Personalized Medicine in Real Time

DNA-Guided Clopidogrel (Plavix®) Management
Pharmacogenetic Foundations and Case Study
Clopidogrel (Plavix®) Leading AntiPlatelet Drug

- Thienopyridine antiplatelet drug
- Irreversibly inhibits ADP receptor
- Marketed as Plavix®, Sanofi-Aventis/BMS
- Second largest selling drug in the world, $9.5B sales 2008
- >22 million prescriptions issued in 2007
- Indicated to prevent death, MI, and stroke in patients with cardiovascular disease
- **Dosing:** Recent MI, stroke, PAD: 75 mg daily
  ACS: 300 mg x 1 → 75 mg daily

Label Revision May 2009: Pharmacogenetics Section

Variance on potency related to CYP2C19 gene polymorphisms
Pharmacogenetic testing can identify genotypes of CYP2C19
Clopidogrel Activation to Metabolite

CYP2C19 Essential in Metabolite Formation

ProDrug, Inactive
Requires metabolism by CYP2C19 for antiplatelet activity

Metabolite, Active
Far more potent as P2Y12 blocker than clopidogrel
Clopidogrel Mechanism of Action
Pharmacokinetics and Pharmacodynamics

- Clopidogrel
- Active metabolite (thiol)
- Cytochrome p450 2C19
- ADP
- 2PY12
- Platelet
- Resting
- Activation

- Genomics
Clopidogrel Response
Wide Range of Efficacy: Resistant Quartile

“Resistance” = 31%

5 uM ADP aggregation after 300 mg loading dose

### CYP2C19 Genotypes, Phenotypes

<table>
<thead>
<tr>
<th>Allele</th>
<th>Change</th>
<th>Metabolizer Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Reference</td>
<td>Functional</td>
</tr>
<tr>
<td>*2</td>
<td>Splicing defect</td>
<td>Null</td>
</tr>
<tr>
<td>*3</td>
<td>Stop codon</td>
<td>Null</td>
</tr>
<tr>
<td>*4</td>
<td>Start codon</td>
<td>Null</td>
</tr>
<tr>
<td>*6</td>
<td>Arg 132 Glu</td>
<td>Null</td>
</tr>
<tr>
<td>*7</td>
<td>Splicing defect</td>
<td>Null</td>
</tr>
<tr>
<td>*8</td>
<td>Trp 120 Arg</td>
<td>Null</td>
</tr>
<tr>
<td>*9</td>
<td>R 144 H</td>
<td>Deficient</td>
</tr>
<tr>
<td>*10</td>
<td>P 227 L</td>
<td>Deficient</td>
</tr>
<tr>
<td>*17</td>
<td>Promoter</td>
<td>Ultra</td>
</tr>
</tbody>
</table>

**Genotypes and Phenotypes**
- **green** = Functional
- **yellow** = Deficient
- **red** = Null
- **blue** = Ultra

**Allele Frequencies**
- *1: Reference (Functional)
- *2: Splicing defect (Null)
- *3: Stop codon (Null)
- *4: Start codon (Null)
- *6: Arg 132 Glu (Null)
- *7: Splicing defect (Null)
- *8: Trp 120 Arg (Null)
- *9: R 144 H (Deficient)
- *10: P 227 L (Deficient)
- *17: Promoter (Ultra)

**Phenotype Examples**
- **AntiPlatelet ProDrug**
  - Clopidogrel (Plavix<sup>®</sup>)
- **Antidepressants**
  - Escitalopram (Lexapro®)
  - Citalopram (Celexa®)
- **Anti-epileptics**
  - Phenytoin (Dilantin®)
  - Diazepam (Valium®)
- **Proton Pump Inhibitors**
  - Omeprazole (Prilosec®)
  - Lansoprazol (Prevacid®)
  - Esomeprazole (Nexium®)
CYP2C19 Carrier Status

N=577 Referrals to Lab Personalized Health

- 71% non-carrier
- 27% single carrier
- 2% double carrier
Frequency of CYP2C19 *17 allele

Patients Referred: Pharmacogenetic Consult

N = 925
Allele frequency = 21.1%
Carrier frequency = 37.7%
HW p-value = 1.0 (perfect)
# CYP2C19 Genotypes, Phenotypes

