Putting Pharmacogenomics into Practice

Daniel Streetman
Sherri J. Willard Argyres

Brought to you by Wolters Kluwer Clinical Drug Information
Housekeeping Items

• Recording and slides will be distributed via email next week

• Please complete the survey at the end of the webinar for a chance to win a Kindle Fire

• Technical issues and questions can be asked via chat in lower left-hand corner of screen
When it comes to drug information, we have you covered.

Clinical Drug Information brings together three leading applications

1. **Medi-Span** - Integrated drug databases used in 60 EMRs, 1,000+ hospitals, 17 out of 20 top-grossing PBMs, and 37,000 retail pharmacies

2. **Lexicomp** - Referential drug information used in more than 2,200 hospitals and by 80,000 mobile users

3. **Facts & Comparisons** - Reference for retail pharmacy used in over 27,000 retail locations by more than 70,000 pharmacists
Daniel Streetman, PharmD, MS

- Pharmacotherapy Specialist in the Metabolism, Interactions, and Genomics Group for Wolters Kluwer Clinical Drug Information

- Prior to coming to Wolters Kluwer, Dr. Streetman was a clinical faculty member at the University of Michigan for nearly eight years. Dr. Streetman received his PharmD from Ohio Northern University and a master’s degree in clinical research design and statistical analysis from the School of Public Health at the University of Michigan and has completed a pharmacy practice residency and a research fellowship in clinical pharmacology, with emphasis in pharmacogenomics.

- He is accredited in Applied Pharmacology by the American Board of Clinical Pharmacology, serves as a reviewer and editor for several professional journals, and has authored more than 20 publications.
Sherri J. Willard Argyres, MA, PharmD, BCPS

• Medical science pharmacist for Wolters Kluwer Clinical Drug Information and a clinical pharmacist for the Drug Use Research and Management program at Oregon State University/Oregon Health and Science University.

• She has seven years of research experience in molecular biology, which she largely gained as a Harvard University graduate student in the Department of Molecular Biology at Massachusetts General Hospital. Dr. Willard Argyres holds a Doctor of Pharmacy degree from Oregon State University/Oregon Health and Science University, Master of Arts degree in microbiology and molecular genetics from Harvard University, and post-graduate certificate in science communications from the University of California at Santa Cruz.
Learning Objectives

1. Provide an overview of pharmacogenomics, including defining key terms and discussing its history

2. Summarize the current state of pharmacogenomics in guidelines and labeling

3. Describe components necessary to translate genetic information into clinical action

4. Describe successes in the clinical implementation of pharmacogenetics
What is *pharmacogenetics*, and why should I care?
Hypotension following Debrisoquine

% Excreted in 8 hrs as

DBQ 4-OH DBQ Ratio

EMs PMs

*Symptomatic hypotension in all 3 PMs but no EMs

Other Significant Reports

- Codeine and respiratory failure \((CYP2D6)^{1,2,3,4,5,6}\)
- Fluoxetine fatality \((CYP2D6)^7\)
- Azathioprine and fatal myelosuppression \((TPMT)^8\)
- Phenytoin toxicity \((CYP2C9)^9\)


CONFIDENTIAL AND PRIVILEGED. FOR INFORMATIONAL PURPOSES ONLY.
Early History: Neuritis, Hemolysis, and Apnea

- **1950s**
  - Isoniazid-associated polyneuritis (*acetylation status; NAT1-2*)
  - Hemolysis following primaquine (*G6PD deficiency*)
  - Prolonged apnea after succinylcholine (*cholinesterase deficiency*)

- **1959: Pharmacogenetics**
  
  "Study of the relationship between individual gene variants and variable drug effects."
Growing understanding and interest

- **1970s thru 1990s**
  - Many more sensitive drugs identified
  - Underlying mechanism in slower and rapid metabolizers
  - Standardized nomenclature

- **1997: Pharmacogenomics**

  "Study of the relationship between variants in a large collection of genes, up to the entire genome, and variable drug effects."
CYP2D6 Variability

Advances in understanding and technology

- Completion of Human Genome Project
  - HapMap, SNP database

  - Mother and daughter: CYP2C19 *17/*17
  - 4 drugs more likely to work; 4 others less likely to work
  - Dose requirements like for 3 drugs

- Explosion of related fields
  - Epigenetics, Proteomics, Bioinformatics, etc.

