Implementation of Pharmacogenomics in Clinical Practice: Barriers and Potential Solutions

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Disclaimer

- Received reagent support from GenMark Dx
Objectives

By the end of this presentation participant should be able to:

1. Describe the Promise of PGx in Personalized Drug Therapy
2. Appreciate the current barriers in clinical adoption of PGx
3. Discuss potential solutions to enhance the adoption of PGx in clinical practice
Many doctors are scrambling to figure out which heart patients should continue to take the top-selling drug Plavix after the Food and Drug Administration warned recently that the blood thinner may not work for everyone.

Plavix, the second biggest selling drug after cholesterol-lowering Lipitor, is intended to prevent blood clots that can cause heart attacks and strokes in patients with advanced cardiovascular disease. It’s also commonly prescribed to patients treated with devices called stents to prop open diseased coronary arteries. Some 2.5 million to 3 million Plavix prescriptions are written in the U.S. every month.

But a genetic variation in a significant minority of patients can prevent the drug from working, or can limit its effectiveness, increasing a patient’s risk for a potentially life-threatening heart attack. The genetic limitation of the drug has been known for well over a year. But the FDA appeared to heighten the alert by placing on March 12 a black-box warning—its most severe safety advisory—on the drug, surprising even cardiologists well informed about the risk.
FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals

Data Summary

Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a Boxed Warning to the label for Plavix, the anti-blood clotting medication. The Boxed Warning is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The Boxed Warning in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.

Plavix is given to reduce the risk of heart attack, unstable angina, stroke, and cardiovascular death in patients with cardiovascular disease. Plavix works by decreasing the activity of blood cells called platelets, making platelets less likely to form blood clots.

For Plavix to work, enzymes in the liver (particularly CYP2C19) must convert (metabolize) the drug to its active form. Patients who are poor metabolizers of the drug, do not effectively convert Plavix to its active form. In these patients, Plavix has less effect on platelets, and therefore less ability to prevent heart attack, stroke, and cardiovascular death. It is estimated that 2 to 14% of the population are poor metabolizers; the rate varies based on racial background.

http://www.fda.gov/drugs/drugsafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm203888.htm
The Promise of PGx

- 4Rs: Right drug, right patient, right dose, right time!
- Maximise drug efficacy
- Decrease ADRs
- Salvage failed drugs
Resurrect 3 “failed” drugs?

<table>
<thead>
<tr>
<th>Company/Drug</th>
<th>Drug Class</th>
<th>Condition</th>
<th>Diagnostic</th>
<th>Biomarker</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCA biopharma</td>
<td>Beta blocker</td>
<td>Heart failure</td>
<td>Efficacy</td>
<td>Polymorphisms in the targeted beta1-adrenergic receptor that affects cardiac output</td>
<td>Not accepted June 2009, resubmission in progress</td>
</tr>
<tr>
<td>Gencaro (bucindolol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>Cox-2 painkiller</td>
<td>Arthritis</td>
<td>Safety</td>
<td>Genes in the major histocompatibility complex (MHC Class II)</td>
<td>Never approved in US, pulled from foreign markets in 2007 due to potential liver toxicity</td>
</tr>
<tr>
<td>Prexige (lumiracoxib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer</td>
<td>Melanoma Melanoma</td>
<td>Safety</td>
<td>Genome studies in progress</td>
<td></td>
<td>Pfizer is conducting a second set of drug trials after finding a biomarker that identifies patients who benefit from the drug</td>
</tr>
<tr>
<td>Tremelimunab</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Barriers to PGx adoption
Translation Issues

- Cost-Effectiveness of PGx/Reimbursements Issues
- Controversial Trials Results (e.g. Cyp2C19 PGx-Clopidogrel)
- Paucity of large Randomized Controlled Trials
- Need for Consensus Guidelines
- Physician Awareness/Understanding

