Improving Patient Outcomes Through Pharmacogenetics

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Director, UF Health Personalized Medicine Program
2015 State of the Union: Precision Medicine Initiative

2016 budget: $215M allocated to Precision Medicine through NIH, FDA, informatics
Precision Medicine Initiative → All of Us

www.allofus.nih.gov
Precision Medicine

Precision medicine is the future of medicine

The concepts are not new, but the tools are much more robust and complex

Pharmacogenetics is among the most actionable elements of precision medicine at present
Clinical Potential of Pharmacogenetics

Patients with same diagnosis

- Predicted increased toxicity risk
  - Decrease dose or use different drug

- Predicted good response to tested drug

- Predicted poor or nonresponse
  - Use different drug
Achieving the clinical potential of pharmacogenetics

- Discovery of genetic variants influencing drug response
- Developing evidence base and tools for clinical use of pharmacogenetics
- Clinical implementation of pharmacogenetics
- Documentation of impact on clinical outcomes
NIH-NHGRI supporting efforts in Genomic Medicine Implementation

IGNITE – Implementing GeNomics In pracTicE Network

- Focused on unravelling the challenges associated with translating genomic medicine to clinical practice
- 6 funded groups:
  - University of Florida
  - University of Indiana
  - Vanderbilt
  - University of Maryland
  - Duke University
  - Mt Sinai Health System

- Website and toolbox: www.ignite-genomics.org
Clinical Implementation of Pharmacogenetics: CPIC Guidelines

• Guidelines for 34 drugs for guiding drug therapy based on germ-line variation
  – Does not include drugs for which therapy is guided based on somatic variation
Two stories of clinical pharmacogenetics implementations and evaluation of impact on outcomes at UF Health:

CYP2C19 & clopidogrel

CYP2D6 & opioids
## CYP2C19

### Gene alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>SNP</th>
<th>CYP2C19 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>N/A</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*17</td>
<td>-808C&gt;T</td>
<td>Gain of function</td>
</tr>
</tbody>
</table>

### Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>NM – Normal Metabolizer</td>
</tr>
<tr>
<td>*1/*2 or *1/*3</td>
<td>IM - Intermediate Metabolizer</td>
</tr>
<tr>
<td>*2/*2, *2/*3, *3/*3</td>
<td>PM - Poor Metabolizer</td>
</tr>
<tr>
<td>*1/*17</td>
<td>RM – Rapid Metabolizer</td>
</tr>
<tr>
<td>*17/*17</td>
<td>UM - Ultrarapid Metabolizer</td>
</tr>
</tbody>
</table>
Metabolism of Clopidogrel

- Common loss of function allele (*2)
  - *2 carriers – approx. 30% of whites; 35% of blacks; up to 70% of Asians
- Clopidogrel in CYP2C19 *2 carriers
  - Reduced generation of active metabolite
  - Reduced effect on platelet reactivity
  - Increased risk of MACE post PCI
CPIC Guidelines: CYP2C19 and Clopidogrel: 2013 Update

ACS/PCI Patients

CYP2C19 Genotyping

UM (*1/*17, *17/*17)

NM (*1/*1)

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

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

Clopidogrel at a standard dose

Alternative antiplatelet (Prasugrel or Ticagrelor)
UF Health Personalized Medicine Program: Clinical launch June 2012

Division of Cardiovascular Medicine
Department of Medicine, College of Medicine

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 [...]
EHR Clinical Decision Support

PROBLEM
This patient's CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for stent 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) 90 mg twice daily
   *Contraindications: History of intracranial hemorrhage, active bleeding, severe hepatic impairment
   *Caution: Aspirin doses >100 mg/day reduce ticagrelor effectiveness and should be avoided.

More information on clopidogrel and CYP2C19

Last CYP2C19=*2*8 on 4/12/2012

Acknowledge Reason:

- Open order: Place order for prasugrel (EFFIENT) 10 mg daily. Note: remove order for clopidogrel on next screen.
  (Last done by Ellen Kershner at 2:50 PM on 4/16/2012)
- Open order: Place order for ticagrelor (BRILINTA) 90 mg twice daily. Note: remove the clopidogrel order on next screen.
  (Last done by Inpatient Physician, MD at 12:12 PM on 5/16/2012)
- Open order: Proceed with clopidogrel (PLAVIX) 75 mg daily. Note: please remove the bottom or second clopidogrel order as it will duplicate.
  (Last done by Inpatient Physician, MD at 12:17 PM on 4/26/2012)
Message sent: This alert has been sent via In Basket
Clopidogrel Pilot: Results