- Technology improvements
  - Point-of-care testing, Decreased cost
- **USA, Europe, Japan**
  - When PGx studies should be performed; Conduct and interpretation of PGx studies; Banking of DNA encouraged

Carvedilol is subject to the effects of genetic polymorphism with poor metabolizers of debrisoquin (a marker for cytochrome P450 2D6) exhibiting 2- to 3-fold higher plasma concentrations of R(+) carvedilol compared to extensive metabolizers. Retrospective analysis of side effects in clinical trials showed that poor 2D6 metabolizers had a higher rate of dizziness during up-titration, presumably resulting from vasodilating effects of the higher concentrations of the α-blocking R(+) enantiomer.


CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect. A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined.

Putting it all into practice

- **Personalized Medicine Coalition**
  - represents innovators, scientists, patients, providers and payers
  - promotes personalized medicine concepts, services and products

- **Clinical Pharmacogenetics Implementation Consortium (CPIC)**
  - Collaboration between PharmGKB and Pharmacogenomics Research Consortium
  - Remove some barriers to implementation of PGx knowledge
  - How information to be used, not whether tests should be ordered

"I want the country that eliminated polio and mapped the human genome to lead a new era of medicine ... Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes -- and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

President Obama on personalized medicine
State of the Union Address
Jan. 20, 2015

[www.personalizedmedicinecoalition.org](http://www.personalizedmedicinecoalition.org)
[www.pharmgkb.org/page/cpic](http://www.pharmgkb.org/page/cpic)
Where are we today with respect to pharmacogenetics?
Lagging behind ...

Pharmacogenomics Knowledge

Clinical Implementation
Are we implementing too slowly?

- Predictions about the role of PGx a bit too optimistic
  - (2002) By 2010, more than half of drugs will have corresponding test

- Many limitations
  - Education
  - Validity/Utility
  - Reliability of testing
  - Cost-effectiveness
  - Legal, ethical issues

Surge in Pharmacogenetics and Pharmacogenomics Literature

Pharmacogenetics in Labeling

- US: >134 labels with PGx information (vs. 76 in 2004)
  - CYP2D6 (36); G6PD (19)
  - EMA: approximately 15% with data relevant to patient care

- Few examples where labeling requires testing
  - Eliglustat
    - CYP2D6 EMs or IMs: 84 mg BID; CYP2D6 PMs: 84 mg QD
  - Carbamazepine
    - "Patients with ancestry in genetically at-risk populations should be screened for ... HLA-B*1502 prior to initiating treatment..."
  - Abacavir
    - "Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended ..."