Wu, Babic & Yeo. Person Med 2009;6:315
Translation Issues

- Patient Awareness vs Physician Readiness: Education efforts needed
- Laboratory Issues/Preparedness to adopt PGx/Informatics
- Lack of in-house expertise for consultations/interpretations: Opportunity for leadership by teaching hospitals

Wu, Babic & Yeo. Person Med 2009;6:315
Reimbursement Issues
Reimbursement – CPT Codes

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>5.60</th>
<th>46.84</th>
</tr>
</thead>
<tbody>
<tr>
<td>83891</td>
<td>Extraction of highly purified nucleic acid</td>
<td>5.60</td>
<td>5.60</td>
</tr>
<tr>
<td>83900</td>
<td>Multiplex PCR for first 2 sequences</td>
<td>23.42</td>
<td>46.84</td>
</tr>
<tr>
<td>83901</td>
<td>Multiplex each additional sequence *1</td>
<td>23.42</td>
<td>23.42</td>
</tr>
<tr>
<td>83914</td>
<td>Mutation Identification by ASPE *6</td>
<td>23.42</td>
<td>140.52</td>
</tr>
<tr>
<td>83912</td>
<td>Interpretation and Reporting</td>
<td>5.60</td>
<td>5.60</td>
</tr>
<tr>
<td>83912-26</td>
<td>Pathologist Interpretation if performed</td>
<td>17.52</td>
<td>17.52</td>
</tr>
</tbody>
</table>

| Total      |                                                        |       | 239.50|

• Currently no specific CPT codes for PGx panels—makes tests appear “less important” to 3rd party payors

• Lack of standardization in test-billing is a deterrent and barrier to implementation

Wu, Babic & Yeo. Person Med 2009;6:315
“At the present time, for patients beginning [vitamin K antagonist] therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C)” (Hirsh J, et al. *Chest*. 2008;71S–109S).

American College of Medical Genetics Working Group reached a more ambivalent conclusion: “[T]here is insufficient evidence, at this time, to recommend for or against routine [genetic] testing in warfarin-naive patients.” The ACMG statement also said, “Prospective clinical trials are needed that provide direct evidence of the benefits, disadvantages, and costs associated with this testing in the setting of initial warfarin dosing” (Flockhart DA, et al. *Genet Med*. 2008;10:139–150).
CMS believes that the available evidence does not
demonstrate that pharmacogenomic testing to predict
warfarin responsiveness improves health outcomes in
Medicare beneficiaries.

Therefore, we are proposing that pharmacogenomic
testing to predict warfarin responsiveness is not
reasonable and necessary under § 1862(a)(1)(A) of
the Social Security Act.

Pharmacogenomic testing to predict warfarin
responsiveness is covered only when provided to
Medicare beneficiaries who are candidates for
anticoagulation therapy with warfarin and only then in
the context of a prospective, randomized, controlled
clinical study.

ACCF/AHA 2010 Recommendations for Antiplatelet Rx Practice

- Careful clinical judgment to assess the importance of the variability in response to clopidogrel

- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism….can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes….

- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined (e.g. CYP 2C19 *2 vs *3 or *4….)

- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, are both important additional considerations.
The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.

- No information that routine testing improves outcome in large subgroups of patients.
- Clinical course of the majority of patients treated with clopidogrel without either genetic testing or functional testing is excellent.
- Genetic testing may be considered in patients believed to be at moderate or high risk for poor outcomes.
“Anyone for a game of Blind Man’s Bluff after dinner?”
• Study will last about four years
• ~1200 patients who are beginning warfarin treatment.
• Conducted at 12 US medical centers funded by the NHLBI
• Primary outcome is time within therapeutic INR in first 4 weeks of anticoagulation
Trials Evaluating Antiplatelet Rx

