Personalized Medicine: Translating Genetic Discoveries to Practice

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Disclosures

• NIH grant funding for pharmacogenetics research and pharmacogenetics clinical implementation
• CPIC Steering Committee member
• No relevant industry relationships to disclose
Personalized Medicine

• Use of information about an individual, including their family history, diseases, environmental factors, and genetic information to personalize or individualize care
  - Disease risk prediction
    • Disease prevention strategies
  - Defining disease phenotype
  - Treatment decisions
Human Genome Project: From 2001 to 2013

- Human Genome Project was a large international effort to sequence the human genome
  - Completed in 2001; after 13 years and $2.7B
  - Delivered one “complete” human genome
- Human genome sequencing - 2011
  - Costs $5K to $20K; and takes a couple weeks
- Human genome sequencing - 2012-13
  - Costs < $1K and takes < 1 day
Human Genome Sequencing and Personalized Medicine

• Expected that genetic data will increasingly be available on patients

• Predictions that in the future, a person’s genome sequence will be part of their medical record
  - Discussions about replacing newborn screening with whole genome sequencing

• Available throughout their lifespan to guide:
  - Disease prevention/risk prediction
  - Disease stratification
  - Treatment strategies (pharmacogenomics)

• At core of the concept is the one-time nature of genotyping and pre-emptive availability of genetic information
Key advances in Genomic Medicine/Personalized Medicine

• Pharmacogenetics
  - Genetic variants in pgx tend to have larger effect sizes
  - Variants generally not associated w/disease risk

• Disease stratification/phenotyping
  - Tumor genotyping common in cancer; defines cancer & used to guide treatment

• Whole exome/genome sequencing for rare, unexplained diseases
Barriers to clinical implementation of pharmacogenetics

Knowledge barriers
- Lack of awareness of the pharmacogenetic data
- Uncertainty on interpretation of pgx genetic test result
- Uncertainty on what action to take based on a pgx test result

Logistical/financial barriers
- Remembering when to order a pgx test
- Turn-around time for pharmacogenetic test
- Cost of pharmacogenetic test
- Concerns about lack of reimbursement for pgx test

Evidence barriers
- Lack of randomized controlled clinical trial data documenting benefit of pharmacogenetic guided treatment approach
- “Genetic exceptionalism” for genetic and pharmacogenetic tests
UF & Shands: Personalized Medicine Program

- Clinical program launched June 25, 2012
  - Aim to overcome many of the barriers to clinical use of pharmacogenetic information
  - Leaders in preparing the healthcare system for genomic revolution, including in pathology
    - UF Pathology Laboratory has leadership role in program
  - Early focus on targeting drug therapy to the individual
    - Pilot with clopidogrel and CYP2C19 genotype
  - Eventually will include disease risk prediction, disease stratification
Guiding Principles of UF PMP

• Ultimate goal is pre-emptive genotyping on broad chip
  - Established tests in UF Pathology Labs
• Regulatory body within the health system that defines PMP examples as clinically actionable in institution
  - P&T, PMP Subcommittee
• Must support genotype data with clinical decision support tools
Roles of PMP Subcommittee to Pharmacy & Therapeutics Cmte

- Evaluate literature basis to support a pgx example as “clinically actionable”
- Define genotypes to be utilized within clinical program
  - E.g. what CYP2C19 SNPs to include
- For DMEs, how to collapse genotypes into predicted drug metabolism phenotypes
- Define recommendations for therapeutic approaches (alternatives) based on genotype
Addition of pharmacogenetics examples to PMP

- If a new pgx example is approved by the P&T committee, and
- If genotype data generated under CLIA/CAP standards are available on that patient in clinical genotype repository
- Then genotype will move to EMR following P&T approval of that gene being clinically actionable
Clinical Genotyping

- Program goal for broad chip for pre-emptive purposes
- Evaluated commercially available chips
  - Due to price, content flexibility, ease of use, turn-around time, elected to develop 256 SNP custom array for use on Life Tech Quant Studio Open Array
- Worked closely with PharmGKB to define chip content
- Genotyping done in CLIA/CAP setting by UF Pathology labs
OpenArray® plates on the QuantStudio™ 12K Flex system

- Nanoliter fluidic technology in conjunction with TaqMan® chemistry
- Mid-density, high-throughput workflow
Custom Plate Design

12 Samples X 256 SNPs
-Select from over 4 million pre-validated SNP assays

Move from DNA to Genotype in 5 hours
-One technician could generate over 12,000 genotypes a day

Highly reproducible results
- Sample concordance rates >99.7%

Each through-hole is filled with 38 nL of reagents
Custom pharmacogenetics chip

Implementing Personalized Medicine: Development of a Cost-Effective Customized Pharmacogenetics Genotyping Array

