Is Genotyping for CYP2C19 Sufficient for Guiding Decision-Making in Clopidogrel Therapy?

KT Jerry Yeo, Ph.D., DABCC, FACB

Professor of Pathology
Medical Director, Clinical Chemistry, Clinical Pharmacogenomics & Clinical Translational Mass Spectrometry Laboratories
Department of Pathology
The University of Chicago
Email: jyeo@bsd.uchicago.edu

Disclosure

• None

Objectives

• Describe the relevant factors affecting Clopidogrel efficacy
• Summarize the limitations of Cyp2C19 genotyping in predicting clopidogrel efficacy
• List alternative strategies to assess clopidogrel efficacy
Adverse Drug Reactions

- >2 million adverse drug reactions (ADRs) occur annually in US
- ~100,000 deaths (4th leading cause of death)
- Overall cost of drug-related morbidity & mortality estimated >$76 billion
- 4% of new drugs are withdrawn due to ADRs
  - 1995-2005: 34 drugs withdrawn mainly due to hepatotoxic or cardiotoxic effects
- Drugs are only effective in 25-60% of patients*

**Variable Therapeutics Response Rates**

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Response Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension Drugs</td>
<td>10-30%</td>
</tr>
<tr>
<td>Heart Failure Drugs</td>
<td>15-25%</td>
</tr>
<tr>
<td>Anti-Depressants</td>
<td>20-30%</td>
</tr>
<tr>
<td>Cholesterol Drugs</td>
<td>20-70%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>60-70%</td>
</tr>
</tbody>
</table>

*Percentage of the patient populations for which any particular drug is ineffective.*

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**Promise of PGx**

- 4Rs: Right drug, right patient, right dose, right time! Right Price
- Maximize drug efficacy
- Decrease ADRs
- Salvage failed drugs (e.g., beta blocker, Bucindolol)

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**Pharmacokinetic/Pharmacodynamic (PK/PD) continuum of Drug Response**

- **Drug Dose** → **Biological Fluid Conc.** → **Effect Site Conc.** → **Pharmacologic Effect**

- **PK Variability**
  - Concentration
  - Liberation
  - Absorption
  - Distribution
  - Metabolism

- **PD Variability**
  - Pharmacodynamics
  - Pharmacogenomics

*Applied Pharmacokinetic and Pharmacodynamic 2005, eds, Piiper, Shaw, Schentag & Evans*
Proteins in Drug Metabolism

- 75% of all drugs are metabolized by CYP3A4 and CYP2D6
- CYP2D6 contributes 20% of all drugs, although it is only 1.5% of total liver content

Proteins Involved in Drug Distribution & Dynamics

- **Drug Transporters:**
  - There are variants involved in Phase II, drug transporters and receptors
  - The MDR1 multixdrug transporter P-gp (P-glycoprotein) is an efflux pump that extrudes diverse hydrophobic drugs and peptides from cells.

- **Drug Targets:**
  - Vitamin K epoxide reductase subunit 1 (VKORC1)
  - Dopamine receptors
  - Serotonin receptors

- **Human Leukocyte Antigen (HLA) System**
  - HLA B variants
  - All these variants together contribute to the genetic differences in patients’ response to drug

FDA Table of PGx Biomarkers

<table>
<thead>
<tr>
<th>Drug</th>
<th>HUGO Symbol</th>
<th>Referenced Subgroup</th>
<th>Labeling Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B</td>
<td>HLA-B*57:01</td>
<td>Boxed warning</td>
</tr>
<tr>
<td>Antidepressants/anti-</td>
<td>CYP2D6</td>
<td>PM</td>
<td>Dosage warning</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>TPMT</td>
<td>PM &amp; PM</td>
<td>Dosage warning</td>
</tr>
<tr>
<td>Arabinoside</td>
<td>LDH</td>
<td>Homozygous familial hypercholesterolemia (HfCHD)</td>
<td>Dosage warning</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>CYP2D6</td>
<td>PM</td>
<td>Precautions</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>PM</td>
<td>Warnings</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>IM &amp; PM</td>
<td>Dosage warning</td>
</tr>
<tr>
<td>Ectonucleoside</td>
<td>CYP2C19</td>
<td>PM</td>
<td>Drug interaction</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>CYP2C19 &amp; UGT1A1</td>
<td>IM &amp; PM</td>
<td>Dosage, drug interaction</td>
</tr>
</tbody>
</table>

