Challenges Associated with Implementing Pharmacogenomics into Clinical Practice

Experience From the INGENIOUS Trial

Kenneth Levy, PhD, MBA
Adjunct Associate Professor of Medicine
Division of Clinical Pharmacology
Indiana University School of Medicine

Why is PGx Testing Important?
Drug Related Adverse Events Impact Patient Care and the Cost of Healthcare

- Rx related AEs cost the US healthcare system ~$136B/YR
- 6-7% of hospitalizations due to Rx related AEs.
- ADRs cause 1 out of 5 injuries or deaths per year to hospitalized patients.
- AEs cause ~100,000 deaths/year (4th leading cause of death).
- >2.2 million serious adverse reactions/year.
- Mean length of stay, cost and mortality for ADR patients are DOUBLE that for control patients.

INGENIOUS (INdiana GENomics Implementation: an Opportunity for the UnderServed)

PI's: Paul Dexter, MD Todd Skaar, PhD

The INGENIOUS trial (NCT02297126) is sponsored by an NIH/NHGRI U01-grant (HG007762)

INGENIOUS Overview

Collaboration:
- Indiana University School of Medicine
- Eskenazi Health System
- Indiana University Institute for Personalized Medicine
- Regenstrief Institute

Study Scope:
- 2,000 patients in study arm
- 4,000 patients in control arm

Study Aims:
Aim 1: To test the hypothesis that a CLIA certified genotyping targeted at 28 widely used drugs is associated with significant reductions in hospital and outpatient costs incurred over a one year period
Aim 2: To test whether pharmacogenetic testing is associated with significant improvements in clinical outcomes over a one year period

INGENIOUS PGx Study

16 genes and 51 variants validated on custom open array in IU’s CLIA certified pharmacogenetics laboratory

<table>
<thead>
<tr>
<th>Genes</th>
<th>Variants Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB1</td>
<td>6</td>
</tr>
<tr>
<td>ABCC4</td>
<td>1</td>
</tr>
<tr>
<td>CP2B6</td>
<td>2</td>
</tr>
<tr>
<td>CP2C9</td>
<td>6</td>
</tr>
<tr>
<td>CP2C19</td>
<td>6</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>13</td>
</tr>
<tr>
<td>OPRM1</td>
<td>3</td>
</tr>
<tr>
<td>OPR4E2</td>
<td>1</td>
</tr>
<tr>
<td>DPD</td>
<td>2</td>
</tr>
<tr>
<td>G6PD</td>
<td>2</td>
</tr>
<tr>
<td>HLA-B</td>
<td>1</td>
</tr>
<tr>
<td>IL28B</td>
<td>1</td>
</tr>
<tr>
<td>ITPA</td>
<td>1</td>
</tr>
<tr>
<td>SLC10A1</td>
<td>2</td>
</tr>
<tr>
<td>TPMT</td>
<td>3</td>
</tr>
<tr>
<td>WDR25</td>
<td>1</td>
</tr>
</tbody>
</table>
### INGENIOUS PGx 27 Targeted Drug List

<table>
<thead>
<tr>
<th>Medication</th>
<th>Genotype/Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptiline</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Codeine</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Pantoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Rasburicase</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>5-Fluorouracil</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Mercaptopurine</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nortriptyline</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Pantoprazole</td>
</tr>
</tbody>
</table>

### INGENIOUS Work Flow

1. **Patient Consented**
2. **Blood Draw/Saliva**
   - **Sample Transported to PGx Lab**
   - **Remaining Sample to IU Biobank**
   - **Sample Analyzed and Results into EMR/CDS**
   - **PGx Reports and Clinical Alerts in EMR**
   - **PGx Consult if requested**

### INGENIOUS PGx Report

**Pharmacogenomic Alert!**

- **This patient has pharmacogenomic information that may impact this prescription**
- **Medication:** Clopidogrel
- **Gene(s) involved:** CYP2C19
- **Phenotype:** Poor Metabolizer
- **Recommendation:** Consider an alternative antplatelet therapy, e.g. prasugrel, or ticagrelor. This patient’s poor metabolizer status predicts poor clopidogrel efficacy.
- **Level of Evidence:** Strong

**Variant Tested:**

- **CYP2C19**

**Interpretation:** This variant predicts that the patient has a *CYP2C19* phenotype and is likely to benefit from a reduced warfarin dose. Physicians should consider adjusting the patient’s warfarin dose accordingly. No additional therapy recommendations are necessary in this case.