www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene(s)</th>
<th>Group(s)</th>
<th>Drug</th>
<th>Gene(s)</th>
<th>Group(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B</td>
<td>CPIC</td>
<td>Ivalaftor</td>
<td>CFTR</td>
<td>CPIC</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>HLA-B</td>
<td>CPIC</td>
<td>Mercaptopurine</td>
<td>DPYD</td>
<td>CPIC</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>CYP2C19, 2D6</td>
<td>CPIC</td>
<td>Nortriptyline</td>
<td>CYP2D6</td>
<td>CPIC</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>TPMT</td>
<td>CPIC</td>
<td>Phenytoin</td>
<td>CYP2C9, HLA-B</td>
<td>CPIC</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>IFNL3</td>
<td>CPIC</td>
<td>Rasburicase</td>
<td>G6PD</td>
<td>CPIC</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>DPYD</td>
<td>CPIC</td>
<td>Ribavirin</td>
<td>IFNL3</td>
<td>CPIC</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B</td>
<td>CPIC</td>
<td>Simvastatin</td>
<td>SLCO1B1</td>
<td>CPIC</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>CYP2C19, 2D6</td>
<td>CPIC, AHA</td>
<td>Tacrolimus</td>
<td>CYP3A5</td>
<td>CPIC</td>
</tr>
<tr>
<td>Clonidogrel</td>
<td>CYP2C19</td>
<td>CPIC</td>
<td>Tamoxifen</td>
<td>CYP2D6</td>
<td>ACMG</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>CPIC</td>
<td>Tegafur</td>
<td>DPYD</td>
<td>CPIC</td>
</tr>
<tr>
<td>Desipramine</td>
<td>CYP2D6</td>
<td>CPIC</td>
<td>Telaprevir</td>
<td>IFNL3</td>
<td>CPIC</td>
</tr>
<tr>
<td>Doxepin</td>
<td>CYP2C19, 2D6</td>
<td>CPIC</td>
<td>Thioguanine</td>
<td>TPMT</td>
<td>CPIC</td>
</tr>
<tr>
<td>Fluourouracil</td>
<td>DPYD</td>
<td>CPIC</td>
<td>Trimipramine</td>
<td>CYP2C19, 2D6</td>
<td>CPIC</td>
</tr>
<tr>
<td>Imipramine</td>
<td>CYP2C19, 2D6</td>
<td>CPIC</td>
<td>Warfarin</td>
<td>CYP2C9, VKORC1</td>
<td>CPIC, ACMG</td>
</tr>
<tr>
<td>Interferons</td>
<td>IFNL3</td>
<td>CPIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>EGAPP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Royal Dutch Guidelines:  53 drugs, 11 genes

Personalized Medicine Programs

- St Jude Children's Hospital (PG4KDS)¹
- Vanderbilt University (PREDICT)²
- University of Florida³,⁴
- University of Chicago⁵
- Mt Sinai Medical Center (BioMe program; CLIPMERGE-PGx)⁶
- Coriell Institute for Medical Research
- University of Maryland (PAP3)⁷
- Mayo Clinic (RIGHT protocol)⁸
- Indiana Institute of Personalized Medicine⁹
- eMERGE-PGx (multicenter)¹⁰

Outline

- Define clinical implementation of pharmacogenetics
- Provide a sample description of the systematic process of implementing a preemptive genotyping program
- Identify the components necessary to translate pharmacogenetics into clinical action
- Identify stakeholders in providing educational resources
- Provide examples of potential pharmacogenetic associations that have been validated or investigated
- Provide examples of educational and clinical support tools
Definition: Clinical Implementation of PG

The incorporation of pharmacogenetics into routine clinical care by developing and implementing processes to perform and interpret pharmacogenetic tests for variants that have been clinically validated —adapted from Mary Relling

CONFIDENTIAL AND PRIVILEGED. FOR INFORMATIONAL PURPOSES ONLY.
Sample preemptive PG program “process”

- Analyze processes and perform drug utilization review
- Evaluate clinical evidence of PG association
- Build tables to translate genotype into phenotype

Adapted from U of Florida. References for preemptive genotyping programs at end of slides.
Develop CDS and integrate into EMR

Obtain approvals

Educate staff
Launch program

Adjudicate patient results

Evaluate programmatic outcomes

CONFIDENTIAL AND PRIVILEGED. FOR INFORMATIONAL PURPOSES ONLY.
## Characteristics of ideal PG educational resource

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total respondents (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How to interpret pharmacogenomic test results</td>
<td>88.4% (260)*</td>
</tr>
<tr>
<td>Recommendations for prescribing</td>
<td>88.1% (259)</td>
</tr>
<tr>
<td>Effect of genetic variation on mechanism of drug action</td>
<td>79.9% (235)</td>
</tr>
<tr>
<td>Demographics of populations likely to carry variations</td>
<td>76.9% (226)</td>
</tr>
<tr>
<td>References (such as scientific literature)</td>
<td>69.0% (203)</td>
</tr>
<tr>
<td>List of laboratories offering testing</td>
<td>63.9% (188)</td>
</tr>
<tr>
<td>Description of pharmacogenomic information in drug labeling</td>
<td>62.2% (183)*</td>
</tr>
<tr>
<td>Format</td>
<td></td>
</tr>
<tr>
<td>Web-based</td>
<td>67.7% (199)</td>
</tr>
<tr>
<td>Mobile application (for smartphone or tablet)</td>
<td>56.2% (165)</td>
</tr>
<tr>
<td>Incorporated within EMR</td>
<td>34.0% (100)*</td>
</tr>
<tr>
<td>Pop-up reminders within prescribing system</td>
<td>23.4% (69)</td>
</tr>
<tr>
<td>Print materials</td>
<td>18.7% (55)</td>
</tr>
</tbody>
</table>