Source: [FDA Table of PGx Biomarkers](http://www.fda.gov/drugs/scientificresearch/researchareas/pharmacogenetics/ucm083378.htm)
**Clopidogrel (Plavix)**

- Dual antiplatelet therapies of aspirin and clopidogrel for preventing atherothrombotic events post MI is standard of care.
- Interindividual variability in response to clopidogrel (multifactorial).
  - Lack of compliance
  - Obesity, insulin resistance
  - Nature of coronary event
  - Genetic factors in absorption and metabolism?
  - Hyper-responsiveness associated with poorer clinical outcomes
  - Precise mechanisms unknown—likely multifactorial.

**Clopidogrel Metabolism**

- Prodrug requiring activation to active metabolite by CYP450 enzymes.
- Esterases shunt most (85% dose) to inactive metabolites.

**Clopidogrel Action**
Evidence for CYP2C19 Genotyping

Risk for CYP 2C19 carriers

Risk of Stent Thrombosis
Correlation of CYP genotype-phenotype

POCT PGx (Cyp2C19)-pushing the envelope?

Clin Pharm Consortium Guidelines for Clop PGx
Are we ready for Prime Time?

Clopidogrel Case

- 79 yo male with EKG and cardiac troponin elevations suggestive of AMI
- Three drug eluting stents:
  - First proximal obtuse marginal: 2 stents
  - Left circumflex: 1 stent
- Antiplatelet therapy
  - Plavix (clopidogrel) and aspirin
- Patient was high risk clinically, with a lot of underlying coronary artery disease and extensive stenting.
- There was a great deal of concern for ensuing thrombosis on re-admission and a platelet aggregation study was requested.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype</th>
<th>Result</th>
<th>SNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C19</td>
<td>*1/*17</td>
<td>C/T</td>
<td>-806 C&gt;T</td>
</tr>
<tr>
<td>2C9</td>
<td>*1/*2</td>
<td>C/T</td>
<td>430 C&gt;T</td>
</tr>
</tbody>
</table>

So what do these results mean??
- Predicted 2C19 phenotype = Ultrametabolizer
- Predicted 2C9 phenotype = Intermediate metabolizer
- Would predict that patient will do well on Clopidogrel therapy
POCT Platelet Function Testing-Accumetrics VerifyNow®

Interpretations

**P2Y12 Reaction Units (PRU)** indicates the amount of ADP-mediated aggregation specific to the platelet P2Y12 receptor.

**BASE (Base PRU)** indicates the amount of mediated aggregation specific to the platelet P2Y12 and ADP receptors. The BASE result is normalized to report units that are equivalent to baseline (per-drug PRU) values.

Percent (%) P2Y12 inhibition is the percent change from baseline aggregation, and is calculated from the PRU result and the BASE result.

- Patients with high residual platelet reactivity are at greater risk for ischemic events, including myocardial infarction and stroke.
- High residual platelet reactivity is defined in the package insert as ≥300 PRUs.
- Low platelet reactivity is associated with major bleeding.

Platelet Aggregation Studies

1. **Accumetrics VerifyNow Whole Blood Assay**

<table>
<thead>
<tr>
<th>Result Name</th>
<th>Result (Units)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2Y12 Reactivity Unit</td>
<td>396 PRU</td>
<td>210-325</td>
</tr>
<tr>
<td>Platelet Reactivity BASE</td>
<td>235 Base PRU</td>
<td>230-370</td>
</tr>
<tr>
<td>P2Y12% Inhibition</td>
<td>0 %</td>
<td></td>
</tr>
</tbody>
</table>
Patient on ASA & Clopidogrel: Lumi-Aggregometer

Big Discordance

• There is an apparently large discordance between the CYP 2C19 genotype results vs platelet function testing for this patient on Clopidogrel!!
• Further investigations for more genes and serum measurement for clopidogrel

