Pharmocogenetics, Clinical Avatars and Predictions of Personalized Medicine

Progress on a 2009 ARRA EUREKA Award
Method and model development
Exploratory simulations and analysis
Preliminary results

Peter J. Tonellato
Laboratory for Personalized Medicine
Center For Biomedical Informatics
Harvard Medical School

National Library of Medicine
Nov 2009
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A Biomedical Informatics Perspective:
- A Few Preliminaries
  - ‘Square peg in a round hole’
  - Modified approach to ‘translational’ research
  - Platform for translational research
- Method and Clinical Avatars
- Tools and Preliminary Results
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Square Peg – Round Hole
Pharmacogenetic POC

- Anticoagulant drug with narrow therapeutic window
- Used in wide array of conditions → diverse patient population
- Individualized prescription
- Requires careful patient monitoring
  - Patient’s International Normalized Ratio (INR) instrumental in maintaining therapeutic Warfarin dose
  - Genetic markers used to determine which patients are predisposed to slower or faster than ‘normal’ Warfarin absorption rates
Background

• Highly effective and commonly prescribed anticoagulant
  – 2 million warfarin users annually
  – 30 Million prescriptions annually
• One of the most common causes of serious adverse drug reaction (ADR)
• CYP2C9 and VKORC1 genotypes account for up to 60% of the variability in dose recommendations
  – Over 50% of dose variance attributed to personal health profile factors including genetic, gender, age, ethnicity, race, weight/height, and current drug regimen factors
  – Nomograph modifications emerging – Currently seven actively recruiting studies registered in clinicaltrials.gov (Florida, Intermountain, Hadassah, National Taiwan, Creighton, Brigham and Womens, Marshfield)
  – Brian Gage, Wash U., indicates as few as 40 patients can be used to modify algorithm (warfarindosing.org), personal communication with Matt Tector.

• *If all warfarin patients’ dosage adjusted to genotype*:
  – 85,000 bleeding events avoided
  – 17,000 strokes avoided
  – Results in $1.1 Billion health care costs savings

Pharmacogenomic Labeling

August 16, 2007 – “In Milestone, FDA Pushes Genetic Tests Tied to Drug …

warfarin’s label will carry new information describing the role of genetics in dosing. The label will say that a lower initial warfarin dose ‘should be considered for patients with certain genetic variations.’”

- The Wall Street Journal

“This information will benefit patients because it will describe why patients with a variation in the CYP2C9 and/or VKORC1 genes may need a lower warfarin dose than patients with the usual forms of these genes.”

- U.S. Food and Drug Administration
Risk prediction

Pharmacogenomics

New Therapies

From - Personalized Medicine – How the Human Genome Era Will Usher in a Healthcare Revolution
Francis S. Collins, M.D., Ph.D., Director, NHGRI
February 10, 2005
Alert

Evaluate appropriate warfarin dosage. Patient at increased risk to warfarin complications

Patient Status

CYP2C9*2 HET
CYP2C9*3 HET

Standard of Care

Today’s Algorithm:
Patient’s estimated initial warfarin dose:
??.? mg / day

Pharmacogenetic Summary: Warfarin Translational Study
No associated genotyping data available for this subject.

Utilization Status

# CHF Hospital Stays (past 12 months) : 0
# CHF ER Visits (past 12 months) : 0
# Outpatient Visits (past 12 months) : 5

# Hospital Stays (past 12 months) : 0
# ER Visits (past 12 months) : 0
# Comorbid Conditions : 5

Past Medical History

Arrhythmias
Atrial Fibrillation and Flutter
Hypertension

Arrhythmias or Blocks - Ventricular
Depression
Thyroid Disease
Wisconsin Demonstration Project:
Optimized Warfarin Dosing with Genetic-Based Predictive Dose Algorithms

Aurora Health Care Patient Totals

Electronic data available for over 3,000,000 patients

Warfarin Usage

<table>
<thead>
<tr>
<th>Aurora Warfarin Usage Summary</th>
<th>2006</th>
<th>2007</th>
</tr>
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<tbody>
<tr>
<td># of Patients by:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin Usage</td>
<td>Actual</td>
<td>Est.</td>
</tr>
<tr>
<td></td>
<td>25,000</td>
<td></td>
</tr>
<tr>
<td>Warfarin Usage &amp; Stroke</td>
<td>1,500</td>
<td></td>
</tr>
<tr>
<td>Warfarin Usage &amp; Thrombotic Event</td>
<td>3,000</td>
<td>4,000</td>
</tr>
<tr>
<td>Evidence of Warfarin Usage &amp; INR &gt; 3.0</td>
<td>10,000</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

