Pharmacogenetics in Practice: Implementation and Outcomes

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Learning Objectives

• Describe the evidence base and guidelines for use of genetic information to guide treatment decisions for commonly used medications
• Explain the rationale and process for integrating genotyping into clinical practice to guide prescribing decisions
• Evaluate data documenting the impact of genotype-guided therapy on clinical outcomes
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 Use of Pharmacogenetics

Population with a given disease:
- Same therapy for all
- Intolerance
- Good response
- No response
Metabolism of Drugs

Active drug

↑ metabolism
↓ metabolism
No metabolism

Prodrug (Inactive)

Metabolism

Genetic variation:

Inactive drug

Active drug
UF Health
Precision Medicine Program (PMP)

CYP2C19-Clopidogrel (Shands) 6/25/12
2012

IFNL3-PEG-IFNα 7/1/14
2014

CYP2C19-Clopidogrel (Jacksonville) 4/28/16
2016

CYP2C19-PPIs 1/24/17
2018

CYP2D6-Opioids (Surgery) 6/2018
2019

Oncology Supportive Care

2013

TPMT-Thiopurines 2/3/14
2015

CYP2D6-Opioids (Primary Care) 5/11/15

2017

CYP2D6/CYP2C19-SSRIs 10/12/16

2019

PGx Consult Clinic 9/2018

Panel/preemptive Testing

Pharmacogenomics 2017; PMID 28346068
# CYP2C19-Clopidogrel

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
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<tbody>
<tr>
<td>Evidence that genotype influences drug response?</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical Pharmacogenetics Implementation Guidelines?</td>
<td>✓</td>
</tr>
<tr>
<td>Alternative drug or dosing available?</td>
<td>✓</td>
</tr>
<tr>
<td>Reimbursed by many payers?</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical trial data available on clinical utility?</td>
<td>✗</td>
</tr>
</tbody>
</table>

 Clin Pharmacol Ther 2018; PMID 29280137

cpicpgx.org
pharmgkb.org
Clopidogrel Metabolism

Prodrug (inactive)

- Poor metabolizers (PMs)
  - 2-4%
Clopidogrel Metabolism

Prodrug (inactive)

CYP2C19 metabolism

Active form

• Poor metabolizers (PMs)
  – 2-4%

• Intermediate metabolizers (IMs)
  – 20-30%
Outcomes Based on RCT and Registry Post-Hoc Analyses

Meta-analysis of 9 trials and 9685 clopidogrel-treated high risk patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PM/IM vs other</th>
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<tbody>
<tr>
<td>MACE*</td>
<td>HR 1.57 (1.13-2.16)</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>HR 2.81 (1.81-4.37)</td>
</tr>
</tbody>
</table>

*Major adverse cardiovascular events (CV death, MI, or stroke)
FDA-Approved Clopidogrel Label

WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of clopidogrel bisulfate results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Clopidogrel bisulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.
CPIC Guidelines for Clopidogrel


ACS/PCI Patients

CYP2C19 Genotyping

RM (*1/*17)
UM (*17/*17)

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

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

PM

Clopidogrel at a standard dose

Alternative antiplatelet (Prasugrel or Ticagrelor)

CPIC: Clinical Pharmacogenetics Implementation Consortium
CYP2C19-Clopidogrel Implementation at UF Health

• Implemented in June 2012 as part of routine clinical practice
  – Test added to standard order set
  – Run in UF Health Pathology Labs
  – CYP2C19 genotype placed in the EHR

• Recommendations for alternative therapy provided for loss-of-function allele carriers

Best Practice Advisory – Poor Metabolizer

PROBLEM
This patient’s CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel and elevated risk for stent thrombosis and other cardiovascular events after PCI.