Complex Workup & Final Interpretations

• Drug Measurement
  • TOF MS of plasma showed presence of parent and metabolite of Clopidogrel (courtesy of Dr Alan Wu, UCSF)
• Genotypes
  • CYP 2C19 *1/*17: Extensive-to-Ultrapid metabolizer; sufficient activation to 2-oxoclopidogrel
  • CYP 3A4 G>A Mutant: Carriers of A allele has better response to clopidogrel due to less activation of GP IIb/IIIa platelet receptors.
  • ABCB1 C/C: No increased risk
  • ITGA2 (Integrin A2), C/T Het: Carriers of T allele show increased thrombotic risk
  • P2Y12, C/T Het: Carriers of T allele show increased adverse events with clopidogrel

Summary: Transport and metabolism are sufficient. However, clopidogrel resistance is predicted due to variant platelet receptors.
Patient on ASA & Prasugrel

Prasugrel therapy resulted in 62% inhibition in platelet function

Summary

• In this patient, CYP2C19 genotyping alone will have predicted clopidogrel to be effective
• However platelet function testing showed no inhibition by clopidogrel
• Switching to Prasugrel showed appropriate platelet function inhibition

Schema-UCM ARIVE PCI Study
VerifyNow PFT vs Genotypes

LTA PFT vs Genotypes

Non-genetic Factors

- Age
- Diet
- Drug-Drug interactions
- Organ function
- Nature and severity of disease

Our genotype remain stable over lifetime and effects can be profound

Source: Nature Reviews / Drug Discovery
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 alters clopidogrel metabolism, which 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...)

Recommendations (Cont)

- 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.

New Oral P2Y12 antagonists for ACS treatment

- Current standard therapy is combination of aspirin and clopidogrel
- Prasugrel
  - Prodrug, needs activation
  - More potent and constant platelet inhibition, but has significantly higher risk of fatal bleeding
  - No need for PGx

JACC 2010;56:321-341

New Oral P2Y12 antagonists for ACS treatment

- Current standard therapy is combination of aspirin and clopidogrel
- Prasugrel
  - Prodrug, needs activation
  - More potent and constant platelet inhibition, but has significantly higher risk of fatal bleeding
  - No need for PGx

JACC 2010;56:321-341
Ticagrelor

- Cyclopentyltriazolopyrimidine class
- Significantly reduced the composite endpoint of cardiovascular death, MI or stroke compared with clopidogrel, without an increase in the rate of overall major or fatal bleeding
- CYP3A4 and CYP3A5 appear to be primarily responsible for the formation of AR-C124910XX
- Not affected by ABCB1 and CYP2C19 variants
- CYP 3A4 inhibitors (ritonavir, fluconazole) & inducers (rifampicin) can affect drug efficacy
- Increasingly been used in ED for high-risk ACS patients sent to cath lab

Ticagrelor & CYP 2C19

Conclusions

- CYP2C19 genotyping alone may not be sufficient to predict clopidogrel efficacy
- May require other genes, e.g. ABCB1, P2Y12, etc.
- Premature to consider POCT CYP2C19 for limited allele
- Non-genetic factors (drug-drug interactions, smoking, ethnic group, etc) may also contribute
- Platelet function testing will detect the effectiveness of oral P2Y12
- Advent of new oral antiplatelet medications may obviate these PGx tests—a moving target.
The Near Future??

Acknowledgements

• Collaborators
  • Jonathan L. Miller, MD, PhD (Coagulation Medical Director, Coagulation Laboratory)
  • Sandeep Nathan, MD (Interventional Cardiologist)
  • Xin Yi, PhD (Clinical Chemistry Fellow)
  • Alan HB Wu, PhD (UCSF)
  • Dennis J. O’Kane, PhD (formerly SNP Laboratory, Mayo Medical Labs)

Thank You - Questions?
Questions-of-the-Day

• Do you think we should perform clopidogrel pharmaco-genotyping given that PFT better reflect the effectiveness of drug?

