Novel Methods to Test Precision (Personalized) Medicine

CCC Forum 2015

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Vanderbilt University Medical Center
Nashville, TN
Organizing framework

<table>
<thead>
<tr>
<th>Personalized Plan of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personalized Prevention</td>
</tr>
<tr>
<td>Risk prediction</td>
</tr>
<tr>
<td>preventative measures</td>
</tr>
<tr>
<td>Personalized Diagnostics</td>
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<tr>
<td>Screening, early</td>
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<tr>
<td>detection, accurate</td>
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<tr>
<td>diagnoses</td>
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<tr>
<td>Personalized Treatment</td>
</tr>
<tr>
<td>Therapy, monitoring</td>
</tr>
<tr>
<td>pain management, life</td>
</tr>
<tr>
<td>plan, palliative care</td>
</tr>
</tbody>
</table>
Evolutionary Plan

We are ~here

SNP Pharmacogenetics
- Concurrent drugs, Comorbidities
  - Social/family hx
  - Allergies

Sequencing/dz susceptibility

psychosocial factors

Much else
It’s time to move forward

• Health System Formularies (BCBS, VUMC)
• Clinical Practice Committee, P&T Committee
• Advanced Informatics with decision support and analytics:
  – StarPanel
  – VOOM with outpt decision support
  – HEO with inpt decision support
  – RxStar with decision support
  – MyhealthatVanderbilt
• Meaningful use improvements
• Leadership unity and national thought leaders
Hand washing
Flu vaccination for all healthcare workers

Equipoise

Discovery
Clinical testing

Translational Space

Early concept of benefit: but not sure when, for whom, how, outcome measures, or potential risks.

Benefits established, learn how to best implement

Quality Improvement
Clinical practice

Active Projects

Risk of:
readmission
pressure ulcers
Chlorhexidine baths
N.S. vs. L.R.
Create Reusable Infrastructure

- Ethics, regulatory and community
- Biomedical informatics and IT infrastructure
- Pharmacogenomics and clinical relevance (evidence synthesis and review)
- Clinical outcomes and health economics
- Implementation/logistics/operations
- Provider and patient communication and education
Vanderbilt Institute for Clinical and Translational Research (VICTR)

*Translational Space between research and clinical operations*

**PREDICT** – Vanderbilt’s initial clinical foray into personalized medicine – prospective genotyping

**MyCancerGenome** – personalized cancer dx, treatment and clinical trials
National Problem

- 5.3% of hospital admissions due to adverse drug reactions
- Adverse drug reactions are 4th-6th leading cause of mortality in the US
- Over 200 drug labels now suggest pharmacogenomic testing to guide therapy – and the FDA has mandated testing for 4 of these (3 are cancer drugs)

Personalized Medicine 8:421, 2011
PREDICT Prognostic Model

- Implemented January 2012
- Predicts probability of patient receiving clopidogrel, a statin, or warfarin within three years based on information contained within a patient’s EMR:
  - Demographics
  - Weight or BMI (where height is available)
  - Hypertension
  - Diabetes
  - Coronary artery disease
  - Atherosclerosis
  - Congestive heart failure
  - Atrial fibrillation
  - Dialysis
  - Previous clot

Schildcrout et al, CPT 2012
A Case for Prospective Genotyping

52,942 Vanderbilt “Medical Home” patients followed for up to 5 years....

How many patients received drug(s) that have a recognized pharmacogenetic story?

Estimated number of severe adverse events mitigated: 383

Schildcrout et al, CPT 2012
The PREDICT panel tests 184 SNPs within 34 genes known to impact drug therapy.

Clopidogrel, simvastatin, warfarin, tacrolimus, and thiopurine gene results are currently available in StarPanel.

Other drug-genome interactions (DGIs) will be added with no need to retest these patients.