REASONS
Reduced clopidogrel activation with 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
• Prasugrel 10 mg/day
• Ticagrelor 90 mg twice daily
Multisite Investigation of Outcomes with Implementation of CYP2C19 Genotype-Guided Antiplatelet Therapy after PCI

Clin Pharmacol Ther 2018; PMID 29280137
JACC Cardiovasc Interv 2018; PMID 29102571
Study Population by CYP2C19 Group and Antiplatelet Therapy

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

JACC Cardiovasc Interv 2018; PMID 29102571
Risk of Major Adverse Cardiovascular Events

Death, MI, or ischemic stroke (MACE)

LOF-Clop vs. LOF-Alt
Adjusted HR 2.26 (1.18-4.32), P=0.013

Non-LOF vs. LOF-Alt
Adjusted HR 1.14 (0.69-1.88), P=0.600

JACC Cardiovasc Interv 2018; PMID 29102571
Risk of Death, MI, or Ischemic Stroke (MACE)

Risk driven by CYP2C19 intermediate metabolizers (IMs)

Cumulative MACE (%)

- IM_Clopidogrel
- NON-LOF
- IM_Alternative

Log-rank p=0.003
Log-rank p=0.155

Time to MACE (month)

Number at risk:
- IM_Clopidogrel: 219, 109, 88, 75, 62, 38, 5
- Non-LOF: 1243, 759, 636, 577, 451, 293, 28
- IM_Alternative: 299, 219, 198, 175, 146, 100, 12

JACC Cardiovasc Interv 2018; PMID 29102571
Risk of Death, MI, or Ischemic Stroke (MACE)

Risk highest in those with ACS indication at index PCI

![Graph showing cumulative MACE rate over time]

<table>
<thead>
<tr>
<th>NO. at risk</th>
<th>LOF_Clopidogrel</th>
<th>Non-LOF</th>
<th>LOF_Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>145</td>
<td>61</td>
<td>47</td>
<td>40</td>
</tr>
<tr>
<td>237</td>
<td>162</td>
<td>147</td>
<td>132</td>
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<tr>
<td>828</td>
<td>504</td>
<td>422</td>
<td>374</td>
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<td></td>
<td>281</td>
<td>218</td>
<td>185</td>
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<tr>
<td></td>
<td>185</td>
<td>111</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>12</td>
<td></td>
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</table>

N=1210

LOF-Clop vs. LOF-Alt
Adjusted HR 2.87 (1.35-6.09)

Non-LOF vs. LOF-Alt
Adjusted HR 1.26 (0.70-2.23)

JACC Cardiovasc Interv 2018; PMID 29102571
Summary: CYP2C19 and clopidogrel

- Data across 7 institutions and over 1,800 patients suggest:
  - Clinical implementation of pharmacogenetic testing is feasible
  - Genotype-guided antiplatelet therapy reduces MACE in post PCI patients
- RCT confirmed that a CYP2C19-guided approach, including clopidogrel, is non-inferior to ticagrelor and prasugrel for clinical outcomes and superior for bleeding risk
POPular Genetics: Genotype-guided P2Y\textsubscript{12} Inhibitors in Primary PCI

NEJM 2019; PMID 31479209

A Primary Combined Outcome

Noninf: $p < 0.001$
Super: $0.87$ (0.62-1.21), $p = 0.40$

No. at Risk
- Standard-treatment group: 1246, 1218, 1202, 1198, 1193, 1185, 1179, 1178, 1173
- Genotype-guided group: 1242, 1213, 1203, 1201, 1197, 1191, 1187, 1184, 1177
**POPular Genetics:** Genotype-guided P2Y\textsubscript{12} Inhibitors in Primary PCI