• What are the advantages/disadvantages?
Prediction of hepatitis C treatment outcomes using Pharmacogenomics

Alan H.B. Wu, Ph.D.
American Association for Clinical Chemistry
Chicago, IL July 30, 2014

Sings/symptoms of acute HCV

- Fever and fatigue
- Dark urine, clay colored stools
- Abdominal pain
- Loss of appetite
- Nausea and vomiting
- Joint pain
- Jaundice

Hepatitis C infection risks
CDC.gov/hepatitis

- Current or former IV drug user
- Recipient of clotting factor concentrates before 1987
- Recipients of blood transfusion or organ transplants before 1992 (blood screening began)
- Chronic hemodialysis patients
- Known exposures to
  - Healthcare workers after a needlestick
  - Recipients of blood or organs from a HCV-positive donor
- Persons with an HIV infection
- Children born to HCV-positive mothers
**Hepatitis C chronic infection**

CDC.gov/hepatitis

- 75-85% will develop chronic infection
- 60-70% will develop chronic liver disease
- 5-20% will develop cirrhosis over 20-30 y
- 1-5% will die from chronic infection (cirrhosis or liver cancer)

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**Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection**

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**Diagnostic tests and results in suspected HCV infections**


<table>
<thead>
<tr>
<th>Initial tests</th>
<th>Confirmatory tests</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>Recombinant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>immunoblot</td>
<td>HCV RNA PCR</td>
</tr>
<tr>
<td>Neg</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>Neg</td>
</tr>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
</tr>
</tbody>
</table>

No infection or very early
Current
False +ve
Past
Hepatitis C genotyping map

Global distribution of HCV genotypes

Key

Type 1: 72%
Type 2: 16-19%
Type 3: 8-10%
Type 4-9: 1-2%

Recombinant immunoblot for Hep. C

Hepatitis C proteins detected
Ortho RIBA-2:
  5-5-5, c100-3, c33c, c22-3
RIBA-3:
  NS5, c100-3, c33c, c22-3
Welcozyme
  NS5, NS4, NS3, core

Dual therapy for hepatitis C

- **Interferons**: mediated through inhibition of viral penetration or uncoating, inhibiting viral replication or translation of viral proteins, and/or viral assembly and release.
- **Pegylated interferon**: protects interferon from proteolytic degradation and reduces its immunogenicity.
- **Ribavirin**: inhibits the replication of a wide range of RNA and DNA viruses.
Interferon alfa vs. dual therapy with ribavirin  

<table>
<thead>
<tr>
<th>Response</th>
<th>Interferon 24 wk</th>
<th>Interferon 48 wk</th>
<th>Interferon+rivavirin 24 wk</th>
<th>Interferon+rivavirin 48 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 copies/mL</td>
<td>29%</td>
<td>24%</td>
<td>53%</td>
<td>50%</td>
</tr>
<tr>
<td>Biochemical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal ALT</td>
<td>24%</td>
<td>28%</td>
<td>58%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Can we improve on therapeutic predictions?

Can we improve on therapeutic predictions?

Translation of PGx into clinical practice

Conversion of genotype data directly into clinical management decisions:

1. Optimizing dosing for maximum efficacy and toxicity avoidance  
   CYP 2C9 and VKORC1 for warfarin, CYP P450 for tamoxifen

2. Selecting drugs that avoids catastrophic side effects.  
   HLA testing to avoid Stevens Johnson Syndrome (e.g., abacavir, carbamazepine), TPMT for bone marrow suppression by azothioprine

3. Selecting drugs that have the highest rate of therapeutic efficacy  
   CYP 2C19 for clopidogrel vs. prasugrel or ticagrelor
**PGx for hepatitis is unique**

1. Optimizing dosing for maximum efficacy and toxicity avoidance
   Dosage duration (12 vs 24 vs 48 weeks)
2. Selecting drugs that avoids catastrophic side effects.
   Protection against hemolytic anemia
3. Selecting drugs that have the highest rate of therapeutic efficacy
   Dual vs. triple vs. multiple antiviral therapies alone

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**Recent chronology of IL28 treatment and PGx testing**

- Sept. 2009: genetic variants in IL28B described in *Nature*
- March 2010: IPTA gene variants described as protective against hemolytic anemia
- May 13, 2011: boceprevir FDA cleared (protease inhibitor)
- May 23, 2011: telaprevir FDA cleared (protease inhibitor)
- November 22, 2013: simeprevir FDA cleared (protease inhibitor)
- December, 2013: sofosbuvir FDA cleared (nucleotide analog NS5B polymerase inhibitor)
- 2014: CAP implements proficiency testing program
- With directly acting anti-viral therapies, is IL28B genotyping already dead?

