“INdiana GENomics Implementation Opportunity for the UnderServed”

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Indiana University Dept of Medicine
Division of Clinical Pharmacology

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Genomic Medicine X
Silver Spring, MD
Requirements for genetic testing implementation

1. Have clinical value in the practice setting
   AND
2. Be economically viable in such settings
   i. Genetic testing should only be widely implemented if it can be shown to be high value medicine.
   ii. Genetic testing will only be widely implemented if providers are properly incentivized to adopt it

Economic analysis alongside clinical studies will generate the information needed to support widespread adoption
Pharmaco-genetic-economic research requires an interdisciplinary approach

Informaticians (Regenstrief, CCBB)

Geneticists (IIPM, IUSM, IUSON)

Economists (IUSPH)
Indiana Genomics Implementation Opportunity for the Under Served

Acronym: InGenIOUS funded by NHGRI-IGNITE

Testing the effect of prospective, reactive pharmacogenetics genotyping on health care costs and adverse events.

Endpoints:

- Total health care costs
- Adverse events

Eskenazi & IU Health patients randomized to 2,000 genotype guided therapy
4,000 standard of care (not contacted)
INGENIOUS drug list

- Amitryptyline
- Aripiprazole
- Atazanavir
- 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
<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene</th>
<th>Gene</th>
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</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>VKORC1</td>
<td>CYP2C19</td>
<td>TPMT</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>ITPA</td>
<td>CYP3A5</td>
<td>SLC01B1</td>
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<tr>
<td>CYP2B6</td>
<td>HLA-B</td>
<td>CYP4F2</td>
<td>DPYD</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>G6PD</td>
</tr>
</tbody>
</table>
Codeine prescription

Is it for a child for a tonsilectomy or adenoidectomy

FDA recommends against using codeine in these patients “Strong”

CYP2D6 Genotype

- Poor metabolizer (AS = 0)
  - Do not use codeine due to ineffectiveness “Strong”

- Intermediate metabolizer (AS = 0.5)
  - Normal dosing “Moderate”

- Extensive metabolizer (As=1.0-2.0)
  - Normal dosing “Strong”

- Ultrarapid metabolizer (AS >2.0)
  - Do not use codeine due to risk of overdose “Strong”

AS = Activity Score:
- 0 = two nonfunctional alleles
- 0.5 = one nonfunctional and one partial function alleles
- 1.0 = two partial function or one full function and one nonfunctional alleles
- 1.5 = one functional and one partial functional alleles
- 2.0 = two full functional alleles
- >2.0 more than two alleles

Classification of recommendation: based on the strength of the literature base:
Strong, moderate, or weak.
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
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

Exclude duplicates

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

Control arm subjects entered into RedCap

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

Fail to reach w/1 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)

Patient entered into RedCap and into PowerTrials

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

PGx lab notifies INGT of sample receipt

Subject does not complete on-line consent w/1 2 days. Re-contact via phone

Subject does not complete on-line consent w/1 2 days. Re-contact via phone

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

INGT notifies provider of any actionable recommendations

Refuse. Enter into RedCap

Refuse. Enter into RedCap

Subject sent to closest IUH draw station

Subject sent to closest IUH draw station

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

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

• Current enrollment:
  - Genotyped arm: ~500 subjects
  - Control arm: ~1,300 subjects

• Current enrollment rate:
  - Genotyped arm 20-30 per week.
  - Control arm 50-60 per week.

• Includes subjects from Eskenazi and 6 of the 18 IU Health hospitals and associated clinics with additional hospitals continuing to be added.
**Numbers of each trigger medication enrolled in the INGENIOUS trial**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
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<tbody>
<tr>
<td>tramadol</td>
<td>289</td>
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<tr>
<td>PPI’s</td>
<td>258</td>
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<tr>
<td>Codeine</td>
<td>184</td>
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<tr>
<td>Clopidogrel</td>
<td>177</td>
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<tr>
<td>Escitalopram</td>
<td>165</td>
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<tr>
<td>Amitriptyline</td>
<td>170</td>
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<tr>
<td>Warfarin</td>
<td>145</td>
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<tr>
<td>Citalopram</td>
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<tr>
<td>Aripiprazole</td>
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<td>Venlafaxine</td>
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<tr>
<td>Nortriptyline</td>
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<td>Phenytoin</td>
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<td>Azathioprine</td>
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<td>Doxepin</td>
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<td>Tacrolimus</td>
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<td>Capcitabine</td>
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<td>Efavirenz</td>
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<td>Simvastatin</td>
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<td>Atomoxetine</td>
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<td>Voriconazole</td>
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<tr>
<td>Mercaptopurine</td>
<td>2</td>
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<tr>
<td>5-Fluorouracil</td>
<td>3</td>
</tr>
</tbody>
</table>
INGENIOUS Actionable Results

A significant number of actionable results (recommended change in selection or dose of drug) are being reported to Eskenazi providers.

20% of Actionable results required clinical pharmacologist engagement.

* Data from INGENIOUS Redcap Database of 214 Complete Results
Indiana University Precision Genomics Oncology Clinic

- 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.
- Working to extract PGx results from whole genome sequencing.
<table>
<thead>
<tr>
<th>CYP3A</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP2B6</th>
<th>CYP2C9</th>
<th>TPMT</th>
<th>DPYD</th>
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<tr>
<td><img src="green.png" alt="Green Light" /></td>
<td><img src="green.png" alt="Green Light" /></td>
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</table>

<table>
<thead>
<tr>
<th>Liver Function</th>
<th>Renal Function</th>
<th>Stomach pH</th>
<th>QTc</th>
<th>Cardio-toxicity</th>
<th>Peripheral Neuropathy</th>
<th>HTN</th>
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<tbody>
<tr>
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<td>M</td>
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John Doe  March 2 2017
On behalf of the Indiana University site of the NIH-IGNITE network

IU Health Precision Genomics Clinic

Funding:
NIH-NHGRI IGNITE network
IU School of Medicine Strategic Research Initiative
IU Precision Medicine Initiative-Grand Challenge
Indiana Institute for Personalized Medicine
Extra slides
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>
</tr>
<tr>
<td>ITPA</td>
<td>C/C</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>DYPD</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>CYP4F2</td>
<td>*1/*1</td>
<td>Normal Metabolizer</td>
</tr>
<tr>
<td>G6PD</td>
<td>No variant detected</td>
<td>Normal Metabolizer</td>
</tr>
<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>
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<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>
Frequency of concurrent medication use in patients in the Precision Genomics Clinic is high

Hyder, 2015, unpublished
Many patients have at least one Cytochrome P450 Enzymes Inhibited or Induced

Hyder, 2015, unpublished
Genomic guided therapy improves outcomes

Radovich et al., Oncotargets 2016
Genomic guided therapy improves outcomes

Radovich et al., Oncotargets 2016
Other items to discuss