• First year, *CYP2C19* ordered on patients with LHC for suspicion of coronary disease
  – 1097 with *CYP2C19* test ordered
  – PCI only – 247/291 patients (84%)
    • First 2 months (June and July 2012) 30/48 (63%)
    • Last 2 months (May and June 2012) 40/41 (98%) <0.001
  – Actionable genotypes post-PCI – n=80
    • 6/6 (100%) PMs had drug therapy changed
    • 50/74 (67%) IMs had drug therapy changed
CYP2C19 genotype/phenotypes and treatment at 2 years

Total with PCI and genotype: n=408

LOF carriers: n = 126; 31%

LOF carriers with alternative therapy: N=68; 54%

Alternative tx: prasugrel in 84%

UM = RM and UM = 30%
Successful clinical implementation but…

does it matter clinically?

UF data suggest genotype guided approach leads to reduced rates of death, heart attack and stroke.
Genotype-guided antiplatelet therapy: 7 academic medical centers in US

Total Cohort n=1815

LOF n=572 (31.5%)
- Clopidogrel n=226 (39.5%)
- Alternative n=346 (60.5%)*†

non-LOF n=1243 (68.5%)
- Clopidogrel n=1050 (84.5%)
- Alternative n=193 (15.5%)†

*p<0.0001 for ALTERNATIVE between LOF and NON-LOF groups
†Prasugrel comprised >60% of ALTERNATIVE therapy

LOF = Loss of function
Outcomes with *CYP2C19* genotype-guided antiplatelet therapy

LOF = Loss of function

Log-rank *p*=0.016

**Cumulative MACE Rate (%)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>LOF_CLOP</th>
<th>LOF_ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

NO. at risk

<table>
<thead>
<tr>
<th>LOF_CLOP</th>
<th>226</th>
<th>112</th>
<th>89</th>
<th>76</th>
<th>63</th>
<th>39</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOF_ALT</td>
<td>346</td>
<td>245</td>
<td>221</td>
<td>195</td>
<td>161</td>
<td>112</td>
<td>9</td>
</tr>
</tbody>
</table>

JACC Cardiovasc Interven, 2018 PMID 29102571
Outcomes with *CYP2C19* genotype-guided antiplatelet therapy

Adjusted Hazard Ratio
LOF-Clopidogrel vs LOF Alternative: 2.21 (1.13-4.33)  \( p=0.021 \)
LOF-Alternative vs non-LOF: 0.81 (0.48-1.35)  \( p=0.41 \)

LOF = Loss of function
Summary: 
* CYP2C19 and clopidogrel

- Data across 7 institutions and nearly 2,000 patients suggest:
  - Clinical implementation of pharmacogenetic testing is feasible
  - *CYP2C19* genotype to guide antiplatelet therapy leads to antiplatelet Rx changes
  - Genotype-guided antiplatelet therapy reduces MACE in post PCI patients
## CYP2D6

### Gene alleles

<table>
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<th>Allele</th>
<th>CYP2D6 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>Normal function</td>
</tr>
<tr>
<td>*3, *4, *5</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*10, 41, others</td>
<td>Reduced function</td>
</tr>
</tbody>
</table>

### Phenotype

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<thead>
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<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1, *1/*2, *2/*2</td>
<td>NM – Normal Metabolizer</td>
</tr>
<tr>
<td>Reduced fxn + LOF</td>
<td>IM - Intermediate Metabolizer</td>
</tr>
<tr>
<td>*4/*4, *4/*5, etc</td>
<td>PM - Poor Metabolizer</td>
</tr>
<tr>
<td>*1/*1xN, *1/*2xN, etc</td>
<td>UM – Ultra Metabolizer</td>
</tr>
</tbody>
</table>
CYP2D6 Phenotypes

- PM – 5-10%
- IM – 2-11%
- UM – 1-2%
- NM – 80-87%

Many important drug interactions
- CYP2D6 strong inhibitors (e.g. fluoxetine) phenoconvert to PM
- CYP2D6 moderate inhibitors (e.g. fluvoxamine), reduce activity 1/2
CYP2D6 & opioid metabolism

- Tramadol
- Hydrocodone
- Oxycodone

PMID 24458018
CPIC guidelines: codeine & tramadol

PMID 24458018 (CPIC) and 27335380 (St Jude)
UF CYP2C6 genotype-guided opioid pain study

- Enrolled 480 primary care patients with chronic pain (> 3 months)
- Patients randomized 2:1 to genotype intervention or usual care
- Baseline and 3 month patient reported outcomes of pain and other measures using PROMIS measures
  - Baseline median pain score = 6.7
UF CYP2C6 genotype-guided opioid pain study