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**GWAS study**


3 kb upstream from the type II interferon IFN-λ.
Allele frequencies for rs12979860

Spontaneous viral response rates

IL28b in hep. C Type 1

Caucasians. Similar results seen for Asians and Blacks
### Meta-analysis for hepatitis C treatment

**Rangnekar et al. Alim Pharmacol Ther 2012;36:104-14.**

#### Asian HCV genotype 1

<table>
<thead>
<tr>
<th>Author</th>
<th>OR (95% CI)</th>
<th>SVR in CC</th>
<th>SVR in CT/TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayes</td>
<td>0.53 (0.30, 0.93)</td>
<td>31/168</td>
<td>64/294</td>
</tr>
<tr>
<td>Kurokawa</td>
<td>4.51 (3.50, 10.31)</td>
<td>172/345</td>
<td>25/151</td>
</tr>
<tr>
<td>Taiyaki</td>
<td>12.09 (6.64, 22.36)</td>
<td>121/196</td>
<td>15/118</td>
</tr>
<tr>
<td>Lin</td>
<td>4.25 (1.96, 9.02)</td>
<td>23/77</td>
<td>4/92</td>
</tr>
<tr>
<td>Shi</td>
<td>2.50 (0.90, 8.54)</td>
<td>31/45</td>
<td>4/90</td>
</tr>
<tr>
<td>Huang</td>
<td>0.92 (0.44, 1.18)</td>
<td>121/187</td>
<td>10/39</td>
</tr>
<tr>
<td>Hepass</td>
<td>0.88 (0.74, 1.07)</td>
<td>127/219</td>
<td>10/80</td>
</tr>
<tr>
<td>Akutsu</td>
<td>4.80 (2.60, 9.00)</td>
<td>95/100</td>
<td>10/89</td>
</tr>
<tr>
<td>Overall</td>
<td>0.96 (0.99, 0.99)</td>
<td>1155/1901</td>
<td>141/711</td>
</tr>
</tbody>
</table>

### Meta-analysis for hepatitis C treatment

**Rangnekar et al. Alim Pharmacol Ther 2012;36:104-14.**

#### African American HCV genotype 1

<table>
<thead>
<tr>
<th>Author</th>
<th>OR (95% CI)</th>
<th>SVR in CC</th>
<th>SVR in CT/TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson</td>
<td>5.43 (2.70, 10.64)</td>
<td>20/425</td>
<td>37/658</td>
</tr>
<tr>
<td>McCarthy</td>
<td>1.46 (0.14, 15.15)</td>
<td>1/8</td>
<td>4/45</td>
</tr>
<tr>
<td>Defing</td>
<td>3.62 (0.85, 15.48)</td>
<td>3/59</td>
<td>32/90</td>
</tr>
<tr>
<td>Overall</td>
<td>4.63 (2.02, 9.52)</td>
<td>27/55</td>
<td>73/983</td>
</tr>
</tbody>
</table>

### Algorithm for IL28b haplotype analysis

**Fischer et al. Hepatol 2012;55:1700-10**

<table>
<thead>
<tr>
<th>SNP</th>
<th>12979860</th>
<th>SNP</th>
<th>8099917</th>
<th>SVR Incidence</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>TT</td>
<td>67%</td>
<td>31%</td>
<td>8099917 testing is unnecessary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>71%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>100</td>
<td>0.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>TT</td>
<td>55%</td>
<td>22%</td>
<td>8099917 differentiates high SVR vs. low SVR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>40%</td>
<td>30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>40%</td>
<td>0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>TT</td>
<td>50%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td>43%</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>31%</td>
<td>4%</td>
<td></td>
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</tr>
</tbody>
</table>
GWAS for variants that predict Hb drop
Fellay et al. Nature 2010;464:405-8