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Population</th>
<th>Selection Criterion</th>
<th>Outcome</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIFT</td>
<td>Observational, prospective cohort study (GRAVITAS substudy) (PD study)</td>
<td>Up to 2000</td>
<td>Stable CAD or NSTEMI ACS undergoing DES</td>
<td>Patients with high residual platelet activity (HRPA) 12- to 24-h post-DES randomized to: 1) standard 75 mg clopidogrel, or 2) high-dose clopidogrel (additional 600 mg followed by 150 mg daily)</td>
<td>Association of CYP2C19 genotype with RPA (VerifyNow) on standard dose of clopidogrel or incremental change RPA on high-dose clopidogrel</td>
<td>6 mo</td>
</tr>
<tr>
<td>(NCT00992420)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl: M.J. Price</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel Pharmacogenomics Project</td>
<td>Randomized, open-label, crossover, phase 0 (PD/PK study)</td>
<td>200</td>
<td>Stable CAD</td>
<td>Screen for CYP2C19*2 LOF allele; randomize eligible patients to clopidogrel 75 mg or 150 mg daily × 30 d and then crossover</td>
<td>Change in RPA (VerifyNow, optical aggregometry); measurement of active metabolites</td>
<td>90 d</td>
</tr>
<tr>
<td>(NCT01097343)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pl: J. Dharmaavaram</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Pl: J.S. Rossi</td>
<td></td>
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</tr>
<tr>
<td>CLOVIS-2</td>
<td>Randomized, open-label, phase III, crossover (PD/PK study)</td>
<td>120</td>
<td>Post-MI, &lt;45 y and enrolled in AFIUJ registry</td>
<td>Comparison of 2 loading strategies of clopidogrel (300 mg vs. 900 mg) in 2 genetic profiles: wild-type 2C19<em>1 and carriers of 2C19</em>2 (homozygous or heterozygous)</td>
<td>Inhibition of RPA (IRPA) by optical aggregometry; measurement of active metabolites</td>
<td>6 h postclopidogrel loading dose</td>
</tr>
<tr>
<td>(NCT00822666)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pl: J.-P. Collet</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pl: G. Montalescot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role of CYP2C19 Polymorphism in the Drug Interaction Between Clopidogrel and Omeprazole</td>
<td>Observational, case-crossover, phase IV (PD/PK study)</td>
<td>75</td>
<td>Healthy volunteers</td>
<td>Subjects with CYP2C19*2/*3 LOF allele, and age- and gender-matched wild-type control randomized to clopidogrel + omeprazole vs. clopidogrel × 1 wk, and crossover</td>
<td>Platelet inhibitory response to clopidogrel; measurement of active metabolites</td>
<td>3 wk</td>
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<tr>
<td>(NCT01094275)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
### Trials (cont)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI 56 Mega (58a)</td>
<td>Randomized treatment sequence (PD study)</td>
<td>275</td>
<td>Stable CAD</td>
<td>Patients on clopidogrel 75 mg and genotyped for CYP2C19 alleles will be treated with biweekly dose of clopidogrel “(75 mg to 300 mg daily, depending on genotype).”</td>
</tr>
<tr>
<td>Pilot Study 747656</td>
<td>Observational prospective cohort (PD study)</td>
<td>42</td>
<td>Stable CAD on clopidogrel therapy</td>
<td>Patients with HRPA on clopidogrel 75 mg and genotyped for CYP2C19 alleles treated with double-dose clopidogrel (150 mg)</td>
</tr>
<tr>
<td>19012193) Jeong</td>
<td>Randomized, active-control, single-blind (PD study)</td>
<td>134</td>
<td>Stable CAD, elective PCI</td>
<td>Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 200 mg vs. cloostazol 100 mg bid + 75 mg clopidogrel + ASA 200 mg (triple therapy)</td>
</tr>
<tr>
<td>I2C19 915733) Kim</td>
<td>Randomized, active-control, open-label (PD study)</td>
<td>80</td>
<td>Acute MI, post-PCI</td>
<td>Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 100 mg vs. cloostazol 100 mg bid + 75 mg clopidogrel + ASA 100 mg (triple therapy)</td>
</tr>
</tbody>
</table>
Trials (cont)