Of 14,134 VUMC patients genotyped through PREDICT to date:

- 3,110 (22%) are at risk for reduced antiplatelet effect of clopidogrel
- 3,616 (26%) are at risk for simvastatin-induced myopathy
- 9,748 (69%) would benefit from genotype-guided tailoring of initial warfarin dose
PREDICT implementation requires coordination across multiple domains

In press, Peterson et al., Genetics in Medicine 2013
Pre-Implementation Scientific Review

- Significant association between risk allele and adverse clinical event
- Strength of evidence for drug-gene interaction
- National guidelines from professional societies, FDA, etc.
- Patients identifiable before they receive the drug
- Alternative therapy or alternate strategy available
- Internal validation of established DGI association (if possible)

**Discovery:** Preliminary genetic associations

**BioVU Study:** Identify subjects, phenotype and genotype

**Replication:** Replicate significant associations

**Clinical Implementation:** Implement genetic testing via PREDICT pipeline

- Assessment of genotype data as high quality in CLIA lab
- High prevalence of drug utilization (≥3% of VUMC population)
State of the Evidence: 2013
Clopidogrel - CYP2C19 “Loss of function” variants

• 10 Meta-analyses summarizing hundreds of articles with primary data
  – 6 report an impact on MACE: Major Adverse Coronary Events
  – 4 report no significant impact

• Most recent systematic review:
  Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines 2013 Update*

PREDICT: Phenotype Assignment Algorithm

CYP2C19 - Clopidogrel

*17 = CYP219 Gain of Function Variant

<table>
<thead>
<tr>
<th>CYPC19 Genotype</th>
<th>Drug Metabolism Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(X)/</em>(X)</td>
<td>Poor metabolizer</td>
</tr>
<tr>
<td><em>1/</em>(X)</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>*17/17</td>
<td>Rapid metabolizer</td>
</tr>
<tr>
<td>*(X)/17</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>*1/17</td>
<td>Normal (Extensive) metabolizer</td>
</tr>
<tr>
<td>*1/1</td>
<td>Uncharacterized genotype</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>
**PREDICT: Therapeutic Alternative Algorithm**

- **Normal, Rapid, Indeterminate or Uncharacterized metabolizer?**
  - **CYP2C19 - Clopidogrel**
    - Standard Prescribing Process
  - **Contraindications**
    - Age > 75 years
    - Weight < 60 kg
    - History stroke or TIA
    - Severe Liver Disease
    - Intracranial Bleed
  - **None**
    - Prasugrel (10mg daily)
    - Or Ticagrelor (90 mg 2x daily)
    - Or Clopidogrel (150 mg daily)*
  - **No liver or active bleeding**
    - Ticagrelor (90 mg 2x daily)
  - **Otherwise**
    - Continue Clopidogrel

* Discontinued as Therapeutic Option
PREDICT: Prognostic Model
Identifying Candidates in the EHR

This patient has been identified by the PREDICT system as highly likely to benefit from genetic information obtained from a blood test.

Order the genetic blood test?

Yes. I have or will discuss this test with the patient. (Use Test Panel Code = PDX)

- OOPC (launch manually after Save)
- HEO-full version (launch manually after Save)
- Paper Order (use Lab Requisition form)

No. I will not order the genetic test because:

- Patient declined testing
- I was not able to discuss the test with the patient
- Genetic tests have already been performed

This patient has a calculated risk score of 86% which means the patient is a good candidate for the PREDICT genetic test.

The risk score is the probability that a patient will begin clopidogrel, simvastatin, or warfarin therapy within 3 years; the algorithm is based on demographic variables and relevant past medical history (e.g., hypertension, diabetes, coronary disease, dialysis, atrial fibrillation, atherosclerosis, congestive heart failure, and other conditions).
Personalized Medicine

Each person responds differently to medicines. Your genes play a role in how you respond to medicines. Many factors, including your genes, are used to choose the right medicine and dose for you. Based on your history, your provider has ordered a test to learn more about which drugs are right for you. Having this information can help predict and prevent bad drug side effects.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Does your genetic test result affect your response to medicines?</th>
<th>Show more?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel/Plavix®</td>
<td>Yes</td>
<td>Show more &gt;</td>
</tr>
<tr>
<td>Simvastatin/Zocor®</td>
<td>No</td>
<td>Show more &gt;</td>
</tr>
<tr>
<td>Tacrolimus/Prograf®</td>
<td>No</td>
<td>Show more &gt;</td>
</tr>
<tr>
<td>Thiopurine Therapy</td>
<td>No</td>
<td>Show more &gt;</td>
</tr>
<tr>
<td>Warfarin/Goumadin®</td>
<td>Yes</td>
<td>Show more &gt;</td>
</tr>
</tbody>
</table>

