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Disclaimer

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The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.

Train-the-Trainer Agenda

1. Introduction
   - Objective of PharmGenEd™ program
   - Shared curriculum and format
   - Introduction of author
2. Review of educational content for selected therapeutic area
3. Future webinar dates
   - Program implementation
   - Other therapeutic areas
4. Contact information
5. Survey instruments
   - Post training survey for trainers
6. Question & Answer (Q & A) session

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The "Pharmacogenomics Education Program: Bridging the Gap between Science and Practice" (PharmGenEd™) is an evidence-based pharmacogenomics education program designed for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.

The overall objective of the PharmGenEd™ program is to increase awareness about current knowledge of the validity and utility of pharmacogenomic tests and the potential implications of benefits and harms from use of the tests.

### Shared Curriculum

- Educational Materials (each 1 hour)
  - Asthma
  - Cardiology I (warfarin & statins)
  - Cardiology II (clopidogrel & beta blockers)
  - Concepts and clinical applications
  - Economic issues
  - Oncology I (solid tumors)
  - Oncology II (hematologic malignancies)
  - Psychiatry I (depression)
  - Psychiatry II (antipsychotics)

Future webinar dates for these sessions will be provided later.

### Therapeutic Area Discussion

- Format
  - Patient case
  - Gene/Allele of interest
  - Functional effect
  - Population prevalence
  - Clinical relevance (dosing/selection, efficacy, and toxicity)
  - Genomic test and testing recommendation
  - Patient case summary

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University of California, San Francisco
Learning Objectives

• Upon completion of this program, participants will be able to:
  – Identify specific drug therapies used in which pharmacogenomic testing can be applied in the clinical setting
  – Summarize evidence-based recommendations for pharmacogenomic testing
  – Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence

Outline

• Clopidogrel pharmacogenomics
  – CYP2C19 genotype description
  – CYP2C19 gene associations with clopidogrel response
  – Clinical applications

• Beta-blocker pharmacogenomics
  – ADRB1 and ADRB2 genotype descriptions
  – Genetic association with beta-blocker response
  – Clinical applications

Patient Case 1

• JM is a 55-year old Caucasian male with hypertension and dyslipidemia who suffers a non-ST-elevation myocardial infarction
• He undergoes percutaneous coronary intervention (PCI) with placement of 2 drug-eluting stents
  – Weight: 80 kg
  – Allergies: NKDA
  – Genotype: CYP2C19*2/*2
Patient Case 1 (continued)

- He started clopidogrel 300mg loading dose, followed by 75mg maintenance dose
- Question: Based on JM’s genotype, is it appropriate to start clopidogrel? If not, what is the alternative therapy?

Clopidogrel Pharmacogenomics: Clinical Relevance

- Clopidogrel background
  - Thienopyridine that inhibits the P2Y12 receptor
  - Reduces risk for stent thrombosis (Steinhubl et al 2002).
  - Approximately 25% of patients are non-responders to clopidogrel (Combescure et al 2010).
  - Variability is largely attributed to differences in clopidogrel pharmacokinetics

---

Clopidogrel Pharmacogenomics

- At least 25 CYP2C19 polymorphic variants have been identified
- Functional Effect:

<table>
<thead>
<tr>
<th>Allele</th>
<th>Nucleotide Change</th>
<th>Type of Variant</th>
<th>CYP2C19 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>N/A</td>
<td>N/A</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>Splicing defect</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>Stop codon</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*4</td>
<td>1A&gt;G</td>
<td>Exon SNP</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*5</td>
<td>1297C&gt;T</td>
<td>Exon SNP</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*17</td>
<td>-808C&gt;T</td>
<td>Promoter SNP</td>
<td>Gain of function</td>
</tr>
</tbody>
</table>

Mega et al 2009
Momary 2010
**Clopidogrel Pharmacogenomics**

- **Functional Effect (Cont.):**
  - *CYP2C19* alleles confer the following phenotypes:

