“Indiana Genomics Implementation Opportunity for the Underserved”

Todd Skaar, Ph.D.

Associate Professor
Indiana University Dept of Medicine
Division of Clinical Pharmacology

Duke Center for Applied Genomics and Precision Medicine
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**Indiana Genomics Implementation Opportunity for the Under Served**

Acronym: InGenIOUS funded by NHGRI-IGNITE

Testing the effect of pharmacogenetics genotyping on health care costs in an under served population.

Endpoints:
- Total health care costs from EHR
- Adverse events
- Eskenazi & IU Health patients randomized to
  - >1,300 genotype guided therapy
  - >3,100 standard of care
Role of cytochrome P450s in drug metabolism

Major mechanism of elimination for half of the 200 most commonly prescribed drugs.

Can activate or inactivate drugs.

FDA requires screening for metabolism and drug interactions

Genetic variants do same as PK drug interactions

Voluntary submission of PGx data
FDA suggests voluntary testing

Guidance for Industry
Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

OMB Control Number 0910-0557
Expiration Date: 05/31/2014
See additional PRA statement in section VIII of this guidance
(Note: PRA information added 07/29/2011)
The FDA has highlighted pharmacogenomic biomarker information in >100 drugs.

Includes:
Expression of drug target
Genetic variant affecting:
  • Targets
  • Drug disposition (metabolism, transport)
  • HLA
Role of CYPs in drug metabolism

Despite effort to avoid CYP metabolism in drug development, they are still a major route of elimination in newly approved drug.

Cerny 2016, Drug Metab Disp 44:1246
## Drugs and genes included in InGenIOUS

<table>
<thead>
<tr>
<th>Clinical Drug Targets (24)</th>
<th>Gene</th>
<th>Alleles</th>
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<tbody>
<tr>
<td>azathioprine*, mercaptopurine*, thioguanine*</td>
<td>TPMT</td>
<td>*2, *3, *4</td>
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<tr>
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<td>CYP4F2</td>
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<th>Clinical Drug Targets</th>
<th>Gene</th>
<th>Alleles</th>
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<td>HLA-B</td>
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<td>5-fluorouracil*</td>
<td>DPYD</td>
<td>*2A, *9A</td>
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<td>dapson*, rasburicase*, tenofovir*</td>
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<td>tenofovir*</td>
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InGenIOUS Genotyping

51 SNPs in 16 genes

Genotyping assays:

Instrument: QuantStudio (Life Technologies, Inc)

Genotyping using OpenArrays™ (TaqMan assays)

Copy number variations (CYP2D6) (TaqMan assays) using 96-well plates

Accurate, flexible (sample number, changing assays, data output), good throughput, simple workflow

CLIA approved, CAP certified
INGENIOUS Enrollment

Recruiting from 192+ clinical sites utilizing in-person and on-line methods collecting blood or saliva for genotyping

Enrollment 4/1/2015 to 4/10/2018

18,603 Alerts Received

1,273 Genotyped Arm

3,068 Control Arm

14,262 Randomized, pending, unable to reach or declined

Eskenazi Health System
(4/1/2015 to present)

• 1 Hospital location
• 70+ in and outpatient sites
• Phone recruitment
• In-person enrollment

Indiana University Health System
(2/1/2017 to Present)

• 14 of 16 Hospital locations
• 122 outpatient clinics
• Phone recruitment
• On-line enrollment
INGENIOUS Monthly Enrollment

INGENIOUS Enrollment History and Projections
Through March, 2018

- Genotyped Actual
- Genotyped Projected
- Control Actual
- Control Projected
- Enrolled but failed genotyping

Time periods from April 2015 to June 2018 are shown on the x-axis.
Y-axis ranges from 0 to 3500.
INGENIOUS Monthly Enrollment

INGENIOUS Enrollment History and Projections
Through March, 2018

- Genotyped Actual
- Genotyped Projected
- Control Actual
- Control Projected
- Enrolled but failed genotyping
On average the enrollment success rate of enrollment at IUH is 3 times greater than at Eskenazi Health.
For each subject enrolled in the study, RAs must contact ~ 5 times the number of potential candidates when recruiting from Eskenazi vs. IUH
### INGENIOUS Race Distribution