Drug-Genome Interaction w/patient-Friendly text
Validation of Clopidogrel-CYP2C19 Interaction in BioVU

VUMC validation: 96% of cases are post-PCI

Kaplan–Meier survival estimates for CYP2C19*2

Log rank test
P value = 0.005

Normal Metabolizer
Poor or Intermediate Metabolizer

Delaney, JT  Clin Pharmacol Ther  2012 91:257
Prognostic and Pathogenetic Value of Combining Clinical and Biochemical Indices in Patients With Acute Lung Injury

Lorraine B. Ware, MD, FCCP; Tatsuki Koyama PhD; D. Dean Billheimer, PhD; William Wu, PhD; Gordon R. Bernard, MD, FCCP; B. Taylor Thompson, MD; Roy G. Brower MD; Theodore J. Standiford, MD; Thomas R. Martin, MD; Michael A. Matthay, MD, FCCP; and the NHLBI ARDS Clinical Trials Network*

Clinical Markers:
- Age
- Etiology
- APACHE III
- Pplat
- No. organ failures
- A-a gradient

Biomarkers:
- ICAM
- IL-6
- IL-8
- TNFR
- Protein C
- PAI-1
- SP-D
- VWF

Ware et al CHEST 2010; 137(2):288–296
AUC Calculations for Various Models
Ware et al CHEST 2010; 137(2):288–296
Optimizing pain management in the ICU

Words used to describe the experience of being intubated:

<table>
<thead>
<tr>
<th>Torture</th>
<th>Agitated</th>
<th>Constantly fighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misery</td>
<td>Panic</td>
<td>Angry</td>
</tr>
<tr>
<td>Pain</td>
<td>Uncomfortable</td>
<td>Hurt</td>
</tr>
<tr>
<td>Choking</td>
<td>Unhappy</td>
<td>Aggravated</td>
</tr>
<tr>
<td>Gasping</td>
<td>Scared</td>
<td>Wore out</td>
</tr>
<tr>
<td>Drowning</td>
<td>Gagging</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Horrific</td>
<td>Frustrated</td>
<td>Ripping</td>
</tr>
</tbody>
</table>

“Pain management was the key issue in each patient’s lived experience.”

PREDICT: CYP2D6 and pain management

Are we underestimating pain management needs in CYP2D6 PMs?

A 2013 study of 121 post-operative patients given oxycodone 0.05 mg/kg before emerging from anesthesia and patient-controlled analgesia (PCA) for the subsequent 48 postoperative hours suggests that CYP2D6 PMs require higher oxycodone doses for adequate analgesia.

My Cancer Genome

Mia Levy, MD, PhD
William Pao, MD
Vanderbilt University Medical Center
Mission of My Cancer Genome

To curate and disseminate knowledge regarding the clinical significance of genomic alterations in cancer
Worldwide Collaboration

- 65 Contributors
- 21 Institutions
- 10 Countries
Thank You!
PREDICT Results in Patient Web Portal
My Health at Vanderbilt

Drug-Genome Interaction w/patient-friendly text

<table>
<thead>
<tr>
<th>4Q09</th>
<th>1Q10</th>
<th>2Q10</th>
<th>3Q10</th>
<th>4Q10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ethics/regulatory/community</strong></td>
<td>Assess ethical landscape/determine ethical challenges</td>
<td>Determine options for genotyping as part of routine care</td>
<td>Research execution and legal authorization</td>
<td>Create patient notification mechanisms</td>
</tr>
<tr>
<td><strong>Bioinformatics and IT infrastructure</strong></td>
<td>Identify EMR-derived, drug outcome phenotypes and incorporate information into decision support</td>
<td>Outpatient Rx system and inpatient order system preparation for logic/rules engine</td>
<td>Development/testing of new decision support logic, integration with existing systems/order sets</td>
<td>Clinical information systems move to production</td>
</tr>
<tr>
<td><strong>Pharmacogenomics and clinical relevance</strong></td>
<td>Validate genetic-based drug outcome phenotypes in the patient population and model relative contributions to clinical event prediction</td>
<td>Create/implement genomic evidence review procedures and committee to assess additive value of genotypes in AE prediction and strength of the evidence</td>
<td>Select initial SNP panel and obtain P&amp;T approval</td>
<td>Initial SNP finalization: move to pt care</td>
</tr>
<tr>
<td><strong>Clinical outcomes and health economics</strong></td>
<td>Determine desired process and outcomes measures for each drug–gene interaction</td>
<td>Implement mechanisms to capture the impact of genetic information on drug ordering</td>
<td>Health-care outcomes study design</td>
<td>Determine cost-effectiveness study needs</td>
</tr>
<tr>
<td><strong>Implementation/logistics/operations</strong></td>
<td>Patient stratification and selection for testing</td>
<td>Develop long-range plan for genotyping and compliant procedures for blood sample collection</td>
<td>CLIA-approved laboratory location prepared and equipment acquired/installed</td>
<td>Identification of initial pt pop: implementation of consent and collection procedures</td>
</tr>
<tr>
<td><strong>Provider and patient communication and education</strong></td>
<td>Determine awareness and education levels/gaps for various audiences</td>
<td>Create and test printed educational material for patients and evidence synthesis for providers</td>
<td>Go-live announcement</td>
<td></td>
</tr>
</tbody>
</table>
K-means cluster analysis (heat map) and gene ontologies of leukocytes when exvivo whole blood is stimulated with either lipopolysaccharide (LPS) or heat-killed Staphylococcus aureus (SAC).

