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.

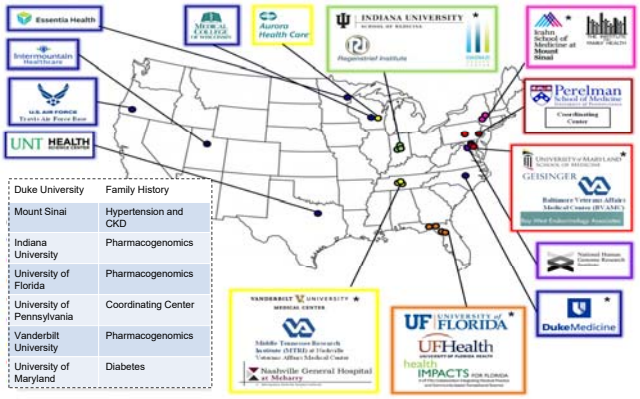
INGENIOUS (INdiana GENomics Implementation: an Opportunity for the UnderServed)

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

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

IGNITE NETWORK

Duke, Indiana, Mount Sinai, Univ. of Florida, Univ. Maryland and Vanderbilt



Duke University	Family History
Mount Sinai	Hypertension and CKD
Indiana University	Pharmacogenomics
University of Florida	Pharmacogenomics
University of Pennsylvania	Coordinating Center
Vanderbilt University	Pharmacogenomics
University of Maryland	Diabetes

INGenious Overview

INGenious

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 51variants validated on custom open array in IU's CLIA certified pharmacogenetics laboratory

Genes	Variants Tested
ABCC2	6
ABCC4	1
CYP2B6	2
CYP2C19	6
CYP2C9	6
CYP2D6	13
CYP3A5	3
CYP4F2	1
DPYD	2
G6PD	2
HLA-B	1
IL28B	1
ITPA	1
SLCO1B1	2
TPMT	3
VKORC1	1

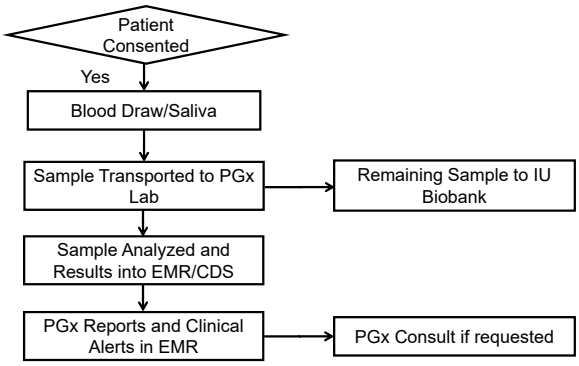
INDIANA UNIVERSITY SCHOOL OF MEDICINE

INGENIOUS PGx 27 Targeted Drug List

- Amitryptyline
- Aripiprazole
- Atomoxetine
- Azathioprine
- Capcitabine
- Citalopram
- Clopidogrel
- Codeine
- Doxepin
- Efavirenz
- Escitalopram
- Esomeprazole
- 5-Fluorouracil
- Lansoprazole
- Mercaptopurine
- Nortriptyline
- Omeprazole
- Pantoprazole
- Phenytoin
- Rasburicase
- Simvastatin
- Tacrolimus
- Thioguanine
- Tramadol
- Venlafaxine
- Voriconazole
- Warfarin

INGENIOUS Work Flow

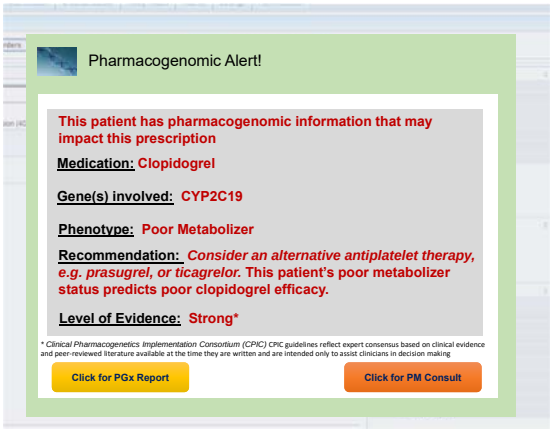
INDIANA UNIVERSITY SCHOOL OF MEDICINE



PGx EMR Alerts

Created by Clinical Decision Support Rules

INDIANA UNIVERSITY SCHOOL OF MEDICINE



INGENIOUS PGx Report

Page 1

INDIANA UNIVERSITY SCHOOL OF MEDICINE

The Pharmacogenomics Laboratory
Indiana University School of Medicine
975 W. Walnut St.
Indianapolis IN 46202
(317) 274-0143
CLIA # 15D0647198 • CAP# 1678930

Patient Name:	XXXXXX XXXXXX	Date of Report:	~~12/16/2015~~
MRN:	1232456789	Drugs of Concern	warfarin
ID number:	PGX12-3456		
DOB:	11/11/1940		
Gender:	FEMALE		
Ordering Physician:			
Specimen:	Whole blood (EDTA)		
Date of Collection:	12/16/2015		
Date of Receipt:	12/16/2015		

Test Name: Pharmacogenomics Panel

Results: **See Table**

CYP2C9	*1/*3	Reduced/Intermediate Metabolizer
VKORC1	G/G	Normal Metabolizer
CYP4F2	*1/*3	Reduced/Intermediate Metabolizer

INTERPRETATION
This result predicts that this individual has a reduced function phenotype and is likely to benefit from a reduced warfarin dose. Dosing recommendations may need to be modified by other clinical factors (eg, age, weight, concurrent medications, and liver disease). Standard INR monitoring is still required.