*NEJM* 2019; PMID 31479209

### B Primary Bleeding Outcome

Super: 0.78 (0.61-0.98), $p = 0.04$

<table>
<thead>
<tr>
<th>Days since Index PCI</th>
<th>Standard-treatment group</th>
<th>Genotype-guided group</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>1246</td>
<td>1242</td>
</tr>
<tr>
<td>45</td>
<td>1193</td>
<td>1208</td>
</tr>
<tr>
<td>90</td>
<td>1168</td>
<td>1193</td>
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<td>135</td>
<td>1155</td>
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<td>180</td>
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<td>1162</td>
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<td>225</td>
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<td>270</td>
<td>1113</td>
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<td>315</td>
<td>1106</td>
<td>1134</td>
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<tr>
<td>360</td>
<td>1094</td>
<td>1121</td>
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**CYP2D6 Genotype and Opioid Metabolism**

- Poor metabolizers (PMs)
  - 5-10%
  - 2 no-function alleles

Tramadol • CYP2D6

0-desmethyl-tramadol
CYP2D6 Genotype and Opioid Metabolism

- **Poor metabolizers (PMs)**
  - 5-10%
  - 2 no function alleles
- **Intermediate metabolizers (IMs)**
  - 2-11%
  - Reduced fxn + no fxn allele

Tramadol → CYP2D6 ↓↓↓

0-desmethyl- tramadrol ↓↓↓
**CYP2D6 Genotype and Opioid Metabolism**

- Poor metabolizers (PMs)
  - 5-10%
  - 2 no function alleles
- Intermediate metabolizers (IMs)
  - 2-11%
  - Reduced fxn + no fxn allele
- Normal metabolizers (NM)s)
  - 80-90%
  - Normal enzyme activity

Drugs shown:
- Tramadol
- 0-desmethyl-tramadol
- Duloxetine
- Fluoxetine
- Paroxetine
- Bupropion
CYP2D6 Genotype and Opioid Metabolism

- **Poor metabolizers (PMs)**
  - 5-10%
  - 2 no function alleles
- **Intermediate metabolizers (IMs)**
  - 2-11%
  - Reduced fxn + no fxn allele
- **Normal metabolizers (NMs)**
  - 80-90%
  - Normal enzyme activity
- **Ultra-rapid metabolizers (UMs)**
  - 1-2%
  - >2 fully functional CYP2D6 alleles

- Tramadol
  - CYP2D6
  - 0-desmethyl-tramadol

- Codeine → Morphine
  - Hydrocodone → Hydromorphone
  - Oxycodone → Oxymorphone
2 yo boy rx’d codeine/APAP s/p adenotonsillectomy died post-op day 2. Found to be a CYP2D6 UM and increased morphine concentrations.

Full-term breastfed male infant found dead on day 12, and blood concentrations of morphine were found to be in toxic range. Mother was taking codeine and had UM phenotype.

5 yo male rx’d tramadol s/p adenotonsillectomy developed severe respiratory depression. Recovered after naloxone. Had CYP2D6 UM phenotype and toxic O-desmethytramadol concentrations.
Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy and many of the children had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 (CYP) 2D6 polymorphism (see WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS/CAREGIVERS, NURSING MOTHERS). TYLENOL® with Codeine is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of TYLENOL® with Codeine tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine (see WARNINGS, PRECAUTIONS).

Safety Announcement

[1-11-2018] The U.S. Food and Drug Administration (FDA) is requiring safety labeling changes for cough and cold medicines containing codeine or hydrocodone to limit the use of these products in children younger than 12 years and older because the risks of these medicines outweigh their benefits in children younger than 12 years of age. The FDA is also requiring the addition of safety information about the risks of misuse, abuse, addiction, and death, and slowed or difficult breathing to the Boxed Warning, our most prominent warning, for prescription cough and cold medicines containing codeine or hydrocodone.

We are taking this action after conducting an extensive review and convening a panel of experts to determine the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death with these medicines outweigh their benefits in patients younger than 18.
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

**CYP2D6 Genotype**

- **Ultra-rapid Metabolizer**
  - Avoid codeine because of toxicity risk. Tramadol not a good alternative.