Components of translating PG into clinical action

- The selection of clinically actionable gene-drug associations for implementation
- The availability of commercially available pharmacogenetic tests
- The interpretation of pharmacogenetic tests
- The development of educational and clinical decision support tools
Identifying clinically actionable pharmacogenes

- FDA Biomarker list: http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

- Prescribing information

- Pharmacogenetic consortia guidelines, such as the Clinical Pharmacogenetic Implementation Consortium (CPIC): https://www.pharmgkb.org/

- Medical guidelines provided by professional societies and specialist organizations

- Research literature, published in journals as well as documentation part of FDA drug approvals

- Companies who specialize in providing clinical information
Selection of pharmacogenetic tests


The laboratory should be able to provide information about:

- The indication for ordering the test
- The variants tested
- The limitations of the test

Note: For tests, such as those for metabolizing enzymes, clinical sensitivity and specificity in laboratory documentation refers to the ability to identify, for example, metabolizer status. For example, a test for CYP2D6 metabolizer status will be able to classify >95% of Caucasians as PM, EM, IM, or UM (i.e., sensitivity of 95%). But this says nothing about the test’s ability to correctly determine a safety or efficacy outcome.
- Transparent test results that indicate
  - the subject’s genotype
  - whether the variant of interest was detected
  - translate the genotype to a drug-associated predictive phenotype, eg,
    - HLA-B*57:01 allele-abacavir detected: increased risk for hypersensitivity
    - CYP2D6 diplotype (combinations of functional, nonfunctional, decreased function, and increased function alleles) phenotypes: poor, intermediate, extensive, and ultrarapid metabolizer

- Note: These are not always consistently defined. This affects interpretation and transportability of genetic testing information, so it’s important to have the genotype accompany the phenotype.
Resources for interpretation of PG tests

- Pharmacogenetic consortia guidelines
- Medical guidelines provided by professional societies and specialist organizations
- Companies providing clinical information-enabled tools and software solutions
- Prescribing information
- Health insurance companies
- Laboratories
Elements of interpretation

- Based on a review of the literature and the reason for testing, an assessment of the
  - Evidence of association (clinical validity)
  - Evidence of testing benefit (clinical utility)

- Recommendations for whether or not to test (in reactive testing)
  - For example, choice of another medication, choice of alternate dosing, phenotyping, monitoring, not recommended for action
Genetic mutations for targeted therapies

- Cancer pharmacogenes
  - Targeted therapies for somatic cell mutations, eg,
    - BRAF-tyrosine kinase inhibitors (eg, melanoma)
    - ALK-crizotinib (eg, non-small cell lung cancer)
  - Biomarkers predictive of efficacy, eg,
    - KRAS-cetuximab (eg, colorectal cancer)
- Disease causing germline mutations with targeted therapies
  - CFTR-ivacaftor (cystic fibrosis)
“Normal” germline variants

- Predict efficacy, eg,
  - CYP2C19-clopidogrel (PCI)
  - CYP2D6-tamoxifen (breast cancer)
  - CYP2D6-codeine (pain management)

- Predict adverse events, eg,
  - HLA-B*57:01-abacavir (SJS/TEN)
  - HLA-B*15:02-carbamazepine (SJS/TEN)
  - SLCO1B1-simvastatin (myopathy)
  - UGT1A1-pazopanib (hyperbilirubinemia)
Genotype-guided dosing, eg,

