Pharmacogenomics based personalized medicine: Are the standards of evidence requirements different from standards for Clinical-Based Personalized Medicine?

Devender S. Dhanda MS MBA,
Greg F. Guzauskas MPH PhD, David L. Veenstra PharmD PhD
Pharmaceutical Outcomes Research and Policy Program
University of Washington, Seattle, WA, USA
Personalized Medicine: Will There be a Right Time to Implement?

- Over 140 US FDA approved drugs have PGx information on labels
- Up to 50% of drugs under development – associated biomarker program\(^2\)
- Fewer than 10% of drugs will be launched with companion diagnostics – potential risks for PGx evidence generation & reimbursement bottlenecks\(^2\)
- Issue more prominent for germline variations used to inform usage of existing off-patent drugs – ownership of evidence generation issues
- Drugs – pathways of evidence generation and reimbursement systems
- Pharmacogenomics Tests – uncertainty regarding level of evidence and who is responsible for evidence generation

Personalized Medicine: Will There be a Right Time to Implement?

• Genomics information similar to other medical/health information

• EGAPP working group – 6 out of 8 evaluations have “insufficient evidence” ³

• Clinicians/consumers/policy makers frustrated and still have to make decisions based on insufficient evidence ¹

• **Should we defer** the decision-making in clinical practice until sufficient evidence - may take decades (Khoury et al) and millions of dollars? ²

Pharmacogenomics = “Insufficient evidence”? ⁴

Warfarin Case study

• Widely prescribed for prevention of thromboembolic events
• Narrow therapeutic index
• Up to 20-fold inter-individual dose variation
  – Partly due to gene variations in CYP2C9 and VKORC1
  – difficult to determine the exact dose
• Under dosing – Thrombo-embolic events (TEs)
• Overdosing – Bleed events
• Interacts with more than 800 drugs
  – Interaction with Amiodarone due to inhibition of CYP2C9
  – Amiodarone increases the levels of warfarin resulting in bleed events
Warfarin Case Study: A Tale of Two Scenarios

Pharmacogenomic Scenario

- Exposure = CYP2C9 and VKORC1 gene variants
- Recommendation – Insufficient evidence

DDI Scenario

- Exposure = Amiodarone (CYP2C9 inhibitor)
- Recommendation – Standard of care

The 8th American Academy of Chest physicians (ACCP) Guidelines state, “…without evidence from randomized trials, we suggest against the use of pharmacogenetics-based initial dosing.”

The ACCP Guidelines state, “…in patients who are taking medications known to increase sensitivity to warfarin (e.g., amiodarone), we recommend the use of a starting dose <5mg.”

3 Antithrombotic and Thrombolytic Therapy, 8th Ed : ACCP Guidelines: ANTITHROMBOTIC AND THROMBOLYTIC THERAPY, 8TH ED: ACCP GUIDELINES | June 2008
Value of Information (VOI) Analysis: Uncertainty Estimation for Evidence Levels

• VOI is a reflection of current evidence in a decision problem as well as the value of collecting future evidence

• We propose to utilize VOI to quantitatively estimate the evidence levels given the current uncertainty in the PGx and DDI evidence for warfarin (EVPI as an indicator of uncertainty)

• **Objective:** To quantitatively compare the evidence levels of a PGx–based scenario to its analogous clinical based scenario utilizing the VOI analysis.
Markov models for PGx and DDI

Cumulative meta-analysis of PGx dosing and W+A DDI

VOI analysis – EVPI and EVPPI based on cumulative meta-analysis
Two Markov Models – PGx and DDI

- Both the models are analogous
- **Difference in inputs** - RR-Bleed, RR-Clot, and cost of amiodarone and cost of PGx test
Cumulative Meta-analysis DDI Approach (Major Hemorrhage)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Cumulative statistics</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower limit</td>
<td>Upper limit</td>
</tr>
<tr>
<td>Zhang et al 2006</td>
<td>0.352</td>
<td>3.120</td>
</tr>
<tr>
<td>Vitry et al 2011</td>
<td>1.625</td>
<td>3.805</td>
</tr>
<tr>
<td>Lam et al 2013</td>
<td>1.793</td>
<td>3.582</td>
</tr>
</tbody>
</table>

Studies included for the cumulative meta-analysis of warfarin-amiodarone DDI model