Table 4. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Population</th>
<th>Selection Criterion</th>
<th>Outcome</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEL-2C19 (NCT00891670)</td>
<td>Randomized, active-control, open-label (PD study)</td>
<td>80</td>
<td>Stable CAD, Elective PCI</td>
<td>Patients genotyped for CYP2C19 variants randomized to high-dose clopidogrel (150 mg) + ASA 100 mg vs. cilostazol 100 mg bid + 75 mg clopidogrel + ASA 100 mg (triple therapy)</td>
<td>Maximum platelet aggregation (optical aggregometry; VerifyNow)</td>
<td>30 d</td>
</tr>
<tr>
<td>SPICE (NCT00930670)</td>
<td>Randomized, active-control, open-label (PD study)</td>
<td>320</td>
<td>Stable CAD, elective PCI with BMS</td>
<td>Subjects genotyped for CYP2C19 alleles and treated with clopidogrel randomized to statin + PPI or statin + H2RA</td>
<td>Change in RPA (optical aggregometry; VASP)</td>
<td>30 and 60 d</td>
</tr>
<tr>
<td>Influence of CYP2C19 Genetic Variants on Clopidogrel in Healthy Subjects (NCT00413608)</td>
<td>Observational, active-control, open-label (PD/PK study)</td>
<td>30</td>
<td>Healthy volunteers</td>
<td>Patients genotyped for CYP2C19 variants with HRPA on clopidogrel 75 mg (“bad responders”) will be given 150 mg clopidogrel and compared with results of 75 mg clopidogrel in “good responders”</td>
<td>Change in RPA (optical aggregometry); measurement of active metabolites</td>
<td>7 d</td>
</tr>
</tbody>
</table>

Trials Evaluating Clinical Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Recent NSTEMI or STEMI ACS with or without primary or delayed PCI</th>
<th>Genotype-guided comparison of clopidogrel (75 mg daily) in extensive metabolizers (CYP2C19*1/*1) and prasugrel (5 mg or 10 mg daily)</th>
<th>CV death, nonfatal MI, or nonfatal stroke</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeCCO (NCT00995514)</td>
<td>Observational, prospective cohort, open-label, active control, noninferiority study (outcome study)</td>
<td>14 600</td>
<td></td>
<td></td>
<td></td>
<td>6 mo</td>
</tr>
</tbody>
</table>
Some Good News
Mayo-Medco Warfarin Study

For patients on Warfarin:
- 900 patients followed over 6 months for hospital utilization rates based on genotype-guided dosing
- 2500 patients control-no genotype performed
- Hospitalization rates decreased by 30% when genotype information was available

Epstein et al., JACC 2010;55:2804
Medco also plans new services for genetic tests...it’s launching a service for health insurers that would administer coverage for high-tech lab tests.....
Meta-Analysis by Mega et al

JAMA 2010;304:1821
Risk of Stent Thrombosis

Mega et al. JAMA 2010:304:1821

Figure 3. Stent Thrombosis by CYP2C19 Genotype

A. Carriers of 1 or 2 CYP2C19 Reduced-Function Alleles vs Noncarriers

<table>
<thead>
<tr>
<th>CYP2C19 Reduced-Function Alleles, No. of Events/No. of Individuals at Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>Increased Risk in Noncarriers</th>
<th>Increased Risk in Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCELSIOR 1 or 2</td>
<td>0.67 (0.06-5.09)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRITON-TIMI 38 1</td>
<td>3.09 (1.19-8.00)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRITON-TIMI 38 None</td>
<td>6.04 (1.75-20.82)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFIJI</td>
<td>2.55 (1.14-5.70)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RECLOSE 1</td>
<td>2.45 (1.08-5.55)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISAR</td>
<td>4.78 (0.43-52.69)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>2.81 (1.81-4.37)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