JA Johnson¹,², BM Burkley¹, TY Langae¹, MJ Clare-Salzler³, TE Klein⁴ and RB Altman⁴,⁵,⁶

Includes 256 SNPs from 120 genes, for potential future clinical use

Clin Pharmacol Ther 2012; PMID 22910441
Final custom 256 SNP chip

- Custom 256 SNP panel content was created through collaborations with Stanford
  - SNP selection based on levels of evidence in clinical annotations on PharmGKB

- Specifics of chip:
  - 120 genes, including drug metabolism, drug transporter, drug target, other literature-based genes
  - About $32 per sample or 12¢ per SNP (array costs only, not including labor, costs for test validation and ongoing assay QC etc)

- Unique relative to commercially available chips that others are using
  - Content beyond drug metabolism and drug transporter genes
  - Array costs 1/10th or less that of commercial arrays
  - Can adjust content based on new evidence
  - Faster turn-around time; less hands on technician time
Laboratory medicine intersection with genomic medicine: challenges

• Pathology report for genetic data
  - How to differentiate life-time result in the EMR so it does not “get lost”
  - What to do when the evidence changes/evolves

• Billing
  - Who will pay, for what tests, and how much?
  - How to overcome the current financial barriers/incentives that discourage the cost-effective approach of generating large amounts of data at one time
  - How do Pathology Labs get reimbursed for continuing “interpretation”
  - Issues of billing for a multiplex assay
  - How to cover costs for future SNP validation and QC
UF Personalized Medicine Program: Clopidogrel Pilot

UF delvers 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 [...]

Read More

Clopidogrel (Plavix)

• Antiplatelet drug that prevents blood clots
  - Commonly used post ACS, post PCI, primary or secondary stroke prevention and other indications
  - #3 seller of all drugs in the US ($)
    • $4.7B in 2010
    • 25M prescriptions
Metabolism of Clopidogrel

Clopidogrel

2-Oxo-clopidogrel

SR26334 (inactive)

R-130964 (active)

CYP1A2
CYP2C19
CYP2B6
CYP3A
CYP2C9
CYP2C19
CYP2B6

Mega JL. NEJM 2009;360:354-60
**CYP2C19 and clopidogrel**

- **Common genetic polymorphisms in CYP2C19 that lead to loss of protein function**
  - Poor metabolizers - homozygotes, no functional enzyme; *2*2 - 2-3% of whites; 4% of blacks; 10-25% of Asians
  - Intermediate metabolizers - heterozygotes, $\frac{1}{2}$ normal enzyme function
    - Approximately 25-30% of blacks and whites, 60-70% of Asians

- **Intermediate and poor metabolizers have:**
  - Reduced active metabolite concentrations for clopidogrel
  - Reduced ex-vivo antiplatelet effect
### B Carriers of 1 CYP2C19 Reduced-Function Alleles vs Noncarriers

**CYP2C19 Reduced-Function Alleles, No. of Events/No. of Individuals at Risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>1 Individuals (Risk)</th>
<th>None Individuals (Risk)</th>
<th>Hazard Ratio (95% CI)</th>
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<tr>
<td>CLARITY-TIMI 28</td>
<td>8/73</td>
<td>10/150</td>
<td>1.64 (0.65-4.17)</td>
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<tr>
<td>EXCELSIOR</td>
<td>5/226</td>
<td>7/554</td>
<td>1.75 (0.56-5.53)</td>
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<td>83/1064</td>
<td>1.55 (1.07-2.25)</td>
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<tr>
<td>AFUJI</td>
<td>13/64</td>
<td>11/186</td>
<td>5.42 (2.23-13.18)</td>
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<td>FAST-MI</td>
<td>53/577</td>
<td>193/1573</td>
<td>0.73 (0.54-0.99)</td>
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<tr>
<td>RECLOSE</td>
<td>13/221</td>
<td>14/525</td>
<td>2.25 (1.06-4.78)</td>
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<td>ISAR</td>
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<td>1.25 (0.90-1.73)</td>
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<tr>
<td>CLEAR-PLATELETS</td>
<td>5/63</td>
<td>4/160</td>
<td>3.45 (0.93-12.89)</td>
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<tr>
<td>Intermountain</td>
<td>65/330</td>
<td>141/906</td>
<td>1.29 (0.96-1.73)</td>
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<tr>
<td><strong>Overall</strong></td>
<td>256/2544</td>
<td>582/6923</td>
<td>1.55 (1.11-2.17)</td>
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</tbody>
</table>