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al 2013</td>
<td>Patients 65 years and older on 6 months or more on warfarin. (60,497 patients with warfarin usage)</td>
<td>Hospitalization for hemorrhage.</td>
<td>aHR – 2.45 (1.49-4.02)</td>
</tr>
<tr>
<td>Vitry et al 2011</td>
<td>Patients 65 years and older (17,661 patients with warfarin usage)</td>
<td>Bleeding related hospitalization</td>
<td>aRR-3.33 (1.38-8.00)</td>
</tr>
<tr>
<td>Zhang et al 2006</td>
<td>Caremark enrolled members (17,895 patient used warfarin)</td>
<td>Minor or major hemorrhage</td>
<td>aOR- 0.98 (0.83, 1.16)</td>
</tr>
</tbody>
</table>
Per Patient EVPI for Warfarin PGx $100K WTP

- **PGx Test Cost - $175**

- **Huang et al and Caraco et al**

- **Burmester et al**

- **Kimmel et al & Jonas et al.**

- **Verhoef et al, Pirmohammed et al**

**Calender Year**

- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015

**Per Patient EVPI**

- $0
- $250
- $500
- $750
- $1,000
- $1,250
- $1,500
- $1,750

**Log Scale (RR Bleed) from Cumulative Meta-analysis**
Expected Value of Partial Perfect Information (EVPPI) for PGx and DDI

EVPPI for PGx and W+A DDI Models

- RR Bleeding: PGx = $36, DDI = $99
- RR stroke: PGx = $68, DDI = $118
- Total EVPI: PGx = $142, DDI = $215
Comparison of Patient Level EVPI at $100K WTP for Different Warfarin PGx Test Costs

<table>
<thead>
<tr>
<th>PGx Test Cost</th>
<th>Patient Level EVPI at $100K WTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 Test</td>
<td>$107</td>
</tr>
<tr>
<td>$50 Test</td>
<td>$119</td>
</tr>
<tr>
<td>$100 Test</td>
<td>$130</td>
</tr>
<tr>
<td>$175 Test</td>
<td>$142</td>
</tr>
<tr>
<td>$250 Test</td>
<td>$159</td>
</tr>
</tbody>
</table>
Conclusions

• The evidence levels for warfarin pharmacogenomics and warfarin-amiodarone DDI appear to be similar
  ▪ The value of perfect information is higher for DDI because of greater uncertainty in the stroke risk due to dose reduction of warfarin
  ▪ The value of perfect information is higher for higher PGx test cost
  ▪ Main contributors of uncertainty for both PGx and DDI – bleed and stroke risk

• Our findings suggest that policies for implementation of pharmacogenomics-based testing should be comparable to the DDI-based clinical decisions, which is not the case currently in both clinical and reimbursement guidelines
Acknowledgements

• Personalized Medicine Economics Research (PriMER) grant
• Dr. David Veenstra PharmD, PhD
• Dr. Anirban Basu PhD
• Dr. Josh Carlson MPH, PhD
• Greg Guzauskas MPH, PhD
APPENDIX
SLIDES
Probability of Making Optimal Decision

Probability of making optimal decision of DR vs No DR of Warfarin (DDI Model) and PGx vs Std Dosing of warfarin (PGx Model) at $100K WTP - by Calendar Year

PGx Test cost - $175
Probability of Making Optimal Decision Decreases with Higher PGx Test Cost

Probability of Making an Optimal Decision at Different Test Cost

- DDI (L+V)
- $250 Test
- $175 Test (Current)
- $100 Test
- $50 Test
- $25 Test
- $0 Test

Legend:
- WTP $150K
- WTP $100K
- WTP $50K
<table>
<thead>
<tr>
<th>PGx Scenario</th>
<th>Drug-drug Interaction (DDI) Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical situation</strong></td>
<td>Warfarin to be initiated</td>
</tr>
<tr>
<td><strong>Exposure</strong></td>
<td>$CYP2C9$ and $VKORC1$ variants</td>
</tr>
<tr>
<td><strong>Bleed Risk</strong></td>
<td>$2.26 (1.36, 3.75)^6$</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>PGx dosing</td>
</tr>
<tr>
<td><strong>Tx. Effect</strong></td>
<td>$0.60 (0.29, 1.22)$</td>
</tr>
<tr>
<td><strong>Evidence Level</strong></td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>
Per Patient EVPI with Time for Warfarin PGx $100K WTP

- Warfarin PGx EVPI - Current test cost ($175)
- PGx EVPI Test Cost $0
- PGx EVPI Test Cost $250
CYP2C9 and VKORC1 Variants (PGx Model)

Amiodarone (DDI Model)

Inactivated Clotting Factors

Active Clotting Factors

Inactive metabolites

CYP2C9

Oxidized Vitamin K

Reduced Vitamin K

VKORC1 Carboxylase

Warfarin (S)

Warfarin (R)

CYP1A1

CYP1A2

CYP3A4