B. Carriers of 1 CYP2C19 Reduced-Function Alleles vs Noncarriers

<table>
<thead>
<tr>
<th>CYP2C19 Reduced-Function Alleles, No. of Events/No. of Individuals at Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>Increased Risk in Noncarriers</th>
<th>Increased Risk in Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCELSIOR 1</td>
<td>0.61 (0.07-5.44)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRITON-TIMI 38 None</td>
<td>2.65 (0.96-7.30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TRITON-TIMI 38 1</td>
<td>7.75 (2.10-28.60)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFIJI</td>
<td>2.41 (1.06-5.55)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RECLOSE 1</td>
<td>2.39 (1.03-5.54)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISAR</td>
<td>2.57 (0.16-40.99)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>2.67 (1.69-4.22)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

C. Carriers of 2 CYP2C19 Reduced-Function Alleles vs Noncarriers

<table>
<thead>
<tr>
<th>CYP2C19 Reduced-Function Alleles, No. of Events/No. of Individuals at Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>Increased Risk in Noncarriers</th>
<th>Increased Risk in Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 38 2</td>
<td>6.79 (1.42-32.53)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFIJI</td>
<td>5.46 (1.05-28.38)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RECLOSE 2</td>
<td>1.95 (0.92-4.13)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ISAR</td>
<td>3.21 (0.42-24.60)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>34.41 (2.15-551.50)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Overall</td>
<td>3.97 (1.75-9.02)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Correlation of CYP genotype-phenotype

Holmes et al. JAMA 2011:306:2704
~1/3 of patient on clopidogrel (loading dose 600mg or maintenance dose 75 mg/d) show high on platelet reactivity (HTPR)

Prasugrel 10mg significantly decreased platelet reactivity compared to high-dose clopidogrel (150 mg/d maintenance) for HTPR patients

High clopidogrel dose is largely ineffective in the presence of Cyp2C19 *2 allele; in non-carriers both drugs have similar effects
## Table 1 Assigning likely CYP2C19 phenotypes based on genotypes

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrapid metabolizer: normal or increased activity (~5–30% of patients)</td>
<td>An individual carrying two increased-activity alleles (*17), or one functional allele (*1) plus one increased-activity allele (*17)</td>
<td>*1/*17, *17/*17</td>
</tr>
<tr>
<td>Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)</td>
<td>An individual carrying two functional (*1) alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)</td>
<td>An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8)</td>
<td>*1/*2, *1/*3</td>
</tr>
<tr>
<td>Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)</td>
<td>An individual carrying two loss-of-function alleles (*2–*8)</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
</tbody>
</table>

For some rare genotype combinations metabolic phenotypes are difficult to predict; see Supplementary Table S3 online.
## Table 2  Clopidogrel therapy based on CYP2C19 phenotype for ACS/PCI patients initiating antiplatelet therapy

<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&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Clopidogrel label-recommended dosage and administration</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM) (*1/*2)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer (PM) (*2/*2)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
<td>Strong</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

<sup>a</sup>See Supplementary Data online, Strength of Therapeutic Recommendations.  
<sup>b</sup>The CYP2C19*17 allele may be associated with increased risk of bleeding.  

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**Scott et al. CPT 2011;90:328-332**
Suggested Algorithm

ACS/PCI patient population

Initiate antiplatelet therapy with standard dosing of clopidogrel

*CYP2C19* testing if genotype is unknown

UM
(*1/*17, *17/*17)
Standard dosing of clopidogrel

EM
(*1/*1)

IM
(*1/*2)
Prasugrel or other alternative therapy

PM
(*2/*2)
FDA Initiatives Related to Personalized Medicine

**Companion Diagnostics.** Currently, drugs and diagnostics are regulated by different centers at FDA, making it difficult to coordinate the release of a drug with a companion diagnostic test to guide the drug’s use. The guidance, due out this year, will clarify the agency’s expectations for clinical trials and confidence levels needed to demonstrate that a test can be used for clinical assessments.