**PGx EMR Alerts**

*Created by Clinical Decision Support Rules*

**INGENIOUS PGx Report**

*Page 1*

**Sample Tested:** 

- **Test Name:** Pharmacogenomics Panel

**Results:**

- **CYP2C19**: Normal Metabolizer
- **CYP2C19**: Normal Metabolizer
- **CYP2C19**: Normal Metabolizer
- **CYP2C19**: Normal Metabolizer

**INTERPRETATION:** This variant does not have any known pharmacogenomic effects.

**INGENIOUS PGx Report**

*Page 2*

**Genotype/Phenotype Results**

- **Variant Tested:** CYP2C19

**INGENIOUS PGx Report**

*Page 3 (CLIA Requirements)*

**Genotype/Phenotype Results**

- **Variant Tested:** CYP2C19
PGx lab forwards abnormal results to Adjudication Committee. INGENIOUS co-investigator and Fellow pull medication list from EMR and presents to Consult Committee.

Abnormal genotype data (based on CPIC) entered into G3 problem list via MD Fellow (manually Phase I/IT in phases 2 and 3).

Phone Consult with Clinical Pharmacologists
Written consult request through U01 consult committee
Inpatient consult scheduled at MDC through IUH

Key Challenges to PGx Adoption
As identified by IGNITE Common Measures Working Group Analysis

• Lack of reimbursement for many genomic tests
• Few FDA approved or cleared PGx tests
• Lack of Provider knowledge and Education
• Lack of Patient understanding and Education
• EMR systems lacking PGx results entry or reporting
• CDS systems do not support PGx decision making and reporting
• Lack of clinical data supporting benefits of PGx
• Clinician concerns on liability associated with genomic incidentalomes
• Concerns regarding FDA LDT enforcement

How to Address the Challenges
It Starts with Stakeholder Alignment

• Senior Executive leadership (CEO/President, CMO, CFO, Chief Legal Officer and CIO)
• Senior Clinical leadership (clinical divisions, nursing and pharmacy)
• Pathology services
• Clinical staff
• P&T committee
• Third party payers
• Patient advocates (community awareness)

Implementation Team Structure
Many Healthcare Systems Don’t Practice Good Implementation Science

Adminstrative and Marketing Alignment
Legal/Reg Committee
Finance Committee
Informatics Committee
Marketing/PR Committee

Clinical and Technical Alignment
P&T Committee
Clinical Staff
Lab Services
Education Committee

Core Project Leadership Team

Genomic Implementation
Requires Integrations with the Electronic Medical Record and Clinical Decision and Support Systems

EMR is the key to a successful program

• Short-term solution
  ▪ Driven by Informatics Committee
  ▪ Functional specifications require input from stakeholders
  ▪ Lead time – planning, coding, implementing and testing
  ▪ Prioritization (internal and vendor) and funding
  ▪ Data input and data mining critical
  ▪ User defined flexibility (change friendly)

• Long-term Solution
  ▪ EMR systems programming to address genomic medicine
  ▪ Development of standardized CDS algorithms for genomics
Staff Education
It takes time to change clinical practice

Clinical Training:
• Critical for short and long-term sustainability
• Physician, Nursing and Pharmacy teams
• Pre and post-implementation survey (what went well and what can be improved)
• Training and re-training (consider turnover)
• CME/CE (Industry support?)
• Adoption of Clinical Pharmacology into Medical School curriculum

Patient Education
Demystify genetics

Supporting Patient Ownership:
• Alignment of patient education tools and how to deliver (clinical teams)
• Patient education tools must simplify the concept of pharmacogenomics
• Educated patients are associated with better outcomes

Sustainability
In the end, sustainability may boil down to cost justification
Measuring cost effectiveness a challenging task

Hard versus Soft Costs:
• Out of pocket costs (capital and variable costs are straight forward measures
• Ability to capture and quantify Adverse Events
• Compare your adverse event rates (prevalence) to national averages
• Benchmark costs per Adverse Event
• Analyze accuracy of adverse event recording
• Quantifying soft costs takes time (must plan for it)

Technology Adoption Takes Time
Studies providing evidence for improved patient outcomes drive publications and fuel educational programs

National Practice Guidelines
Define Standard of Care
Effectiveness of Pharmacogenomics must be supported by Evidence Based Medicine. Guidelines define requirements and make recommendation for their usefulness in clinical practice

Changing the Standards of Care
Establishing the medical evidence

Defining
Establishing
Creating

Medical intended use
Evidence based Medicine
Spreading the message


Clinical Pharmacogenomics

Conclusions:
• Pharmacogenomic medicine is a powerful tool to inform drug selection and clinical decision-making
• Demonstrated potential to improve efficacy and safety of medications
• As more clinical data emerges and genotyping costs fall, there will be increasing utilization and presence in clinical medicine
• Changes in standards of care take time

Are We There Yet?

“Are we there yet?”
Not Quite, we must continue to align academic research and the IVD industry to expedite adoption of new technology

Questions?