- CYP2B6-efavirenz (HIV)
- CYP2C19-clobazam (Lennox-Gastaut syndrome seizures)
- CYP2D6-eliglustat (Gaucher disease)
- CYP2D6-iloperidone (schizophrenia)
- CYP2C9/VKORC1-warfarin (thromboembolism)
- TPMT-thiopurines (cancer, IBS, rheumatoid arthritis, etc)
- UGT1A1-belinostat (T-cell lymphoma)
Educational and Clinical Support Tools

- Precautions database
  - A look-up tool, much like a drug-drug interaction checker

- Referential information
  - A monograph providing clinical recommendations, pharmacogenetic test interpretation, ratings, supporting literature, and background information

- Electronic Health Records into which clinical support tools have been integrated

CONFIDENTIAL AND PRIVILEGED. FOR INFORMATIONAL PURPOSES ONLY.
Pharmacogenomics Research Network (PGRN) Translational Pharmacogenetics Program (TPP):
- **Goal is to translate widely accepted actionable pharmacogenetic discoveries into real-world clinical practice**

- University of Florida: Personalized Medicine Program

- Vanderbilt University: PREDICT

- University of Maryland: Personalized Anti-Platelet Pharmacogenetics Program
Preemptive PG testing program references

- St. Jude’s Children’s Research Hospital: PG4KDS

- Mayo Clinic: RIGHT Protocol

- eMERGE-PGx Project

- University of Chicago: 1200 Patients Project

CONFIDENTIAL AND PRIVILEGED. FOR INFORMATIONAL PURPOSES ONLY.
Questions?

Please submit your question into the chat box at the lower left-hand corner.
Today’s slides and recording will be sent via email next week.

Complete the survey that will pop up after the webinar to receive a copy of today’s slides and for a chance to win a Kindle Fire!

For more info:
Michelle White, Market Manager
Wolters Kluwer Clinical Drug Information
michelle.white@wolterskluwer.com
Copyright notices and disclaimers

© 2015 CLINICAL DRUG INFORMATION, LLC
© 2015 LEXI-COMP, INC.

THIS PRESENTATION MAY NOT BE COPIED, REPRODUCED, REDISTRIBUTED OR OTHERWISE TRANSMITTED IN ANY FORM OR BY ANY MEANS, IN WHOLE OR IN PART, WITHOUT PRIOR WRITTEN CONSENT FROM WOLTERS KLUWER CLINICAL DRUG INFORMATION. ANY UNAUTHORIZED USE OF COPYRIGHTED MATERIAL INCORPORATED WITHIN THIS PRESENTATION WILL BE SUBJECT TO LEGAL ACTION. THE CONTENT IN THIS PRESENTATION HAS BEEN PREPARED STRICTLY FOR INFORMATIONAL PURPOSES ONLY, AND IS NOT INTENDED OR OFFERED AS LEGAL ADVICE. ALTHOUGH THE INFORMATION PROVIDED IS BELIEVED TO BE RELIABLE AND ACCURATE, ALL INFORMATION IS WITHOUT WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO WARRANTIES OF THE ACCURACY, CURRENCY, COMPLETENESS OF INFORMATION, OR THE SUITABILITY OF THE INFORMATION FOR ANY PARTICULAR PURPOSE. WOLTERS KLUWER CLINICAL DRUG INFORMATION SHALL NOT BE LIABLE FOR ANY DIRECT, INDIRECT, INCIDENTAL, SPECIAL, CONSEQUENTIAL, PUNITIVE OR ANY OTHER DAMAGES ARISING OUT OF THE USE OF ANY INFORMATION DISCUSSED IN THIS PRESENTATION. IN DECIDING YOUR ORGANIZATION’S SPECIFIC TECHNOLOGY, BUSINESS AND LEGAL REQUIREMENTS, YOU MUST NOT RELY ON THE INFORMATION IN THIS PRESENTATION AS A SUBSTITUTE TO ADVICE FROM YOUR OWN LEGAL COUNSEL.