**Validation and use of Genomic Biomarkers in Clinical Trials.** Also due this year, this guidance will inform developers of the criteria FDA will use to vet the usefulness of biomarkers and evaluation of clinical trial data.

**FDA/NIH partnership.** The two agencies will coordinate translational science, under which basic scientific discoveries are developed into treatments, and regulatory science, which needs new tools, standards and approaches to more efficiently evaluate the safety, quality and efficacy of new treatments.

**In vitro multivariate index assays.** CDRH will take a broader look at regulations for laboratory-developed tests for these assays based on the recommendations by the HHS Secretary’s Advisory Committee for Genetics, Health, and Society, as well as a petition submitted by Genentech in 2008.

**Warfarin/Plavix labeling.** In January, FDA updated the label for warfarin to incorporate dosing information based on genotype. The label now recommends that doctors refer to a table of stable maintenance doses observed in patients having different combinations of CYP2C9 and VKORC1 variants, as a guide for selecting the starting dose of warfarin. In March, it added a warning label to Plavix, cautioning that some patients may be poor metabolizers.
A Victory for Personalized Medicine and Patients
Washington, DC - March 24, 2010 — The Personalized Medicine Coalition (PMC) praised the landmark health care reform legislation signed into law this week, noting that it represents the first time the principles of personalized medicine were formally voted on and passed by both houses of Congress and signed into law by a president. Also significant is the bill’s alignment of personalized medicine with the conduct and use of comparative effectiveness research (CER).

http://personalizedmedicinecoalition.org/
Education Efforts
Need for Education
Pharmacogenomic Testing in Current Clinical Practice
Implementation in the Clinical Laboratory

While the basic principles of personalized medicine and pharmacogenomics have been covered by numerous texts, there are none to date that focus on the specific tests themselves that are in current clinical practice and those that are being proposed for implementation in the near future. Pharmacogenomic Testing in Current Clinical Practice: Implementation in the Clinical Laboratory focuses almost entirely on the specifics of each test that is needed to implement these tests into a clinical laboratory. This volume presents the first compilation of the tests currently in routine clinical use. The chapter authors of this unique and invaluable title comprise a range of renowned authorities and investigators who have conducted the essential clinical trials necessary to justify pharmacogenomic testing today. The book is divided into four parts: Basic Concepts, Specific Pharmacogenomic Targets, Drugs that Cause Delayed Hypersensitivity, and Miscellaneous Drugs. Each author provides a pharmacologic background on the target drug, the need for pharmacogenomic testing, and how results can be translated into clinical decisions. Where appropriate, case studies are given to illustrate typical clinical scenarios. An extensive bibliography is provided so that the reader can refer to the original studies. This well-designed resource will appeal to clinical laboratory directors who are contemplating or assigned the task of establishing a pharmacogenomics laboratory and a wide range of clinicians who must interpret results of testing. Focused and immensely useful, Pharmacogenomic Testing in Current Clinical Practice: Implementation in the Clinical Laboratory is a timely and outstanding contribution to the literature and will be instrumental in defining this rapidly growing field.
We need DNA Twist!

Clinical Pharmacology & Therapeutics

Opinion


DNATwist: A Web-Based Tool for Teaching Middle and High School Students About Pharmacogenomics

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Abstract

DNATwist is a Web-based learning tool (available at http://www.dnatwist.org) that explains pharmacogenomics concepts to middle- and high-school students. Its features include (i) a focus on drug responses of interest to teenagers (e.g., alcohol intolerance), (ii) reusable graphical interfaces that reduce extension costs, and (iii) explanations of molecular and cellular drug responses. In testing, students found the tool and topic understandable and engaging. The tool is being modified for use at the Tech Museum of Innovation in California.
Genetics and Drug Response

It takes interaction with the external environment (the drug) to distinguish drug response differences between individuals. These differences are not obvious until exposure to the drug occurs.