Estimated values extrapolated based on analysis of sampled data.
* 2007 Actual values through Aug. Est. values adjust for entire year.
Gender matched age distribution
Difficult to capture longitudinal complexity of dosing (analysis ongoing)
49% of patients seen by 100 Physicians
High percentage of patients related to orthopedics
Orthopedics focus in early rollout
Wisconsin Demonstration Project: Optimized Warfarin Dosing with Genetic-Based Predictive Dose Algorithms

Project was not approved:

- Healthcare practice remained skeptical – insufficient evidence that gene testing and algorithms were sufficiently valuable

- Educational issues with healthcare staff – what are genotypes?

- Technology was premature and ‘square peg’ like compared to best practice devices.

- Access to and quality of EMR data problems.

- A level of patient reluctance

- Cost
Round holes arise in clinical setting
Square Pegs derived from basic research
Translation emerges from Commercial R&D and Regulatory Approval process followed by clinical implementation
Translational Research
Platform for Translational Research

Objective: Create low cost, low administrative footprint Computational Center under typical “academic” and current technical and resource constraints:

- Tremendous Project diversity (scientific, complexity and computationally)
- Multiple project sites
- Multiple US and non-US collaborative project teams
- Diversity of IT experience
- Varying levels of project team access/ resource control
- Limited Resources: Time, AWS services, Administration

Focus: Research objective

IT issues are considered distractions.
Cloud Computing

Amazon Web Services (AWS)

User Application
Linux Server
Amazon EC2 Instances
Oracle AMI
Amazon S3
HPC AMI

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Participants in the ‘Clouded Translational Research’ seminar will conduct a series of exercises in biomedical discovery and translational science using cloud computing technology. Participants represent Harvard, Children’s Hospital of Boston, Brigham and Women’s Hospital, Beth Israel Hospital, Massachusetts General, the Broad Institute, two University of Wisconsin campuses (Madison and Milwaukee) and the Tokyo Medical and Dental University and will learn about and implement databases, analysis tools and web application development environments using the Amazon cloud computing environment – AWS (aws.amazon.com/).


pa·lav·er

/pə ləvər, - ləvər/ noun

1. long parley usually between persons of different cultures or levels of sophistication
2. conference, discussion
3. idle talk
4. misleading or beguiling speech
LPM Project Breakdown/ Categories

**LPM Inelastic**
- Clinical Avatars Project Development
- i2b2 AMI Development
- Clinicalpedia

**LPM Managed Elastic**
- Clinical Avatars Web Deployment
- i2b2 Federated Queries
- NGS RNA Algorithm Testing

**LPM Elastic**
- RoundUp
- SNP/Array/proteomic pipelines
- NGS Individualized Whole Genome Mapping

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Best Practice Cloud Management

Projects → Decision Criteria

AWS/RightScale Main Account

Project Deployment
Server Configuration
SSH Key Pair

RightScale Sub Account
Project Deployment
Server Configuration
RightScale SSH

Inelastic
Managed Elastic
Elastic

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Best Practice Components

- Method to ‘break down’ and categorize projects
- Process to allocate and monitor resources
- Scripts to control applications
  - Shutdown
  - ’cold’ storage (AMI)
  - GITHUB: basecode, database, data, shutdown/startup
  - ‘hot’ start
- Method for coordinating project tasks/activity
- Methods (evolving) for porting ‘highly’ elastic applications.
Clouded Translational Research

Clinical Enterprise

Research Enterprise

Translation

Simulations and Predictions

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Clouded Translational Research

Clinical Enterprise

Research Enterprise

Translation: Clinical

Translation: Research

Simulations and Predictions

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Warfarin Pharmacogenetic Modeling

Method: V 1.0

- **Statistical Characterization**
- **Phenomenological Stochastic Model**
  - Use Avatar Data to Predict Therapeutic Dose
  - Analyze Results
  - Interpretation of Simulation

