel Pilot: Clinical Implementation

- CYP2C19 genotype test added as standard of care for patients in cath lab – Clinical consent
  - CYP2C19 was pre-selected on standard pre-cath order sets
    - Later moved to post-PCI order sets
  - CYP2C19 genotype moves to EMR in all patients, independent of treatment with clopidogrel
Clopidogrel: Year 1 Genotyping

- N = 1,097 patients genotyped

- Genotype results
  - 38.5% - normal metabolizers
  - 26.1% - intermediate metabolizers (actionable)
  - 1.7% - poor metabolizers (actionable)
  - 32.9% - ultra-rapid metabolizers

Clopidogrel: Year 1 Test Adoption

- Year 1 test adoption (all): 74% (1,097/1,479)
  - First 2 months (July/August 2012): 47%
  - Last 2 months (May/June 2012): 83%
  \[
P = 1.201 \times 10^{-16}
\]

- Year 1 test adoption (PCI): 84% (247/291)
  - First 2 months (July/August 2012): 63%
  - Last 2 months (May/June 2012): 98%
  \[
P = 4.344 \times 10^{-5}
\]

Clopidogrel: Year 1 Drug Therapy Changes

- 80 post-PCI patients with actionable genotype
  - Switched to alternate therapy (56/80; 70%)
    - Prasugrel 80%
    - Ticagrelor 9%
    - 3x dose clopidogrel 11%
  - Not switched to alternate therapy (24/80; 30%)
    - Reason for not being switched: Cost, contraindications, and stable on previous therapy
    - Many were unknown why therapy was not switched

Objective

- To examine whether clinical implementation of CYP2C19 genotype-guided antiplatelet therapy (APT) reduces the risk for major adverse cardiovascular events (MACE) within 30 days after PCI.
Methods

• Reviewed EHR for patients who underwent PCI and CYP2C19 genotyping
  • June 25, 2012 – August 2014
  • Collected data through 30 days post-PCI
  • MACE defined as a composite of cardiovascular death, MI, CVA, stent thrombosis*
• Compared MACE between:
  • LOF allele carriers switched or not switched to alternative APT
  • LOF allele carriers switched to alternative APT and non-LOF allele carriers

MACE at 30 days according to *CYP2C19* genotype

- **n=318 post-PCI patients (78% with ACS)**
  - **n=99 with a LOF allele**
    - **n=41** APT not switched
      - Clopidogrel 75 mg/d
    - **n=58** APT switched
      - Prasugrel (n=50)
      - Ticagrelor (n=5)
      - Clopidogrel 225 mg/d (n=3)
  - **n=219 no LOF allele**

**CV death, MI, CVA, stent thrombosis at 30 days**

- **n=5†** 12.2%
- **n=0** 0%
- **n=6** 2.7%

*LOF, loss of function allele (e.g. *CYP2C19* *1/*2 or *2/*2 genotype)
†STEMI (n=3, 1 with stent thrombosis), CVA (n=1), CV death (n=1)
Kaplan-Meier Survival Curve

- LOF switched
- LOF not switched
- Non-LOF

LOF Switched vs. Not switched: $p=0.006$
LOF Switched vs. Non-LOF: $p=0.203$
So why is this not the standard of care?
<table>
<thead>
<tr>
<th>Challenges to Clinical Implementation</th>
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<tbody>
<tr>
<td><strong>Knowledge Gap</strong></td>
</tr>
<tr>
<td>- Pharmacogenomics knowledge</td>
</tr>
<tr>
<td>- Conflicting evidence</td>
</tr>
<tr>
<td><strong>Experience Gap</strong></td>
</tr>
<tr>
<td>- Varying thresholds for clinical utility</td>
</tr>
<tr>
<td>- Genetic testing</td>
</tr>
<tr>
<td>- Financial barriers</td>
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<tr>
<td>- Lack of Infrastructure / Technical issues</td>
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<td>- Clinician resistance to consider PGx information</td>
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Strategy: Evidence Review

- Multidisciplinary committee
- Functions may include reviewing pharmacogenetic evidence, prioritizing implementations and educational initiatives, assessing impact of emerging evidence for ongoing implementations, others
- Possible oversight by P and T Committee
Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Shared effort of PGRN and PharmGKB
- Provides guidelines that enable the translation of genetic results into actionable prescribing decisions
- Designed to help clinicians understand HOW available genotype results should be used to optimize drug therapy, not WHETHER tests should be ordered
Existing Drug-Gene Pairs with CPIC Guidelines

- HLA-B
  - Abacavir
  - Allopurinol
- CYP2C19
  - Clopidogrel
- CYP2C19/CYP2D6
  - TCAs
- CFTR
  - Ivacaftor
- G6PD
  - rasburicase

- TPMT
  - Thiopurines
  - IFNL3 (IL28B)
  - Peginterferon
- CYP2D6
  - Codeine
- DPYD
  - Capecitabine, fluorouracil, tegafur
- CYP2C9, VKORC1
  - warfarin

Strategy: Patient Care Processes

- Laboratory processes
  - How will test be ordered?
  - How will test be processed and resulted?