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<thead>
<tr>
<th>Race</th>
<th>Number</th>
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<td>More than one race</td>
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<tr>
<td>Asian</td>
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<tr>
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<tr>
<td>Native Hawaii/Pacific Islander</td>
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</tr>
<tr>
<td>Total</td>
<td>4495</td>
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Geographic distribution of Indiana MUA/P’s

- 90-98% of patients in IU’s EHR systems are ethnically/racially identified.
- > 83% are Geo-Coded so those in Medically underserved areas and populations (MUA/P’s) can be identified.
- ~ 42% of IUH/Eskenazi patients reside in MUA/P’s that are served by inpatient and outpatient facilities.
INGENIOUS patients in MUA/P’s

- 65% of Eskenazi and 31.5% of IUH INGENIOUS subjects are from medically underserved areas.
1,313 Subjects Genotyped Since 4/1/2015

INGENIOUS Actionable Result Report Through 4/10/2018

- 67% of 878 subjects had no actionable results.
- 33% of 435 subjects had actionable results.

4% (16) actionable results referred to consult committee.

Each actionable result is reviewed by the Clinical Pharmacology Adjudication Committee.
INGENIOUS Enrollment Analysis

- 1,313 subjects genotyped
- 33.1% of subjects genotyped had an actionable result
- Actionable genotype frequency varied significantly by medication
- All actionable genotypes reviewed by adjudication committee

<table>
<thead>
<tr>
<th>Drug</th>
<th># subjects</th>
<th>Actionable</th>
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<tr>
<td>Escitalopram</td>
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<td>42</td>
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<tr>
<td>Amitriptyline</td>
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<td>68</td>
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<tr>
<td>Codeine</td>
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<tr>
<td>Nortriptyline</td>
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<tr>
<td>Omeprazole</td>
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<tr>
<td>Pantoprazole</td>
<td>81</td>
<td>20</td>
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<tr>
<td>Clopidogrel</td>
<td>78</td>
<td>29</td>
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<tr>
<td>Citalopram</td>
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<td>28</td>
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<tr>
<td>Venlafaxine</td>
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<td>34</td>
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<tr>
<td>Aripiprazole</td>
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<td>10</td>
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<tr>
<td>Warfarin</td>
<td>36</td>
<td>14</td>
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<tr>
<td>Esomeprazole</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>Simvastatin</td>
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<td>7</td>
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<tr>
<td>Doxepin</td>
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<td>7</td>
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<tr>
<td>Capecitabine</td>
<td>13</td>
<td>1</td>
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<tr>
<td>Atomoxetine</td>
<td>11</td>
<td>3</td>
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</table>
**INGENIOUS Enrollment Analysis**

- 1,313 subjects genotyped
- 33.1% of subjects genotyped had an actionable result
- Actionable genotype frequency varied significantly by medication
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<table>
<thead>
<tr>
<th>Trigger medication</th>
<th>Trigger Medication Count</th>
<th>Actionable Genotype</th>
<th>Actionable Percent</th>
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<tr>
<td>Efavirenz</td>
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<tr>
<td>Venlafaxine</td>
<td>76</td>
<td>34</td>
<td>44.7%</td>
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<tr>
<td>tramadol</td>
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<td>42.5%</td>
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<td>Warfarin</td>
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<td>Esomeprazole</td>
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<tr>
<td>Clopidogrel</td>
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<td>37.2%</td>
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<td>35.9%</td>
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<tr>
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<tr>
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<td>42</td>
<td>31.6%</td>
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<tr>
<td>Atomoxetine</td>
<td>11</td>
<td>3</td>
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</tr>
<tr>
<td>Pantoprazole</td>
<td>81</td>
<td>20</td>
<td>24.7%</td>
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<tr>
<td>Phenytoin</td>
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<tr>
<td>Aripiprazole</td>
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<tr>
<td>Codeine</td>
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<td>14.0%</td>
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<tr>
<td>Nortriptyline</td>
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<td>9.1%</td>
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<tr>
<td>Capecitabine</td>
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<td>Voriconazole</td>
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<td>Fluorouracil</td>
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<tr>
<td><strong>1313</strong></td>
<td><strong>435</strong></td>
<td></td>
<td><strong>33.1%</strong></td>
</tr>
</tbody>
</table>
Early analysis:
Analysis of how actionable CYP2D6 genotype alters tramadol therapy

• **Scope:**
  – 37 genotyped subjects who received new prescription for tramadol
  – Subjects were enrolled/genotyped and completed at least 1 year follow-up
  – Case review completed for all subjects