- **Analysis and Interpretation of Avatar Population**
  - Instantiation of Clinical Avatar Population

- **Adjustment of the Model**
Algorithms – Gage Model

Dose = exp[0.9751 \times v(y) + (0.4317 \times BSA) - 0.4008 \times c_3(y) -
(0.00745 \times \text{age}) - 0.2066 \times c_2(y) + (0.2029 \times \text{target INR}) - (0.2538
\times \text{Amiodarone use}) + (0.0922 \times \text{Smokes}) - (0.0901 \times \text{African-American race})
+ (0.0664 \times \text{DVT/PE})]

\begin{align*}
  v(y) &= \begin{cases} 
  0 & \text{if VKORC1 -1639 genotype = G/G} \\
  1 & \text{if VKORC1 -1639 genotype = G/A} \\
  2 & \text{if VKORC1 -1639 genotype = A/A}
\end{cases} \\
  c_2(y) &= \begin{cases} 
  0 & \text{if CYP2C9*2 genotype = C/C} \\
  1 & \text{if CYP2C9*2 genotype = C/T} \\
  2 & \text{if CYP2C9*2 genotype = T/T}
\end{cases} \\
  c_3(y) &= \begin{cases} 
  0 & \text{if CYP2C9*3 genotype = A/A} \\
  1 & \text{if CYP2C9*3 genotype = A/C} \\
  2 & \text{if CYP2C9*3 genotype = C/C}
\end{cases}
\end{align*}

Amiodarone use: 
1 if taking, 0 otherwise

African-American race: 
1 if AA, 0 otherwise

Smokes: 1 if yes

DVT/PE: 1 if present

Algorithms – Anderson Model

Dose = 1.64 + exp[3.984 + c(x) + v(x) + g(x) - age*(0.009) + weight*(0.003)]

\[
\begin{align*}
\{ & 0 \quad \text{if genotype } = \text{CYP2C9}\star1/\star1 \\
& -0.197 \quad \text{if genotype } = \text{CYP2C9}\star1/\star2 \\
c(x) &= \{ -0.360 \quad \text{if genotype } = \text{CYP2C9}\star1/\star3 \\
& -0.947 \quad \text{if genotype } = \text{CYP2C9}\star2/\star3 \\
& -0.265 \quad \text{if genotype } = \text{CYP2C9}\star2/\star2 \\
& -1.892 \quad \text{if genotype } = \text{CYP2C9}\star3/\star3
\end{align*}
\]

\[
\begin{align*}
\{ & 0 \quad \text{if VKORC1 1173 genotype } = \text{C/C} \\
v(x) &= \{ -0.304 \quad \text{if VKORC1 1173 genotype } = \text{C/T} \\
& -0.569 \quad \text{if VKORC1 1173 genotype } = \text{T/T}
\end{align*}
\]

\[
\begin{align*}
g(x) &= \{ 0 \quad \text{if gender } = \text{female} \\
& 0.094 \quad \text{if gender } = \text{male}
\end{align*}
\]

# Clinical Avatars (Model data set structure)

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>18 to 24 (21.1%), 25 to 44 (30.3%), 45 to 64 (21.9%), 65 to 94 (26.7%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male {&lt; 18 (51.26%), 18 to 24 (51.11%), 25 to 44 (50.06%), 45 to 64 (48.65%), 65 and over (41.18%)}; Female {&lt; 18 (48.74%), 18 to 24 (48.89%), 25 to 44 (49.94%), 45 to 64 (51.35%), 65 and over (58.82%)}</td>
</tr>
<tr>
<td>Race</td>
<td>White (75.1%), African American (12.3%), Native American (0.9%), Asian (3.6%), Pacific Islander (0.1%), Other (5.5%), Unknown (2.5%)</td>
</tr>
<tr>
<td>Height</td>
<td>Mean: 69.2”, St.D: 6.6”, Min : 56.0”, Max: 82.4”</td>
</tr>
<tr>
<td>Weight</td>
<td>Mean: 189.8 lb, St.D: 59.1 lb, Min: 71.6 lb, Max : 308.0 lb</td>
</tr>
<tr>
<td>Smoker</td>
<td>White - 20%; African American - 21%; Native American - 35%; Asian / Pacific Islander - 11%; Other - 23%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Y - 55%, N - 45%</td>
</tr>
<tr>
<td>DVT</td>
<td>Y - 26.8% N - 73.2%</td>
</tr>
<tr>
<td>VKORC1</td>
<td>A/A - 65%, A/B - 20%, B/B - 15%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*1 - 64.3%, *1/*2 - 18%, *1/*3 - 11.7% , *2/*2 - 2% , *2/*3 - 2.1% , *3/*3 - 0.25%</td>
</tr>
</tbody>
</table>