**Increased Risk in Noncarriers**

**Increased Risk in Carriers**

**P = .01**

### C Carriers of 2 CYP2C19 Reduced-Function Alleles vs Noncarriers

**CYP2C19 Reduced-Function Alleles, No. of Events/No. of Individuals at Risk**

<table>
<thead>
<tr>
<th>Study</th>
<th>2 Individuals (Risk)</th>
<th>None Individuals (Risk)</th>
<th>Hazard Ratio (95% CI)</th>
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<td>TRITON-TIMI 38</td>
<td>4/38</td>
<td>83/1064</td>
<td>1.35 (0.49-3.69)</td>
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<td>AFUJI</td>
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<td>2.85 (1.07-7.59)</td>
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<td>1.73 (0.83-3.62)</td>
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<td>119/1805</td>
<td>0.96 (0.30-3.04)</td>
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<tr>
<td>CLEAR-PLATELETS</td>
<td>1/5</td>
<td>4/160</td>
<td>14.27 (1.57-129.46)</td>
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<tr>
<td>Intermountain</td>
<td>3/14</td>
<td>141/906</td>
<td>1.41 (0.45-4.41)</td>
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<td><strong>Overall</strong></td>
<td>25/197</td>
<td>565/6219</td>
<td>1.76 (1.24-2.50)</td>
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</table>

**Increased Risk in Noncarriers**

**Increased Risk in Carriers**

**P = .002**

FDA Drug Safety Communication: Reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug

Safety Announcement

Additional Information for Patients

Additional Information for Healthcare Professionals

Data Summary

Safety Announcement

[03-12-2010] The U.S. Food and Drug Administration (FDA) has added a Boxed Warning to the label for Plavix, the anti-blood clotting medication. The Boxed Warning is about patients who do not effectively metabolize the drug (i.e. "poor metabolizers") and therefore may not receive the full benefits of the drug.

The Boxed Warning in the drug label will include information to:

- Warn about reduced effectiveness in patients who are poor metabolizers of Plavix. Poor metabolizers do not effectively convert Plavix to its active form in the body.
- Inform healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.
- Advise healthcare professionals to consider use of other anti-platelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.
UF&Shands
Personalized Medicine Program

• Starting with clopidogrel – pharmacogenetic test order is part of standing order set for left heart catheterization
  - CYP2C19 genotype reported to EMR, independent of use of clopidogrel
  - If actionable genotype and clopidogrel Rx, alert fires to clinician

• Genotype data on broad panel allows information available for future
  - E.g. if patient later gets started on warfarin can use those relevant genetic markers to dose warfarin
PROBLEM
This patient's CYP2C19 genotype is associated with impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for silent 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.

OR IF THE ABOVE ALTERNATIVES ARE CONSIDERED INAPPROPRIATE:

(C) Increase dose of clopidogrel (PLAVIX) to 225 mg daily
   *The increased dose has efficacy on platelet reactivity similar to 75 mg daily in normal metabolizers, but patient outcome data are not available.

More information on clopidogrel and CYP2C19

Last CYP2C19-TIP* on 6/19/2012

Acknowledge Reason: [ ]

- [ ] Open order: Place order for prasugrel (EFFIENT) 10 mg daily. Note: remove order for clopidogrel on next screen.
- [ ] Open order: Place order for ticagrelor (BRILINTA) 90 mg twice daily. Note: remove the clopidogrel order on next screen.
- [ ] Open order: Place clopidogrel (PLAVIX) 225 mg daily. Note: remove the original clopidogrel order on next screen.
- [ ] Open order: Proceed with clopidogrel (PLAVIX) 75 mg daily. Note: please remove the bottom or second clopidogrel order as it will duplicate.
Human clinical decision support: Shands Clinical Pharmacy

• Genotypes for impaired/very impaired patients being routed to clinical pharmacist in-basket
  - If carries an actionable genotype, reviews to see if patient got a PCI
  - If drug therapy not changed, follows-up with interventional cardiologist to discuss making a change

• Important piece since genotype might not be available before patient discharged (in which case BPA does not fire)
Research Program Enrollment – Clopidogrel Pilot

- Research informed consent for:
  - Future movement of “clinically actionable” pharmacogenetic test results into medical record
  - Additional use of genetic data for research in integrated data repository
  - Sample to go to institutional biorepository for future research
  - Recontact for future research
CPIC Guidelines

Tricyclic antidepressants: CYP2D6 & CYP2C19, In press
Summary

• Clinical implementation of pharmacogenetics (and other examples in genomic medicine) is increasingly common

• Clinical implementation in pharmacogenetics requires not only a high level of evidence, but lowering of barriers for clinicians to adopt

• Pathology laboratories play critical role in such program
  - Many issues yet to solve including billing for multiplex testing, costs associated with updating actionable SNPs, SNP validations and assay QC

• UF and other institutions have successfully launched clinical implementation programs in pharmacogenetics and genomic medicine
Questions?
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