## Population Frequencies

<table>
<thead>
<tr>
<th>Allele</th>
<th>Genomic position (NCBI website)‡</th>
<th>Amino Acid Change or other effect</th>
<th>Enzymatic Activity</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>European</td>
</tr>
<tr>
<td>*1</td>
<td>wild-type</td>
<td>Reference</td>
<td>common</td>
<td>common</td>
</tr>
<tr>
<td>*2</td>
<td>19154 G&gt;A</td>
<td>Splicing defect</td>
<td>Null</td>
<td>9-15</td>
</tr>
<tr>
<td>*3</td>
<td>17948 G&gt;A</td>
<td>Trp 212 X</td>
<td>Null</td>
<td>0-2</td>
</tr>
<tr>
<td>*4</td>
<td>5001A&gt;G</td>
<td>Start codon</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*5</td>
<td>19294 T&gt;A</td>
<td>Arg 433 Trp</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*6</td>
<td>12748 G&gt;A</td>
<td>Arg 132 Glu</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*7</td>
<td>19294 T&gt;A</td>
<td>Splicing defect</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*8</td>
<td>12711 T&gt;C</td>
<td>Trp 120 Arg</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*9</td>
<td>12784 G&gt;A</td>
<td>Arg 144 His</td>
<td>Null</td>
<td>Rare</td>
</tr>
<tr>
<td>*10</td>
<td>19153 C&gt;T</td>
<td>Pro 227 Leu</td>
<td>Decreased</td>
<td>Rare</td>
</tr>
<tr>
<td>*17</td>
<td>4195C&gt;T</td>
<td>Promoter variant</td>
<td>Increased</td>
<td>18-27</td>
</tr>
</tbody>
</table>

Epidemiology CYP2C19 Polymorphisms Association with Higher Event Rates

Death, MI, Stroke

Carriers, N=395

Noncarriers, N=1064

Patient CTM3 is a 74-year old Caucasian, diabetic man, hx. severe coronary arterial disease who manifested:

- 14 PTCAs, 7 stents, recurrent restenoses over 8 yrs; on clopidogrel 75 mg/d, high platelet reactivity
<table>
<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Antiplatelet Therapy Option to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td>*1/*2, *1/*3</td>
<td>Clopidogrel 225 mg/day or Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg/day, b.i.d.</td>
</tr>
<tr>
<td>*2/*2, *2/*3, *3/*3</td>
<td>Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</td>
</tr>
<tr>
<td>*1/*17</td>
<td>Clopidogrel 75 mg/day with Rapid Effect</td>
</tr>
<tr>
<td>*2/*17, *3/*17</td>
<td>Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</td>
</tr>
<tr>
<td>*17/*17</td>
<td>Clopidogrel 75 mg/day with Rapid Effect or Consider alternatives: Prasugrel 5 or 10 mg/day or Ticagrelor 90 mg, b.i.d.</td>
</tr>
</tbody>
</table>

Note: Interpretations of the March 2010 clopidogrel label revision have become incorporated into recent clinical guidelines. Recommendations regarding patients heterozygous for null alleles call for supra-normal clopidogrel dosing levels.
DNA-Guided Anti-Platelet Rx
CYP2C19 Individualized Decision Support

Post Cardiac Event
High Risk Patients
CV Prophylaxis

CYP2C19 Status

Functional
Clopidogrel

Null
Clopidogrel
Prasugrel
Ticagrelor

Alternatives
Pioneering high complexity pharmacogenetics laboratory + clinical practice

Anchor for commercialization of PhyzioType Systems throughout New England and nationally

Referral Center for Institute of Living + Mood Disorders Program

CT-wide CLP distribution and reimbursement agreement

$1.4M reimbursable revenue 2011

Reimbursement rate >95%

1044 Patients referred in 2011

3059 PhyzioType tests in 2011

Used by 206 Clinicians in 2011

Licensed by CT Dept of Public Health (#CL-0644) + R.I.

CLIA certified and registered (Clinical Laboratory Improvement Amendments)

ID #07D1036625 CMS (Centers for Medicare and Medicaid)

4 successful biannual inspections (most recent June 2011)

53 patient service centers in CT

Subsidiary of Hartford Healthcare
Physician requests HILOmet PhyzioType System and sends patients for blood draw or buccal swab to CLP centers.

Phlebotomist acquires sample and enters the requisition into the CLP system, including activation of claims.

Messengers bring blood or buccal swab sample to LPH for DNA extraction and clinical genotyping.

Genomas prepares reports + drug selection guidance, uploads into the Portal, sends hard copy reports to clinician.

PAYORS
CLP files 3 claims per HILOmet PhyzioType System with payors based on generic molecular diagnostic codes. CLP remits payment to Genomas at a contractually agreed upon rate per component test.
Thank You!

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