- Lower dose requirement
- Higher dose requirement
- Need for alternative drug
- Risk of experiencing drug side effects

The study of how human genetic variation affects drug treatment outcome is called pharmacogenomics.

http://www.dnatwist.org/BDE/index.html
PGx Example

HOW DOES DRINKING ALCOHOL MAKE PEOPLE SICK?

Step 1: ADH enzymes convert alcohol into toxic acetaldehyde.

Step 2: The ALDH2 enzyme transforms acetaldehyde into acetate.

Step 3: Body converts acetate to carbon dioxide and water.

Ugh! I have facial flushing, rapid heartbeat, and nausea! View my genetic profile!

Move slider to left/right to see what happens.

Low ALDH2 Activity Level

High

LEARN ABOUT A DRUG USED TO TREAT ALCOHOLISM
Summary-Solutions

- More evidence-based studies; many underway
- Consensus guidelines on clinically relevant PGx biomarkers and interpretations
  - Better definitions of genotype-phenotype relationships (e.g. Cyp 2C19, 2D6)
  - Standardization of dosing algorithms (Warfarin)
- Institutional expertise and leadership
- Major educational efforts for all health-care professionals; update medical school curriculum to include PGx
- Stronger FDA drug labeling & other initiatives
- Advocacy group like PMC
- Reimbursement by CMS
Conclusions

- Pharmacogenetics will increasingly be used more in clinical decision making in the near future.

- Quantitative measures of the relative risk of toxicity or poor outcome is needed to convince health systems, health professionals, and patients that genome-guided prescribing is important.

- There is a real need for robust economic analyses of pharmacogenetics testing.

- Guidelines, standardized PGx panels, physician education, reimbursements are some of the critical factors in assisting adoption of PGx testing.
The Future

Genomics, Transcriptomics, Proteomics & Metabolomics Interrelationships

Gerszten et al. 2008 Nature 451:949
The future is at our doorstep.

Merging pharmacometabolomics with pharmacogenomics using ‘1000 Genomes’ single-nucleotide polymorphism imputation: selective serotonin reuptake inhibitor response pharmacogenomics
Ryan Abo\textsuperscript{a}, Scott Hebbring\textsuperscript{a}, Yuan Ji\textsuperscript{a}, Hongjie Zhu\textsuperscript{d}, Zhao-Bang Zeng\textsuperscript{d}, Anthony Batzler\textsuperscript{b}, Gregory D. Jenkins\textsuperscript{b}, Joanna Biernacka\textsuperscript{b}, Karen Snyder\textsuperscript{c}, Maureen Drews\textsuperscript{c}, Oliver Fiehn\textsuperscript{f}, Brooke Fridley\textsuperscript{b}, Daniel Schaid\textsuperscript{b}, Naoyuki Kamatani\textsuperscript{g}, Yusuke Nakamura\textsuperscript{g}, Michiaki Kubo\textsuperscript{g}, Taisei Mushiroda\textsuperscript{g}, Rima Kaddurah-Daour\textsuperscript{e}, David A. Mrazek\textsuperscript{c} and Richard M. Weinshilboum\textsuperscript{a}

\textbf{Conclusion} These results indicate that the use of GWAS data to impute SNPs for genes in pathways identified by other ‘omics’ approaches makes it possible to rapidly and cost efficiently identify SNP markers to ‘broaden’ and accelerate pharmacogenomic studies. \textit{Pharmacogenetics and Genomics} 22:247–253 © 2012 Wolters Kluwer Health |
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Self-Study Questions

- List the current major barriers to the implementation of pharmacogenomics in clinical care.
- What is the current controversy in adoption of PGx for clinical use?
- What are the potential solutions required to facilitate wider adoption of pharmacogenomics?