INGENIOUS PGx Report

Page 2

INDIANA UNIVERSITY SCHOOL OF MEDICINE

INTERPRETATION
This result predicts that this individual has a reduced function phenotype and is likely to benefit from a reduced warfarin dose. Dosing recommendations may need to be modified by other clinical factors (eg, age, weight, concurrent medications, and liver disease). Standard INR monitoring is still required.

COMPLETE PANEL RESULTS

Gene	Result	Predicted Metabolizer Status*
TPMT	*1/*1	Normal Metabolizer
CYP2C19	*1/*17	Rapid Metabolizer
SLCO1B1	*1/*1	Normal Metabolizer
CYP2C9	*1/*3	Reduced/Intermediate Metabolizer
VKORC1	G/G	Normal Metabolizer
CYP2D6	*1/*9	Normal Metabolizer
CYP3A5	*3/*3	Poor Metabolizer
CYP3A4	*1/*22	Reduced/Intermediate Metabolizer
CYP2B6	*1/*1	Normal Metabolizer
ITPA	C/C	Normal Metabolizer
DPYD	*1/*1	Normal Metabolizer
CYP4F2	*1/*3	Reduced/Intermediate Metabolizer
G6PD	No variant detected	Normal Metabolizer
IFNL3 (IL28B)	C/T	Reduced/Intermediate Metabolizer

Genotype/Phenotype Results

Interpretation:
Note this individual is a poor metabolizer for CYP3A5. *3/*3 (poor metabolizer) is the most common genotype in the Caucasian population on which most CYP3A5 drug dosing is based.

This report was reviewed and approved by:
V.M. Pratt, Ph.D., FACMG
Director, Pharmacogenomics Laboratory
22 December 2015
Date

INGENIOUS PGx Report

Page 3 (CLIA Requirements)

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Supplemental Information:
Refer to https://www.pharmgkb.org for any drug dosing recommendations. For additional information, please consult with a clinical pharmacology professional to discuss drug and dose selection. Clinical pharmacology or personalized medicine consultative services are available. Call either 317-844-5000 (Inpatient) or 317-274-2810 (Outpatient).
*The predicted metabolizer status is based on genotype alone. Variants not detected by the assay and non-genetic factors can affect metabolizer status.
**The presence of a non-functional allele in combination with a functional allele (intermediate/reduced metabolizer) should be interpreted with caution.

Methodology: Genotyping of the genes and variants listed below was performed by using polymerase chain reaction (PCR) and Taqman® allele discrimination in a custom designed microarray. Copy number for CYP2D6 was performed using the delta delta Ct method.

VARIANTS TESTED:
CYP2B6*6 (c.516G>T), CYP2B6*18 (c.983T>C)
CYP2C9*2 (c.430C>T), CYP2C9*3 (c.1075A>C), CYP2C9*5 (c.1080C>G)
CYP2C9*6 (c.818delA), CYP2C9*8 (c.449G>A), CYP2C9*11 (c.1003C>)
CYP2C19*2 (c.681G>A), CYP2C19*3 (c.636G>A), CYP2C19*4 (c.1A>G)
CYP2C19*6 (c.395G>A), CYP2C19*8 (c.358T>C), CYP2C19*17 (g.-806C>T)
CYP2D6*2 (c.2850C>T and c.4180G>C), CYP2D6*3 (c.2549delA)
CYP2D6*4 (c.1846G>A and c.100C>T), CYP2D6*5 (gene deletion)
CYP2D6*6 (c.1707delT), CYP2D6*10 (c.2851A>C),
CYP2D6*9 (c.2615_2617delAAG), CYP2D6*10 (c.100C>T and c.4180G>C)
CYP2D6*11 (c.1023C>T), CYP2D6*29 (c.3183G>A), CYP2D6*41 (c.2988G>A)
CYP2D6*13N (duplication), CYP2D6*2XN (c.2850C>T, c.4180G>C, duplication)
CYP2D6*4XN (c.1846G>A, c.100C>T, duplication)
CYP1A4*2 (c.-3713T>C), CYP1A4*22 (c.15588C>T), CYP1A5*3 (c.6986A>G)
CYP1A5*8 (c.14690G>A), CYP1A5*7 (c.2713_2713insT)
CYP4F2*3 (c.1800G>A)
DPYD*2 (c.1905+1G>A), DPYD*9 (c.85T>C)
G6PD "A-" (c.202G>A/c.376A>G), G6PD "A" (c.376A>G)
INFL3 rs12979860 (g.39738T>C)
ITPA rs1127354 (c.94C>A)
SLCO1B1*5 (c.521T>C), SLCO1B1*17 (c.-11187G>A and c.521T>C), SLCO1B1*21 (c.-11187G>A)
TPMT *3 (c.460G>A and c.719A>G)
VKORC1 c.-1639G>A (rs9923231)