• **Measurements:**
  – Discontinuation of tramadol
  – Tramadol dose changed, or
  – An alternate opioid prescribed

• **Results:**
  – 15 of 25 (60%) subjects without actionable genotype had some form of therapy change
  – 11 of 12 (92%) of the subjects with actionable genotype had some form of therapy change
Early analysis of tramadol patients:

• Participants who had actionable genotypes were more likely to:
  o Have tramadol or codeine discontinued (p = 0.03);
  o An alternative opioid prescribed within 90 days (p = 0.02)
• Participants less likely to experience constipation (p = 0.04)
• There was no significant difference between actionable and non-actionable genotypes for:
  o Medication dose changes (p = 0.29);
  o Medication refills (p = 0.21);
  o NSAIDS prescribed (p=0.68);
  o Sedation (p = 0.23);
  o Uncontrolled pain (p = 0.60); and
  o DDI (p = 0.71)
• Reduced metabolizers (AS .05 +DDI) were more likely to experience uncontrolled pain (p = .04).
• While not statistically significant, reduced metabolizers were more likely to have their trigger medication discontinued and a NSAID prescribed when compared to all other metabolizers
INGENIOUS Adverse Drug Reaction Analysis:
Status update for data collection

**Test medication list:** clopidogrel, tramadol

**Identify appropriate clinical conditions (search terms) and related ICD-9/10 codes:**

**Select test patient population (subjects completing study)**

Interrogate INPC database for ICD9/10 code listings

Apply ADR Causality using standardized approaches (i.e. Naranjo or Liverpool)

Utilize Regenstrief nDEPTH NLP capability to search test subjects medical records

Collect data and analyze for final approach
Pharmaco-genetic-economic research requires an interdisciplinary approach

Informaticians (Regenstrief, CCBB)

Economists (IUSPH)

Geneticists (IIPM, IUSM, IUSON)
INGENIOUS Health Economic Analysis: Approach and status

Process:
• Eskenazi for process design and testing
• Random selection of 20 subjects
• Collect 24 months of data (12 mo. pre and 12 mo. post)
• Identify billing bundles: pharmacy, hoteling, laboratory, department/procedures and provider charges
• Generate report
• Analyze
• Finalize process and expand to IUH

Results:
• Charges, not costs are reported
• Provider billing gathered and integrated into db separately
• Data volume massive: 7,700 rows of data for 20 subjects
• Charge data over-estimates revenue (reimbursement quite different from what is charged)
• Charge data will differ from one healthcare system to another
What economics-related questions CAN be answered?

Data limitations: most studies in the U.S. rely on readily available administrative data that do not include costs of:

- ICD-9/10, CPT, or HCPCS codes often reflect what is needed to receive reimbursement and, therefore, do not provide the most accurate and complete description of the event
- Consequently, it is not always easy to determine genetic-related events based on CPT or ICD9/10 codes
What economics-related questions CAN be answered?

Modeling limitations: most models consider the average impact of singular genetic tests and do not consider:

- Interactions
- Co-morbidities
- Polypharmacy

EMR data often does not include data after discharging, thus costs, such as long term rehabilitation, are often difficult to capture.

Gene A x Gene B = ?
Published cost utility analyses of personalized medicine tests

n = 59 CUAs of personalized medicine tests

n = 1,385 CUAs of pharmaceuticals.

39% of studies examined tests for somatic mutations versus germline mutations.

Phillips et al, 2014; Genetics in Medicine
Genetic tests on the market

Total of >75,000 tests on the market, 14,000 new ones in the last 4 years
What research tools do we need?

1. Models for economic analysis of precision medicine that address:
   a. All aspects of the costs of precision medicine
   b. Patient variables, such as comorbidities, socioeconomic factors, and race
   c. Cost sensitivity analyses to identify major determinants that impact cost and outcomes

2. Methods for extracting phenotypes from EHRs that are impacted by precision medicine

3. Decision analysis models and cost risk analysis tools to assess cost variables in precision medicine implementation
Factors that payers consider?

1. Insurance companies timelines are often 1 year, due to patient switching companies

2. Payers are custodians of subscribers’ money and funding is, in part, determined by the subscribers’ organizations

3. Relative to many other tests, genomic testing is expensive

4. Genomic results can lead to a wide variety of additional costs, such as counseling, additional testing, and preventative therapies

5. Results of disease risks often have limited clinical utility
INGENIOUS patient feedback about returning genotyping results

Lead by Peter Schwartz, MD, PhD, Director, IU Center for Bioethics.