Inosine triphosphatase (ITPA) gene. Deficiency leads to ITP accumulation in RBCs

IPTA gene variance and Hb protection
Thompson et al. Gastroenterol 2010;139:1181-91

Mechanism of action and clinical consequence of ITPA variant

Mechanism
- ITPA leads to inosine triphosphate accumulation (ITP)
- Ribavirin induces reduction in erythrocyte GTP.
- ITP substitutes for RBC GTP in ATP production?

Clinical consequence
- Escalation of ribaviron dosage for variants to improve SVR
- Reduction monitoring needed for anemia
Directly acting antiviral therapy:

Telaprevir therapy after failed dual tx

Telaprevir causes greater Hb drop, some return to baseline after discontinuation.
Sofosbuvir HCV treatment: Fission trial
Lawitz et al. NEJM 2013;368:1878-87.

Therapeutic approach algorithm for hep. C

DAAV: directly acting antivirals. More intensive therapy in this group

2014 AASLD / IDSA HCV Guidance
Genotype 1 HCV/HIV Coinfection

*Recommended regimen(s) for treatment-naive patients with HIV genotype 1 with a history of PegIFN + RBV nonresponse is the same as for HCV monoinfected patients

**Coadministration of SOF with tipranavir + ritonavir is not recommended due to expected decrease in concentration of SOF

www.hcvguidelines.org
### 2014 AASLD / IDSA HCV Guidance

#### Genotype 2 HCV/HIV Coinfection

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
<th>Allowable Antiretroviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive and prior PegIFN + RBV relapsers</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td>Treatment-experienced (prior PegIFN + RBV nonresponders)</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
</tbody>
</table>

*Coadministration of SOF with tipranavir + ritonavir is not recommended due to expected decrease in concentration of SOF*

### 2014 AASLD / IDSA HCV Guidance

#### Genotype 3 HCV/HIV Coinfection

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
<th>Allowable Antiretroviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive and prior PegIFN + RBV relapsers</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td>Treatment-experienced (prior PegIFN + RBV nonresponders)</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
</tbody>
</table>

*Coadministration of SOF with tipranavir + ritonavir is not recommended due to expected decrease in concentration of SOF*

### 2014 AASLD / IDSA HCV Guidance

#### Genotype 4, 5, 6 HCV/HIV Coinfection

<table>
<thead>
<tr>
<th>Recommended</th>
<th>Alternative</th>
<th>NOT Recommended</th>
<th>Allowable Antiretroviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 4 regardless of treatment history:</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
<tr>
<td>Genotype 5 or 6 regardless of treatment history:</td>
<td>PegIFN + RBV x 24-48 weeks</td>
<td>None</td>
<td>Any regimen with TVR, BOC, or SMV</td>
</tr>
</tbody>
</table>

*Coadministration of SOF with tipranavir + ritonavir is not recommended due to expected decrease in concentration of SOF*
### Economic impact of new hepatitis therapy

![Image of medical equipment]

### Economic model: quality-adjusted life years

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Disease</th>
<th>QALY range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammography screening</td>
<td>breast cancer</td>
<td>10,000-25,000</td>
</tr>
<tr>
<td>Medications</td>
<td>hypertension</td>
<td>10,000-60,000</td>
</tr>
<tr>
<td>Dialysis</td>
<td>ESRD</td>
<td>50,000-100,000</td>
</tr>
<tr>
<td>Implantable defibrillators</td>
<td>AMI &amp; HF</td>
<td>30,000-70,000</td>
</tr>
<tr>
<td><strong>PGx testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine, TPMT</td>
<td>Leukemia</td>
<td>$3000</td>
</tr>
<tr>
<td>Abacavir/HLA*B-5701</td>
<td>HIV</td>
<td>$10-30,000</td>
</tr>
<tr>
<td>Warfarin 2C9 &amp; VKORC1</td>
<td>Atrial fibrillation</td>
<td>$170,000</td>
</tr>
<tr>
<td><strong>Threshold</strong></td>
<td></td>
<td>$55,000</td>
</tr>
</tbody>
</table>

*Cost analysis: sofosbuvir*

Cost analysis: sofosbuvir

Drug costs are higher. Currently $84k for US for 12 weeks
$168k for 24 weeks. What are we willing to pay?