- **Normal Metabolizer**
  - Use codeine at recommended dose
  - Poor response?
    - YES
      - Use alternative

- **Intermediate Metabolizer**

- **Poor Metabolizer**
  - Avoid codeine because of lack of efficacy. Tramadol not a good alternative.
CYP2D6 Genotyping at UF Health

• Implemented in May 2015 in response to request by primary care physicians
  • Genotyping
    – Conducted in UF Health Pathology Laboratories
    – Validated for buccal cell samples

Best Practice Advisory – Intermediate Metabolizer

PROBLEM: This patient's CYP2D6 genotype is associated with decreased production of active form of tramadol. This patient may get LITTLE TO NO PAIN RELIEF with tramadol and other CYP2D6-mediated opioid analgesics such as codeine, hydrocodone, and oxycodone.

RECOMMENDATIONS:

(A) Consider a non-opioid analgesic
  OR
(B) Consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, which are not affected by CYP2D6 metabolism status

More information on tramadol and CYP2D6

For questions about this alert or the Precision Medicine Program, please send us an inbasket message to "P RX UF PMP MONITORING" or call us at (352) 273-6415.
Pragmatic Trial of CYP2D6-Guided Opioid Prescribing

**IMPLEMENTATION Clinics**
- (n=4 clinics, 235 patients)
- Genotyped for CYP2D6 and provided recommendation via consult note

**BASELINE**:
- Collected PROs and DNA sample

**3 MONTHS**:
- Collected PROs

**CONTROL Clinics**
- (n=3, 135 patients)
- Genotyped for CYP2D6

PRO: Patient reported outcomes
CYP2D6-Guided Recommendations

Avoid tramadol and codeine (strong recommendation).
Avoid hydrocodone and oxycodone (moderate recommendation).
Use alternative opioid (e.g. morphine, hydromorphone) or non-opioid (e.g. NSAID).

CYP2D6 Phenotype

Ultra-rapid Metabolizer
Normal Metabolizer
Intermediate Metabolizer
Poor Metabolizer

Continue usual care

CYP2D6 genotype
CYP2D6 inhibitors

Strong inhibitors: bupropion, fluoxetine, paroxetine, quinidine
Moderate inhibitors: duloxetine, fluvoxamine

Poor response?

YES
Baseline Characteristics

• 370/375 completed baseline measures
  – Mean age was 59 years
  – 68% female, 71% white
  – Most common pain management indications were back pain and arthritis
  – Mean pain intensity was 6.55/10
  – 94% on an opioid at baseline
    • 45% on tramadol
    • 25% hydrocodone
    • 3% codeine
**CYP2D6 Phenotype (n=343)**

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genotype only</th>
<th>Genotype + drug interactions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>IM</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>NM</td>
<td>86%</td>
<td>61%</td>
</tr>
<tr>
<td>Other</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Most common CYP2D6 inhibitors: duloxetine, bupropion, fluoxetine, paroxetine

Drug interactions “phenocovered” 28% of NMs to IM/PMs

Genet Med 2019; PMID 30670877
Change in Pain Intensity Composite

- Patients on tramadol, codeine, or hydrocodone at baseline

*p value by ANCOVA adjusted for baseline pain measure, age, sex, race, HTN, anxiety, other psych disorders
CYP2D6 Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

There is wide inter-individual variability in opioid analgesic response

Opioid misuse is largely motivated by the pursuit of physical pain relief

Post-operative opioid prescribing represents a gateway to chronic opioid use

- Evidence of persistent opioid use in ~6% of opioid naïve individuals after an outpatient surgical procedure
- All together, there is a critical need to improve pain control and optimize opioid prescribing

Ann Intern Med. 2017; PMID 28761945
JAMA Surg. 2017; PMID 28403427
CYP2D6 Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

- **Initial Evaluation Visit (surgery decision made)**
  - Patients enrolled; DNA collection

- **Pre-Operative Visit (within 30 days of surgery)**
  - Patient receives Rx; PRO collection

- **Surgery (TKA or THA)**

- **2 weeks Post-Surgery**
  - PRO collection; Opioid consumption assessment

- **Genotype Guided**
- **PGx testing**

- **Usual Care**
- **2:1**

**PRO**: Patient reported outcomes
CYP2D6-Guided Recommendations

- Evidence of lower addiction potential than C-II opioids (PMID 16716877, PMID 2029860)

Avoid tramadol and codeine (strong recommendation).
Avoid hydrocodone and oxycodone (moderate recommendation).
Use alternative opioid (e.g. morphine, hydromorphone) or non-opioid (e.g. NSAID).