Small focus groups (10-15 subjects) with INGENIOUS patients

Asked if they wanted the genotyping reports back

Should their providers have access to it
INGENIOUS patient feedback about returning genotyping results

They want it, and they want all of it.

The want their providers to have access to it.

Not concerned about security of genetic data in the electronic medical records.
High throughput assay to functionally test genetic variants in miRNA binding sites

1. PCR
2. NEBuilder
3. <1 picogram
4. Transformation
5. Scale-up
6. Firefly luciferase cDNA from HEK293 cells
7. Firefly luciferase cDNA from HepG2
8. 5' Barcode
9. Combine
10. Group Reads by Barcode
11. Determine the Variant/Wildtype Ratio
12. Normalize to Input Variant/Wildtype Ratio
13. Validate Functional SNPs by Luciferase Assay

Ipe et al., submitted
Results of the high throughput assay correlate well with traditional luciferase assays.
The impact of the SNPs is cell lines specific

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs#</th>
<th>HEK293</th>
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<td>6.99</td>
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<td>ABCB1</td>
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<td>11.05</td>
<td>24.60</td>
<td>34.06</td>
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<td>42.53</td>
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<td>7.68</td>
<td>17.32</td>
<td>45.26</td>
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<td>12.67</td>
<td>7.78</td>
<td>16.73</td>
<td>46.82</td>
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<td>17.16</td>
<td>17.05</td>
<td>48.67</td>
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<td>11.86</td>
<td>30.16</td>
<td>64.56</td>
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<td>HNF4A</td>
<td>rs11086926</td>
<td>91.29</td>
<td>65.82</td>
<td>75.25</td>
<td>144.76</td>
</tr>
</tbody>
</table>

* *p*-value means not significant (*p*<0.05), but not when corrected for multiple comparisons

Dark blue FDR wt higher
Light blue *p*-value wt higher
Dark red FDR wt lower
Light red *p*-value lower

Ipe et al., submitted
A variant in the CYP2B6 3’UTR is associated with in vivo efavirenz metabolism

Burgess, et al., 2017 Clin Pharm & Ther
High throughput assay for functionally testing SNPs in mRNA splice junctions
Examples of SNPs in splice junctions alter mRNA splicing
INGENIOUS enrollment is completed with a large portion of minority and patients from medically underserved areas and populations.

Actionable genotyping results are common.

Genotyping appears to change the care for patients receiving tramadol.

Patients want the genotyping results to be available to themselves and their health care providers.
Acknowledgments

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**CCBB**
Yunlong Liu

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NIH-NIGMS
NIH-NHGRI (IGNITE)
NIH-NCI
Early analysis:

Poster presented at the 2018 ASCPT Annual Meeting*

- Participants who had actionable genotypes were more likely to:
  - Have tramadol or codeine discontinued ($p = 0.03$);
  - An alternative opioid prescribed within 90 days ($p = 0.02$)
- Participants less likely to experience constipation ($p = 0.04$)
- There was no significant difference between actionable and non-actionable genotypes for:
  - Medication dose changes ($p = 0.29$);
  - Medication refills ($p = 0.21$);
  - NSAIDS prescribed ($p=0.68$);
  - Sedation ($p = 0.23$);
  - Uncontrolled pain ($p = 0.60$); and
  - DDI ($p = 0.71$)
- Reduced metabolizers (AS .05 +DDI) were more likely to experience uncontrolled pain ($p = .04$).
- While not statistically significant, reduced metabolizers were more likely to have their trigger medication discontinued and a NSAID prescribed when compared to all other metabolizers

* C.R. Fulton, M.T. Eadon, K.D. Levy, B.T. Gufford, Z. Desta, P.R. Dexter, and T.C. Skaar
General Project Summary – Current Status

Two Different Workflows Required for Recruitment

Indiana University Health System
- 18 Hospital locations
- 122 outpatient clinics
- On-line recruitment
- Manual screening

Eskenazi Health System
- 1 Hospital location
- 70+ outpatient clinics
- On-line recruitment
- Manual screening
Provider writes script for targeted medication (day 1)

Cerner transfers data to Data Warehouse (day 1)

Cerner screens in DW for inclusion and exclusion criteria and sends encrypted report to INGENIOUS Team (INGT) daily (day 2)