<table>
<thead>
<tr>
<th>CYP2C19 alleles</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 loss-of-function alleles</td>
<td><strong>PM</strong> - Poor Metabolizer</td>
</tr>
<tr>
<td>1 loss-of-function allele</td>
<td><strong>IM</strong> - Intermediate Metabolizer</td>
</tr>
<tr>
<td>No variant allele</td>
<td><strong>EM</strong> - Extensive Metabolizer</td>
</tr>
<tr>
<td>One or two *17 allele(s)</td>
<td><strong>UM</strong> - Ultrarapid Metabolizer</td>
</tr>
</tbody>
</table>

Furuta et al 2007, Sim et al 2006

---

**Clopidogrel Pharmacogenomics: Clinical Relevance**

- **Dosing/Selection**
  - *CYP2C19* PMs and IMs may need higher clopidogrel doses than EMs or alternative therapy.
  - *CYP2C19* UMs may require lower clopidogrel doses than EMs.
- **Efficacy**
  - Meta-analysis of 9684 patients with ACS examined for risk for major adverse cardiovascular events (MACE) with loss-of-function alleles (Mega et al 2009).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Risk ratio (95% CI) for MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMs vs EMs</td>
<td>1.8 (1.2-2.7)</td>
</tr>
<tr>
<td>IMs vs EMs</td>
<td>1.5 (1.1-2.1)</td>
</tr>
<tr>
<td>PMs or IMs vs EMs</td>
<td>1.6 (1.3-2.0)</td>
</tr>
</tbody>
</table>

---

**Clopidogrel Pharmacogenomics: Clinical Relevance**

- **Efficacy (Cont.)**
  - Meta-analysis of 5772 patients examined risk for stent thrombosis with loss-of-function alleles (Mega et al 2009).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Risk ratio (95% CI) for stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMs vs EMs</td>
<td>4.8 (2.0-11.4)</td>
</tr>
<tr>
<td>IMs vs EMs</td>
<td>2.5 (1.6-4.0)</td>
</tr>
<tr>
<td>PMs or IMs vs EMs</td>
<td>2.8 (1.8-4.3)</td>
</tr>
</tbody>
</table>

- Recent trial showed no reduced clopidogrel efficacy with a *2 or *3 allele and improved efficacy with the *17 allele, but was largely limited to patients with ACS or atrial fibrillation who were managed medically (Pare et al 2009).

---

**Population Prevalence**

- Genotype / phenotype prevalence

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>2%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td>African American</td>
<td>4%</td>
<td>30%</td>
<td>45%</td>
</tr>
<tr>
<td>Asian</td>
<td>14%</td>
<td>50%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>


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Clopidogrel Pharmacogenomics: Clinical Relevance

• Toxicity
  – *17 allele associated with an increased risk for bleeding with clopidogrel in patients with coronary artery stent placement (Sibbing et al 2010).
    • Risk highest with *17/*17 genotype
    • Risk ~4-fold higher with *17/*17 genotype compared to the wild-type genotype
  – No association between *17 allele and stent thrombosis

• Genetic Testing
  – FDA-approved AmpliChip CYP450 test available
  – Commercial diagnostic companies also offer testing
  – Positive testing for loss-of-function allele confers:
    • Reduced CYP2C19-mediated conversion of clopidogrel to its active metabolite (Mega et al 2009).
    • Less inhibition of platelet aggregation with clopidogrel (Mega et al 2009).
  – Positive testing for *17 allele confers:
    • Greater platelet response to clopidogrel (Sibbing et al 2010).

Clopidogrel Pharmacogenomics: Clinical Relevance

• Pharmacogenomic Test Recommendations
  – Boxed warning in prescribing information (Plavix Prescribing Information. Revised March 2010).
    • Warns of reduced effectiveness in CYP2C19 PMs.
    • States that genetic testing is available.
    • Advises consideration of alternative treatment strategies in PMs.
    • Does not recommend specific strategies for PMs or include recommendations for IMs or UMs.
  – Testing is not mandated.

Loss-of-function allele

Platelet aggregation testing OR No platelet aggregation testing

Good response

Poor response

Standard dose clopidogrel

High dose clopidogrel

Alternative antiplatelet

Add cilostazol

Consider alternative strategy

Clinical effectiveness not established in clinical outcome trials

**Clopidogrel Pharmacogenomics: Clinical Relevance**

- **Alternative Strategy: Substitute Prasugrel**
  - Provides greater protection against cardiovascular events, but increases bleeding risk compared to clopidogrel (Wiviott et al. 2007).
  - Like clopidogrel, undergoes biotransformation to an active metabolite:
    - **Efficacy is not affected by CYP2C19 genotype** (Mega et al. 2009).