The clinical avatar population and the resulting variables and statistical distributions.
Simulated Patient Populations

• Created to reflect actual population-wide and individual demographic, clinical, and laboratory characterizations
• Rapid simulation analysis of a wide selection of patient population scenarios
• Simulations produce predictive evidence
• Evidence suggests most informative studies/trials.
<table>
<thead>
<tr>
<th>PHI</th>
<th>First Name: Ozzy</th>
<th>CYP2C9: *1/*1</th>
<th>VKORC1: A/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Height: 6’</td>
<td>Weight: 160</td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>CYP2C9: *1/*1</td>
<td>VKORC1: A/A</td>
<td></td>
</tr>
<tr>
<td>PHI</td>
<td>First Name: Animal</td>
<td>CYP2C9: *3/*3</td>
<td>VKORC1: A/B</td>
</tr>
<tr>
<td>Physical</td>
<td>Height: 6’ 6”</td>
<td>Weight: 180</td>
<td></td>
</tr>
<tr>
<td>Genetic</td>
<td>CYP2C9: *3/*3</td>
<td>VKORC1: A/B</td>
<td></td>
</tr>
</tbody>
</table>
The i2b2 use Map.
i2b2 workbench screenshot with:
Warfarin specialty-focused ontology (top left, red box).
Query including genetic criteria (top middle, green box).
Number of patient ‘avatars’ (middle right, red arrow).
Selection of avatars that meet the criteria and one avatar’s amiodarone usage timeframe (bottom center, green arrow).
Three Age Structured CA Populations (I2B2 SHRINE Test)

Clinical avatar populations were simulated for three i2b2 cells, each with a population of 10,000 avatars.

Each cell contains different distributions of Age (blue columns), Gender, Race, Genotype, BMI, Smoker, Amiodarone Use, etc.
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• Methods, Tools and Preliminary Results
### Listing Clinical Avatars

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>CYP2C9</th>
<th>VKORC1</th>
<th>BSA</th>
<th>DVT</th>
<th>Height</th>
<th>Smoker</th>
<th>Target INR</th>
<th>Weight</th>
<th>Amiodarone</th>
<th>Gage Dose</th>
<th>Anderson Dose</th>
<th>WSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>86</td>
<td>M</td>
<td>African-American</td>
<td>2/2</td>
<td>A/B</td>
<td>1.7</td>
<td>N</td>
<td>67</td>
<td>Y</td>
<td>2.5</td>
<td>139</td>
<td>N</td>
<td>2.3</td>
<td>2.9</td>
<td>0.547852</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>Asian</td>
<td>I/3</td>
<td>A/B</td>
<td>1.9</td>
<td>N</td>
<td>65</td>
<td>Y</td>
<td>2.5</td>
<td>170</td>
<td>N</td>
<td>4.1</td>
<td>3.8</td>
<td>0.35013</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>White</td>
<td>I/2</td>
<td>A/B</td>
<td>2.2</td>
<td>N</td>
<td>69</td>
<td>Y</td>
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<tr>
<td>17</td>
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<td>I/1</td>
<td>B/B</td>
<td>2.1</td>
<td>Y</td>
<td>73</td>
<td>N</td>
<td>2.5</td>
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<td>N</td>
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<td>67</td>
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<td>N</td>
<td>71</td>
<td>N</td>
<td>2.5</td>
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<td>4.7</td>
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<td>A/A</td>
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<td>N</td>
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<td>N</td>
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<td>161</td>
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<td>B/B</td>
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<td>16</td>
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<td>A/B</td>
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<td>Y</td>
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<td>2.5</td>
<td>155</td>
<td>N</td>
<td>6.6</td>
<td>6.9</td>
<td>0.185245</td>
</tr>
</tbody>
</table>