Down-regulated by LPS and SAC

Up-regulated by LPS; down-regulated by SAC (n = 155 genes)

Up-regulated by LPS and SAC

Up-regulated by SAC; down-regulated by LPS (n = 208 genes)


© 2005 by the Infectious Diseases Society of America
Presymptomatic Prediction of Sepsis in Intensive Care Unit Patients

R. A. Lukaszewski,1* A. M. Yates,1 M. C. Jackson,1 K. Swingler,2 J. M. Scherer,1 A. J. Simpson,1 P. Sadler,3 P. McQuillan,3 R. W. Titball,5 T. J. G. Brooks,4 and M. J. Pearce1

92 Patients included

Blood samples taken daily

Clinical analysis
Real time RT-PCR

Last sample on day of diagnosis or last day of stay in ICU

No sepsis
67 patients

25 confirmed sepsis
(SEPSIS GROUP)

22 age-matched to sepsis patient
(NON SEPSIS ICU CONTROLS)

45 non-age-matched patients (RT-PCR data not included)

FIG. 1. Summary of the study design.
Presymptomatic Prediction of Sepsis in Intensive Care Unit Patients

% Average Predictive Accuracy

<table>
<thead>
<tr>
<th></th>
<th>Input parameters for network</th>
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<tbody>
<tr>
<td>Cytokines</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
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</tbody>
</table>

* p < 0.05
Clinical relevance of SNPs coding for HMGB1 in patients with major trauma

<table>
<thead>
<tr>
<th>Haplotype (TCG)*</th>
<th>N</th>
<th>ISS</th>
<th>Sepsis, n (%)</th>
<th>MODS score</th>
<th>HMGB1 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 TOG</td>
<td>55</td>
<td>28 ± 10</td>
<td>29 (52)</td>
<td>7.3 ± 3.3</td>
<td>217 ± 98</td>
</tr>
<tr>
<td>1 TOG</td>
<td>303</td>
<td>25 ± 8</td>
<td>105 (35)</td>
<td>6.0 ± 2.6</td>
<td>178 ± 78</td>
</tr>
<tr>
<td>2 TOG</td>
<td>197</td>
<td>25 ± 8</td>
<td>77 (39)</td>
<td>5.7 ± 2.5</td>
<td>161 ± 48</td>
</tr>
</tbody>
</table>

* 3 SNPs seem to act as “tag” SNPs for the entire HMGB1 gene

Zeng et al Surgery 2012; 151:427-36
**PheWAS plot: Estrogen Receptor - 1**

**Validations:**
- Irregular menstrual cycle/bleeding
- Disorders of menstruation and other abnormal bleeding from female genital tract
- Delay in sexual development and puberty NEC
- Noninflammatory disorders of vagina
- Dysmenorrhea
- Fibrosclerosis of breast
- Irregular menstrual bleeding

**Novel associations:**
- Systemic inflammatory response syndrome (SIRS)
- Dependence on respirator [Ventilator] or supplemental oxygen
- Acute and subacute necrosis of liver
- Shock
- Cardiac arrest and ventricular fibrillation
- Sepsis