- *CYP2D6* genotype reported to EHR in about 7 days
- Strong and moderate CYP2D6 inhibitors considered to define CYP2D6 phenotype (PMID 20081063, 17971818)
  - Pharmacogenetics PGY2 resident provided consult note with recommendations in UM, PM, IM
- Physician discretion on whether to adopt recommended changes
UF CYP2C6 genotype-guided opioid pain study: Results

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype (n=438)</th>
<th>Genotype only</th>
<th>Genotype plus drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poor metabolizer</td>
<td>5.2%</td>
<td>18.2%</td>
</tr>
<tr>
<td>• Intermediate metabolizer</td>
<td>5.0%</td>
<td>14.4%</td>
</tr>
<tr>
<td>• Intermediate to normal metabolizer</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>• Normal metabolizer</td>
<td>85.6%</td>
<td>63.2%</td>
</tr>
<tr>
<td>• Normal to ultra-rapid metabolizer</td>
<td>2.3%</td>
<td>2.3%</td>
</tr>
<tr>
<td>• No result or indeterminate</td>
<td>1.4%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Drug interactions “phenoconverted” 98 (22.4%) patients to IM/PM
Change in pain intensity by study arm: IM/PM treated with tramadol, codeine

23% of genotyped patients versus 0% of controls had a \( > 30 \% \) reduction in composite pain intensity (\( p=0.04 \))

Total n=53
- Genotype n=35
- Usual n=18
Change in pain intensity by study: NM treated with tramadol, codeine

17% of genotyped patients versus 18% of controls had a ≥ 30% reduction in pain intensity composite (p=0.91)

- Genotype n = 71
- Usual n = 68
Change in pain intensity by study: IM/PM treated with tramadol, codeine, hydrocodone

No evidence for a genotype-related effect with oxycodone

Total n=85
Genotype n=62
Usual n=23
Drug changes by study arm & genotype

<table>
<thead>
<tr>
<th></th>
<th>Actionable gt</th>
<th>Nonactionable gt</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation</td>
<td>31%</td>
<td>17%</td>
<td>0.0076</td>
</tr>
<tr>
<td>Control</td>
<td>29%</td>
<td>20%</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Dose changes by study arm & genotype

<table>
<thead>
<tr>
<th></th>
<th>Actionable gt</th>
<th>Nonactionable gt</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation</td>
<td>8%</td>
<td>7%</td>
<td>0.74</td>
</tr>
<tr>
<td>Control</td>
<td>0%</td>
<td>2%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

When change was made, how often did it align with consult note recommendation: **97% of time**

When change recommended, how often was it followed (w/in 3 mos): **31% of time**
CYP2D6 genotype-guided pain therapy: Summary

- Clinical implementation is feasible
- Genotype-guided approach has potential to improve pain control
- Availability of genotype at time of physician-patient encounter critical
- When changes are made there is strong adherence to recommendations
- Critical to consider drug interactions and genotype
  - Genotype only: 10% IM/PM
  - Genotype + DI: 30% IM/PM
CYP2D6 genotype guided pain therapy: Next steps

• UF Learning Health System
  – Pain management and opioid prescribing significant concern
  – Post-surgical opioid use leads to about 6% with persistence opioid use at 6 months in opioid naïve patients (PMID 28403427)

• Implement genotype-guided approach in surgical patients
  – Pre-emptive genotype feasible
  – Recommend tramadol as first line in all for whom its appropriate
  – May lead to reduced use of schedule II opioids
Co-medication with CPIC drugs in patients Rx’d w/ tramadol, hydrocodone, or codeine

65% on any non-cancer CPIC drug in one year

Argues for panel-based pharmacogenetic testing
Lessons learned in clinical pharmacogenetic implementations

• Physicians/prescribers will use genotype data to guide treatment decisions
• Genotype should be available at time of patient-physician encounter for its optimal use
• Clear guidance to interpret genotype data must be provided in electronic health record
• Patients are enthusiastic to have information that can personalize their therapy
• Patients with chronic diseases on multiple “pharmacogenetic” (CPIC) drugs
Summary and Conclusions

• Genotype-guided approaches to drug therapy management can improve clinical outcomes
  – *CYP2C19* to guide post-PCI antiplatelet therapy led to improved clinical outcomes (MACE)
  – *CYP2D6* to manage pain therapy suggests improved pain control

• Evidence of impact on clinical outcomes must continue to be generated across multiple drug-gene scenarios in pharmacogenetics for adoption by clinicians and payers
UF Health Personalized Medicine Program
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