*Ultra-rapid Metabolizer*
- Tramadol as the preferred opioid*

*Normal Metabolizer*

*Intermediate Metabolizer*

*Poor Metabolizer*

**CYP2D6 Phenotype**

**CYP2D6 genotype**

**CYP2D6 inhibitors**

- **Strong inhibitors:** bupropion, fluoxetine, paroxetine, quinidine
- **Moderate inhibitors:** duloxetine, fluvoxamine

*Evidence of lower addiction potential than C-II opioids (PMID 16716877, PMID 2029860)*
Preliminary Results

• 200/215 (93%) agreed to participate
• Percent with IM/PM phenotype
  – 11.2% based on genotype
  – 21.4% based on genotype + drug interactions
• Acceptance of recommendations among IM/PMs
  – 21% in guided group vs 100% in control group
  prescribed opioid metabolized by CYP2D6
Summary and Next Steps

• Clinical implementation of pharmacogenetic testing is feasible
• Data suggest that CYP2D6 guided management of chronic pain improves pain control
• NHGRI-funded IGNITE Network to conduct multi-center pragmatic clinical trials
  – CYP2D6-guided management of chronic pain
  – CYP2D6-guided management of acute pain
  – CYP2D6/CYP2C19-guided antidepressant prescribing
ADOPT-PGx

A Depression and Opioid Pragmatic Trial in Pharmacogenomics

Lead Sites: University of Florida Health, Indiana University, and Vanderbilt University

Pain and depression are conditions that impact a substantial proportion of the U.S. population, but finding safe, effective drug therapies for both conditions is challenging. ADOPT-PGx is a pragmatic clinical trial that enrolls patients into three pharmacogenomics (PGx)-guided therapy scenarios: acute post-surgical pain, chronic pain, and depression. For each scenario, participants will be randomized to genotype-guided drug therapy versus usual approaches to drug therapy selection (“usual care”). Changes in patient-reported outcomes representing pain and depression control using standard patient-reported outcomes measurement information system (PROMIS) scales define the primary endpoints. Secondary analyses include safety endpoints, changes in overall well-being, and economic impact represented by differences in healthcare utilization.
Lessons Learned

• Having a physician champion is key
• Prescribers will use genotype/phenotype data to guide treatment decisions
  – Genotype should be available during the patient encounter to optimize prescriber’s ability to act on it
  – Clear guidance is needed through clinical decision support
  – Section of EHR with lifetime (e.g. genetic) results likely optimal
• Normal metabolism phenotype not actionable but informative
• Patients are enthusiastic to have pharmacogenetics data in their medical record
  – > 95% of control arm participants wanted pharmacogenetics reported after trial completed

UF Investigators: Roger Fillingim, PhD; Siegfried Schmidt, MD, PhD; Hari Parvataneni, MD; Chancellor Gray, MD; David Anderson, MD; Yan Gong, PhD; Taimour Langaee, PhD; Cameron Thomas, PharmD

IGNITE Investigators: Craig Lee, PharmD, PhD; Amber Beitelshees, PharmD, MS; Nita Limdi, PharmD, PhD; Phil Empey, PharmD, PhD; Julio Duarte, PharmD, PhD; Todd Skaar, PhD

Funding: NIH/NCATS UF CTSA UL1 TR000064, IGNITE Network grant U01 HG007269 and substantial institutional support from UF and UF Health