  ![Prasugrel Metabolism Diagram](image)

- **Alternative Strategy: Add Cilostazol**
  - Phosphodiesterase III inhibitor with antiproliferative effects
  - Clopidogrel + aspirin + cilostazol prevents restenosis and target vessel revascularization after stent placement compared to clopidogrel + aspirin but leads to increased bleeding risk (Lee et al. 2010).
  - Not specifically studied in patients with CYP2C19 variant alleles.
  - Most data with triple antiplatelet therapy are in Asians, who have a greater prevalence of the CYP2C19 loss-of-function alleles.

**Case 1 Summary**

- **JM has the CYP2C19 genotype associated with the poor metabolizer (PM) phenotype.**
- **Clopidogrel is less protective against adverse cardiovascular events and stent thrombosis in PMs.**
- **Possible Treatment options**
  - Substitute another antiplatelet drug (e.g. prasugrel) for clopidogrel.
  - Use a higher dose of clopidogrel (e.g. 150 mg /day)
  - Add cilastazol.
- **JM should be monitored closely for bleeding.**
Beta Blocker Pharmacogenomics

Patient Case
• CP is a 57-year old non-Hispanic Caucasian man with HTN diagnosed 3 months ago who comes to your clinic for follow up.
  - PMH: hyperlipidemia
  - CP has changed his lifestyle (diet, exercise etc)
  - Vitals: BP 150/87, HR 86
  - Current medications: simvastatin 20 mg po daily
• Genotypes: ADRB1 Ser49Ser/Arg389Arg

Question: Is CP a good candidate for beta blocker therapy?

Beta Blockers: Background
• A widely used drug class
• Antagonize β receptor
• Common Indications
  - Hypertension (HTN)
  - Heart failure (HF)
  - Post acute coronary syndrome (ACS)
• 30-60% of HTN patients treated with a beta blocker fail to achieve adequate blood pressure control

Materson et al 1993, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1982

Beta Blockers: ADRB1
• Gene/Alleles: ADRB1
  - Non-synonymous polymorphisms in ADRB1
  - Ser49Gly (serine to glycine change at position 49)
  - Gly389Arg (glycine to arginine change at position 389)
• Functional Effect:
  – Gly49 allele has a lower number of β1 receptor after exposure to an agonist
  – Ser49 allele may improve β-blocker response
  – Arg389 allele has higher β1 activity and may improve β-blocker response

Mason et al 1999, Rathz et al 2002
Beta Blockers: \textit{ADRB1}

- **Population prevalence (%):**

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasians</th>
<th>African Americans</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gly49</td>
<td>23-29</td>
<td>40-48</td>
<td>26</td>
</tr>
<tr>
<td>Arg389</td>
<td>88-94</td>
<td>79-85</td>
<td>91-96</td>
</tr>
</tbody>
</table>


- **Clinical Relevance: Efficacy**
  - Hypertension: Change in DBP by \textit{ADBR1} genotype
  
  Adapted from (Johnson et al 2003) Liu et al 2006

- **Clinical Relevance: Efficacy**
  - Heart failure
  - Patients with the Arg389Arg genotype tolerated metoprolol initiation better than those who carried a Gly389 allele.
  - Patients with the Arg389Arg genotype had a greater increase in left ventricular ejection fraction with metoprolol
  - Bucindolol reduced the incidence of death and hospitalization in patients with the Arg389Arg genotype while placebo did not.