INGT decrypts report

INGT compares MRNs in report to RedCap db

INGT Randomizes list using on-line randomization tool https://www.randomizer.org/

Exclude duplicates

Control arm subjects entered into RedCap

Subjects to be recruited called by ResNet or CRS (Start day 2)

Fail to reach w/I 5 days. Enter into RedCap

Send letter, check or gift card to fully-enrolled subjects

Patient entered into RedCap and into PowerTrials

INGENIOUS IUH Workflow

Subjects reached Discuss study with subject and provide URL for on-line consent

Subject completes consent

Subject sent to closest IUH draw station

Sample collected and IUH draw station sends to PGx Lab (by day 5)

PGx lab notifies INGT of sample receipt

INGT completes and emails IUH Research Registration/Grant Charge form

Subject does not complete on-line consent w/I 2 days. Re-contact via phone

No Contact, fails to show or refuse. Enter into RedCap

Refuse. Enter into RedCap

Subject does not complete on-line consent w/I 2 days. Re-contact via phone

No Contact, fails to show or refuse. Enter into RedCap

Refuse. Enter into RedCap

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## Example genotype report

<table>
<thead>
<tr>
<th>Gene</th>
<th>Result</th>
<th>Predicted Metabolizer Status*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>SLCO1B1</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*3</td>
<td>Reduced/Intermediate Metabolizer</td>
</tr>
<tr>
<td>VKORC1</td>
<td>G/G</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*6/*6</td>
<td>Poor Metabolizer</td>
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<tr>
<td>ITPA</td>
<td>C/C</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>DPYD</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP4F2</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
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<tr>
<td>G6PD</td>
<td>No variant detected</td>
<td>Normal Metabolizer</td>
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<tr>
<td>IFNL3 (IL28B)</td>
<td>C/T</td>
<td>Reduced/Intermediate Metabolizer</td>
</tr>
<tr>
<td>SV2C</td>
<td>G/A</td>
<td>Increased Risk</td>
</tr>
<tr>
<td>RARG</td>
<td>C/C</td>
<td>Normal Risk</td>
</tr>
<tr>
<td>FCAMR</td>
<td>C/T</td>
<td>Increased Risk</td>
</tr>
<tr>
<td>rs3125923</td>
<td>A/G</td>
<td>Increased Risk</td>
</tr>
<tr>
<td>rs28714259</td>
<td>G/G</td>
<td>Normal Risk</td>
</tr>
</tbody>
</table>
INGENIOUS patient seeing multiple healthcare systems

Small focus groups with INGENIOUS patients
A significant number of actionable results (recommended change in selection or dose of drug) are being reported to Eskenazi providers.

* Data from INGENIOUS Redcap Database of 214 Complete Results

20% of Actionable results required clinical pharmacologist engagement.
Published economic analyses of Personalized Medicine

Cost/QALY

$N = 136$ weighted ratios
% of tests with published cost-utility analyses

- Tests w/ demonstrated clinical utility (N = 6/6) 100%
- Tests that are available (N = 42/156) 27%
- Tests w/ likely clinical utility (N = 2/8) 25%
- Tests w/ FDA label information (N = 15/113) 13%
- Tests in advanced development (N = 18/181) 10%
- Tests on conditions w/ high mortality (N = 5/8) 63%
- Tests on conditions w/ high expenditures (N = 5/8) 63%
Clinical Pharmacogenetics Implementation Consortium

- Guidelines are published in Clinical Pharmacology & Therapeutics and are available on cpicpgx.org

- **Goal**: to provide peer-reviewed, updated, evidence-based, freely accessible clinical guidelines for using genetic information for selected drugs with strong pharmacogenetics evidence.

- Guidelines for 22 drugs already published.

- Being endorsed by the American Society of Health-System Pharmacists and posted on guidelines.gov
Patients with refractory cancers or tumors of unknown origin

Somatic tumor genomics done by Nantomics, Foundation Medicine, or Paradigm.

Germline pharmacogenetics done by Indiana University Pharmacogenomics Laboratory.
INGENIOUS patient feedback about returning genotyping results

Lead by Peter Schwartz, MD, PhD, Director, IU Center for Bioethics.

Small focus groups (10-15 subjects) with INGENIOUS patients

Asked if they wanted the genotyping reports back

Should their providers have access to it

Check Mark Williams article
Check Susan Haga Duke articles