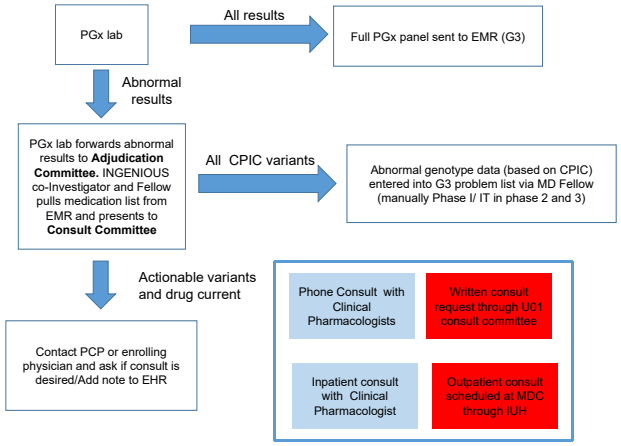
Variants Tested

Analytical sensitivity**: 99% (95% CI 90%-100% when compared against reference method).
Analytical specificity**: 99% (95% CI 94%-100% when compared against reference method).
Limitations: Only the targeted variants will be detected. Mutations or variants in other genes will not be detected. Although rare, false positive or false negative results may occur. All results should be interpreted in context of clinical findings, relevant history, and other laboratory data.

This test was developed and its performance characteristics determined by Indiana University Pharmacogenomics Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. This test is used for clinical purposes. It should not be regarded as investigational or for research. The laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88) as qualified to perform high complexity clinical laboratory testing.

Medical Director: Gail H. Vance, M.D.

INGENIOUS Consult Workflow



The Tug-of-War

for Technology Adoption and Changes to Standards of Care

Researchers, Educators and Clinicians

Payers, Administrators and Regulators

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[1]
- Third party payers
- Patient advocates (community awareness)

[1]*ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System*

Implementation Team Structure

Many Healthcare Systems Don't Practice Good Implementation Science

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[1]

[1] Risk Manag Healthc Policy. 2010;3:61-72. doi: 10.2147/RMHP.S7500. Epub 2010 Oct 14

Sustainability

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

Hard versus Soft Costs:

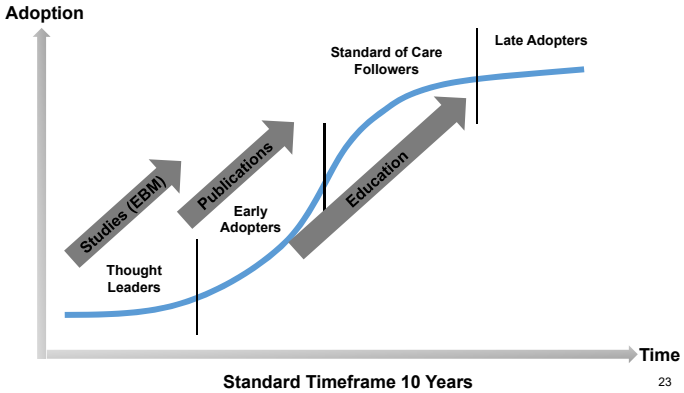
- Out of pocket costs (capital and variable costs are straight forward measures
- Ability to capture and quantify Adverse Events
- Compare your adverse event rates (prevalence) to national averages
- Benchmark costs per Adverse Event
- Analyze accuracy of adverse event recording
- Quantifying soft costs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

Changing the Standards of Care

Establishing the medical evidence

Technology Adoption Takes Time

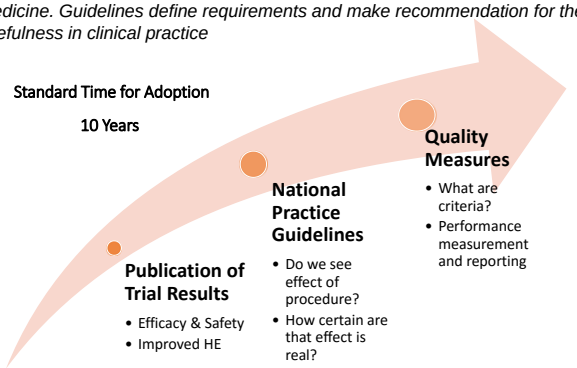
Studies providing evidence for improved patient outcomes drive publications and fuel educational programs



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



Clinical Pharmacogenomics

INDIANA UNIVERSITY SCHOOL OF MEDICINE

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?

INDIANA UNIVERSITY SCHOOL OF MEDICINE

"Are we there yet?"

Not Quite, we must continue to align academic research and the IVD industry to expedite adoption of new technology

INDIANA UNIVERSITY SCHOOL OF MEDICINE

Questions?