ICER for sofosbuvir vs. boceprevir & telaprevir

<table>
<thead>
<tr>
<th>Category</th>
<th>BOC</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL28B CC</td>
<td>$37k</td>
<td>$61k</td>
</tr>
<tr>
<td>IL28B TC/TT</td>
<td>$25k</td>
<td>$30k</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>$22k</td>
<td>$36k</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>$34k</td>
<td>$47k</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>$17k</td>
<td>$26k</td>
</tr>
</tbody>
</table>

Author’s ICER threshold: $32k

CAP survey 2014

General Information

- Do you offer IL28B (rs1297986) analysis as a clinical test? (0) No (1) Yes (2) Not Applicable

- If IL28B (rs1297986) analysis is offered as a clinical test, does your laboratory perform the testing in-house? (0) No (1) Yes

Genotype (Ungraded)

- PEG1.01
  - 659: Heterozygous C/C
  - 661: Heterozygous C/T
  - 663: Homozygous C/C

Interpretation (Ungraded)

- 662: Genotype is more likely to have a sustained virological response (SVR) with pegylated interferon and ribavirin combination therapy
- 663: Genotype is less likely to have a sustained virological response (SVR) with pegylated interferon and ribavirin combination therapy
Strategies for implementation of pharmacogenomics

- Rely on physician ordering/education?
- Public education as to the benefits of pharmacogenomics?
- Linking with pharmacy for new orders for warfarin?
- Justify testing based on drug safety and “Defensive” medicine?
- Educate next generation healthcare professionals

UCSF: facing the academic ivory tower syndrome

Pilot 2013 PGx study: Testing of UCSF Pharmacy students

Volunteers sought. Consent form signed. IL28b and other genes tested
Genomic testing at other institutions

- Used 23andMe as testing platform from saliva
- In addition to PGx, tested predisposition towards genetic diseases (BRCA1, apoE, etc).
- Controversial: genetic counseling not mandatory

What is and isn’t pharmacogenomics

- **Is:** Science of understanding the correlation between an individual patient's genotype and their response to drugs. Understanding why some drugs work well in some patients but not in others.
- **Is not:** Testing is not conducted to determine presence of rare or fatal diseases, and will not have an impact on the ability of an individual to get health insurance, job placement or advancement, etc.

Results of BPS 115 volunteers
IL28b/ITPA gene variants

IL28b CC, ITPA deficiency: no worries
Fran, Michael, Robert

FDA approval is based on dosing to meet the masses (wildtype).

Captain Kirk to Spock: “The needs of the many outweigh the needs of the few.”

IL28b/ITPA gene variants

IL28b CT/ITPA no deficiency:
Harry, Sophia, Johnathan, Wuberg

Concerned. Longer duration of therapy (e.g., 48 vs 24 weeks)
IL28b/ITPA gene variants

IL28b: TT: ITPA non-deficient
Janelle, Oscar, Lisa, Diana

Direct antiretroviral drug

Center for Innovation in Interprofessional Education

The top down approach has largely failed.

Bottoms up approach will take longer but may be best in the long run

Proposed pilot study at UCSF for 2015

Medical student  Faculty mentor  Dental student
Today's patient  Pharmacy student
Nursing student  Graduate student
<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Implementation of pharmacogenomic testing for hepatitis C dual therapy was among the most rapidly adopted PGx lab test in history.</td>
</tr>
<tr>
<td>• If direct acting antiviral therapies dominate hepatitis C therapy, the decline of IL28B PGx testing may be equally impressive.</td>
</tr>
</tbody>
</table>

“Pharmacogenetics: Tailoring treatment for the outliers to increase benefit and reduce harm in people whose drug responses are not “average.”


“For PGx, the needs of the few outweigh the needs of the many.”

Wu, 2009.