- Insurance billing and reimbursement
  - Inpatient versus outpatient
  - Current test reimbursement data (i.e., CPT coding, CMS coverage?)
Strategy: Patient Care Processes

- Provider interpretation and application of results
  - Targeted vs system-wide initiative
  - Clinical decision support via electronic health record or other mechanism
  - Pharmacogenetic consult service or clinical pharmacist presence
  - Documentation of recommendations
EMR Clinical Decision Support

PROBLEM
This patients CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for silent thrombosis or other cardiovascular events following PCI.

REASONS
Reduced clopidogrel activation in this genotype results in significantly reduced platelet inhibition, increased residual platelet aggregation, and decreased clopidogrel efficacy.

RECOMMENDATIONS - MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:
(A) Prescribe prasugrel (EFFIENT) 10 mg daily
   *Contraindications: History of stroke or transient ischemic attack, active bleeding
   *Caution: Increased bleeding risk: Age > 75 years, Body weight < 60 kg
OR
(B) Prescribe ticagrelor (BRILINTA) 80mg twice daily
   *Contraindications: History of intracranial hemorrhage, active bleeding, severe hepatic impairment
   *Caution: Asprin doses >100 mg/day reduce ticagrelor effectiveness and should be avoided.

More information on clopidogrel and CYP2C19

For questions about this alert or the personalized medicine program, please contact: PMP-HELP@cts.uihealth.edu or (312) 380-1441.

Last CYP2C19=2/2 on 6/1/2013

Open order: Place order for prasugrel (EFFIENT) tablet and remove order for clopidogrel
Open order: Place order for ticagrelor (BRILINTA) tablet and remove the clopidogrel order
Open order: Continue to order clopidogrel (PLAVIX) tablet - 75 mg daily please remove the first order as it will duplicate
this slide should be much earlier - in the UF experience portion.

Julie Johnson, 1/14/2014
Strategy: Patient Care Processes

- Provider and staff training/education
  - Pharmacogenetics knowledge and applications to patient care
  - Training for specific procedural or workflow changes
  - In-services, grand rounds, patient care conferences

- Delivering test results to patients
  - Who will notify patients of results? When?
  - Are educational materials needed?
Current Status and Future Directions for UF Health PMP

- TPMT testing for thiopurines
  - Pediatric acute lymphoblastic leukemia
  - Gastroenterology, others

- IL28B (IFNL3) for pegylated interferon
  - Hepatitis C

- CYP2D6 testing for codeine, tramadol
  - Test available clinically for inpatient and outpatient ordering
  - Family medicine pilot program – pain outcomes with CYP2D6-guided therapy
Additional Resources

- Pharmacogenomics Knowledgebase
  - http://www.pharmgkb.org/
- Clinical Pharmacogenetics Implementation Consortium Guidelines
  - http://www.pharmgkb.org/page/cpic
- National Human Genome Research Institute
  - www.genome.gov
- Genetics/Genomics Competency Center for Education
  - http://www.g-2-c-2.org/
- Global Genetics and Genomics Community
  - http://g-3-c.org/en
## Additional Resources

- **Genetics in Primary Care Institute**  
  - [http://www.geneticsinprimarycare.org](http://www.geneticsinprimarycare.org)

- **National Coalition for Health Professional Education in Genetics**  
  - [http://www.nchpeg.org/](http://www.nchpeg.org/)

- **American Pharmacists Association**  
  - APhA DrugInfoLine, Pharmacogenomics Corner:  
    [www.aphadruginfoline.com](http://www.aphadruginfoline.com)
  
  - Pharmacogenomics and MTM White Paper:  
Additional Resources

- American Society of Health-System Pharmacists
  - Pharmacogenomics resources listing: http://www.ashp.org/menu/PracticePolicy/ResourceCenters/Emerging-Sciences/Pharmacogenomics.aspx
  - PGY2 Specialty Pharmacogenetics Residencies
    - UF Health Personalized Medicine Program
    - St. Jude Children’s Hospital

- American College of Clinical Pharmacy
  - Pharmacokinetics/Pharmacodynamics/Pharmacogenomics Practice and Research Network

- American Association of Colleges of Pharmacy
  - Pharmacogenomics Special Interest Group
Acknowledgements

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QUESTIONS?