Generate Avatar Population/Doses/Charts
Analysis of Change in Dose due to Genotypic Variation (Gage Model)
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<table>
<thead>
<tr>
<th>Age</th>
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<td>0.547852</td>
<td>Show</td>
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<td>36</td>
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| « Previous | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | ... | 66 | 67 | Next » |

Generate Avatar Population/Doses/Charts
Progress (Y1 Q1) and Next Steps

• LPM Warfarin Web App Available
• 1 - 100 Million clinical avatar populations and dosing simulations
• Platform supports clinical trial simulation, incidentalome testing, and exploration of metrics for clinical efficacy and outcome
• Exploration of Warfarin ‘Sensitive’ patients

Next Steps
• Improve C.A. population model
• Warfarin PK/PD incorporated into simulation model
• Extend C.A. data model to EMR format
• Consider and test design of clinical trials
• Consider comparative effectiveness simulations
Y1 Q1 Results

NLM Eureka, 1 R01 LM010130-01

All project personnel hired.

New Jobs 3.0
Saved Jobs 2.0

Project partially completed (<50%)

Peer reviewed results appeared in open source publication, Oct, 2009:
www.recovery.gov
   Click on Massachusetts
      Click on Congressional District 8
         Click on Academic
            Click on Harvard Medical School
               Click on CBMI
                  Click on LPM
Warfarin Pharmacogenetic Modeling
Method: V 1.+

1. Statistical Characterization
   → Phenomenological Stochastic Model
   → Use Avatar Data to Predict Therapeutic Dose
   → Interpretation of Simulation
   ← Adjustment of the Model
   ← Instantiate Clinical Avatar Population

2. Analysis and Interpretation of Avatar Population
   ← Analyze Results

National Library of Medicine
Nov 2009
Y1 Q2

- LPM Warfarin Web App Available
- 1 - 100 Million clinical avatar populations and dosing simulations
- Platform supports clinical trial simulation, incidentalome testing, and exploration of metrics for clinical efficacy and outcome
- Exploration of Warfarin ‘Sensitive’ patients

Next Steps

- **Improve C.A. population model**
- **Warfarin PK/PD incorporated into simulation model**
- **Extend C.A. data model to EMR format**
- Consider and test design of clinical trials
- Consider comparative effectiveness simulations
Program Milestones:

- Established Clouded Translational Research Platform
- Refined a TR Methodology
- Created Tools:
  - Clinical Avatar Simulator
  - Pharmacogenetic Predictive Modeling Simulator
- Pharmacogenetics Test Case: Warfarin Dosing
- Method and Clinical Avatars
- Preliminary Studies and Results
Wisconsin Demonstration Project:
Optimized Warfarin Dosing with Genetic-Based Predictive Dose Algorithms

Project was not approved:

• Healthcare practice remained skeptical – insufficient evidence that gene testing and algorithms were sufficiently valuable

• Educational issues with healthcare staff – what are genotypes?

• Technology was premature and ‘square peg’ like compared to best practice devices.

• Insufficient patient buy-in

• Access to and quality of EMR data problems.

• Cost
Personalized Medicine: Scientific and Policy Challenges:

1. Push sequencing technology to achieve wide availability of the $1000 genome within the next 5 years
2. Make sure that “meaningful use” in health IT includes genomic information
3. Identify additional environmental contributions to common disease
4. Implement a better system for oversight of genetic tests
5. Conduct rigorous PGx studies on multiple drugs
6. Widen the translational pipeline
7. Promote rigorous health economics research to assess value of personalized medicine
8. Develop a process to shorten dramatically the time from evidence generation to practice change
Acknowledgements

Laboratory for Personalized Medicine

Vincent Fusaro*
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Rimma Pivovarov*
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Dan Chen
Haiping Xia
Sumana Ramayanam
Kumiko Oohashi

Wall Lab:
Dennis Wall*
Parul Kudtarkar*
Mike Banos*
Tom Monaghan

Amazon:
Kurt Messersmith
Tenesha Gleason
Peter Sirova

*NLM Eureka, 1 R01 LM010130-01
National Library of Medicine
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