Pepeñe et al. 2003, Pacanowski et al. 2008

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Beta Blockers: **ADRB1**

- **Clinical Relevance: Toxicity**
  - No literature related to pharmacogenomics impacting drug toxicity

- **Clinical Relevance: Selection/Dosing**
  - No literature related to pharmacogenomics impacting drug selection/dosing
  - Beta blockers may be a better choice to reduce BP for Caucasians and Asians than for African Americans

  Beitelshees et al 2006

Beta Blockers: **ADRB1**

- **Pharmacogenomic Testing and Test Recommendations**
  - FDA-cleared *ADRB1* genetic test unavailable
  - The FDA and health professional organizations do not recommend for or against beta blocker genetic testing

Beta Blockers: **ADRB2**

- **Gene/Alleles: ADRB2**
  - 2 common non-synonymous polymorphisms
  - Arg16Gly - Gln27Glu

- **Functional Effect**
  - Arg16Gly: conflicting data
  - Glu27 has a greater agonist-mediated receptor down-regulation

  Green et al 1994

**Population prevalence (%)**:

<table>
<thead>
<tr>
<th>Allele</th>
<th>Caucasians</th>
<th>African Americans</th>
<th>Asians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gly16</td>
<td>84-90</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Glu27</td>
<td>44</td>
<td>34</td>
<td>17</td>
</tr>
</tbody>
</table>


Shin et al 2007
Beta Blockers: \textit{ADRB2}

- **Clinical Relevance: Efficacy**
- Acute coronary syndrome (ACS)
- In a prospective cohort of 735 patients
  - The Gln27Gln genotype had a higher mortality rate than Glu27 carriers
  - The Arg16Arg/Gln27Gln genotype had the highest mortality rate

\textit{Lanfear et al 2005}

- **Clinical Relevance: Toxicity**
  - No literature related to pharmacogenomics impacting drug toxicity was found

- **Clinical Relevance: Selection/Dosing**
  - No literature related to pharmacogenomics impacting drug selection/dosing was found

- **Pharmacogenomic Testing and Test Recommendations**
  - FDA-cleared \textit{ADBR2} genetic test unavailable
  - The FDA and health professional organizations do not recommend for or against beta blocker genetic testing

---

**Patient Case Summary**

- CP has the following genotype of \textit{ADRB1 Ser49Ser/Arg389Arg}.
  - This genotype has been associated with a better blood pressure response to a beta blocker.
  - CP does not have a contraindication to a beta blocker therapy.
  - CP is a good candidate for beta blocker therapy.

- The \textit{ADRB2} polymorphisms have not been consistently associated with BP responses to a beta blocker.
Beta Blockers: Summary

• *ADRB1* polymorphisms may influence efficacy of a beta blocker in hypertension and heart failure.
  – Their roles in toxicity and dosing/selection of a beta blocker is currently unclear
• *ADRB2* polymorphisms may influence efficacy of a beta blocker in post-acute coronary syndrome.
  – Their roles in toxicity and dosing/selection of a beta blocker is currently unclear

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  – Ashley To, BA

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References


References
Future Webinar Dates
(all times are PST)

- **Oncology II: Hematologic Malignancies**
  - Tuesday, Aug. 10, 2010 10am-12pm – COMPLETED
- **Concepts and Clinical Applications**
  - Wednesday, August 11, 2010 – COMPLETED
- **Psychiatry II: Antipsychotics**
  - Tuesday, Aug. 24, 2010 10am – 12pm – COMPLETED
- **Oncology I: Solid Tumors**
  - Thursday, Aug. 26, 2010 10 am – 12 pm – COMPLETED
- **Cardiology I: Warfarin and Statins**
  - Tuesday, Sept. 21, 2010 10 am – 12 pm – COMPLETED
- **Cardiology II: Clopidogrel and Beta Blockers**
  - Thursday, Sept. 23, 2010 10 am – 12 pm
- **Economic Issues**
  - Tuesday, Oct. 12, 2010 9:30 am – 11:30 am

Survey Instruments: Evaluation

- Faculty trainers will complete a Post-Training Survey
  - Evaluate knowledge, attitudes, and self-efficacy
- All survey materials will be mailed after completion of all webinars in October 2010

Future Webinar Dates
(all times are PST)

- **Psychiatry I: Depression**
  - Thursday, Oct. 21, 2010 10 am – 12 pm
- **Asthma**
  - TBD
- **PharmGenEd™ Program Implementation**
  - Thursday, Aug. 12, 2010: 10 am – 12 pm – COMPLETED
  - Thursday, Sept. 9, 2010: 10 am – 12 pm – COMPLETED

Please register at www.pharmacogenomics.ucsd.edu to download materials prior to the scheduled webinar.