“Implementation of pharmacogenomics at Indiana University”

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Division of Clinical Pharmacology

Duke Center for Applied Genomics and Precision Medicine
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Outline

Brief background of how we got to the current status of pharmacogenetic testing

InGenIOUS study

IU Precision Genomics Oncology Clinic

Efforts to discover additional variants for potential implementation
“Every active drug is a poison, when taken in large enough doses; and in some subjects a dose which is innocuous to the majority of people has toxic effects, whereas others show exceptional tolerance of the same drug.”

Archibald Garrod, The inborn factors of disease. 1931
In the 1950’s, Kalow discovered that exaggerated responses to some drugs was due to enzyme deficiencies

Prolonged effects of succinylcholine, a muscle relaxant, was due to the patients’ defect in cholinesterase activity (Kalow, 1957).

Isoniazid, antimalaria drug, causes peripheral neuropathy in some patients due to a lack of N-acetyl-transferase (Kalow, 1962).

Reviewed in:
Evolution of pharmacogenomics and genetic variation in the CYP enzymes.
Chapter 1 of the book: Pharmacogenomics, Applications to Clinical Care, 3rd ed.
The FDA has highlighted pharmacogenomic biomarker information in >100 drugs.

Includes:
- Expression of drug target
- Genetic variant affecting:
  - Targets
  - Drug disposition (metabolism, transport)
  - HLAs
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
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype

KR Crews¹, A Gaedigk², HM Dunnenberger³, TE Klein⁴, DD Shen⁵,⁶, JT Callaghan⁷,⁸, ED Kharasch⁹ and TC Skaar⁷


Updated guideline, Clin Pharm Ther 95:376, 2014

Available at: http://cpicpgx.org
CYP2D6 converts codeine to morphine
Cytochrome P450 2D6 (CYP2D6) Pharmacogenomics

In USA and European populations:
5-7% of the general population inherit CYP2D6 genes that are not functional (poor metabolizers)

~20-30% have some, but reduced activity (intermediate metabolizers)

1-2% of the general population inherit CYP2D6 genes that are super active (ultrarapid metabolizers)

In Asian populations:
Less poor metabolizers (no activity), but higher number of intermediate metabolizers (reduced activity).

Some African and Middle East popn’s 30% ultrarapids
CYP2D6 poor metabolizers do not convert codeine to morphine

Kirchheiner, et al., Pharmacogenomics J 2006
CYP2D6 poor metabolizers get little benefit from codeine

### Codeine therapy recommendations based on CYP2D6 phenotype

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>Strong</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>15–60 mg every 4 h as needed for pain (label recommendation)</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Begin with 15–60 mg every 4 h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopioid. Monitor tramadol use for response.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol.</td>
<td>Strong</td>
</tr>
</tbody>
</table>

* Clin Pharm Ther. 2012 91:321-6
Requirements for genetic testing implementation in precision medicine

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)

Richard L. Roudebush VAMC
What economics-related questions SHOULD be answered?

Which questions should receive highest priority and by whom?

In a rapidly evolving field, how do we anticipate future priorities?
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?

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

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

- Interactions
- Co-morbidities
- Polypharmacy

Gene A x Gene B = ?
**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

- 2,000 genotype guided therapy
- 4,000 standard of care
Drugs and genes included in InGenIOUS

<table>
<thead>
<tr>
<th>Clinical Drug Targets (24)</th>
<th>Gene</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>azathioprine*, mercaptopurine*, thioguanine*</td>
<td>TPMT</td>
<td>*2,*3,*4</td>
</tr>
<tr>
<td>azathioprine*, mercaptopurine*, thioguanine* ribavirin*</td>
<td>ITPA</td>
<td>rs1127354</td>
</tr>
<tr>
<td>amitriptyline*, clopidogrel*, voriconazole*</td>
<td>CYP2C19</td>
<td>*2,*3,*4,*6,*8,*17</td>
</tr>
<tr>
<td>simvastatin*</td>
<td>SLCO1B1</td>
<td>*5,*17</td>
</tr>
<tr>
<td>phenytoin*, warfarin*, glyburide*</td>
<td>CYP2C9</td>
<td>*2,*3,*5,*6,*8,*11</td>
</tr>
<tr>
<td>warfarin*</td>
<td>VKORC1</td>
<td>*2</td>
</tr>
<tr>
<td>warfarin*</td>
<td>CYP4F2</td>
<td>*3</td>
</tr>
<tr>
<td>amitriptyline*, atomoxetine*, codeine*, normiptiline*, doxepin*</td>
<td>CYP2D6</td>
<td>*2,*3,*4,*5,*6,*7,*8,*9,*10,*17,*29,*41,*1XN,*2XN,*4XN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Drug Targets</th>
<th>Gene</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegylated interferon*</td>
<td>IL28B (IFNL3)</td>
<td>rs8099917</td>
</tr>
<tr>
<td>tacrolimus*</td>
<td>CYP3A5</td>
<td>*3,*6,*7</td>
</tr>
<tr>
<td>efavirenz*, methadone*</td>
<td>CYP2B6</td>
<td>*6,*18</td>
</tr>
<tr>
<td>abacavir*, Phenyoitin*</td>
<td>HLA-B</td>
<td>*5701</td>
</tr>
<tr>
<td>5-fluorouracil*</td>
<td>DPYD</td>
<td>*2A,*9A</td>
</tr>
<tr>
<td>dapsone*, rasburicase*</td>
<td>G6PD</td>
<td>rs1050828, rs1050829</td>
</tr>
<tr>
<td>tenofovir*</td>
<td>ABCC4</td>
<td>rs1751034</td>
</tr>
<tr>
<td>tenofovir*</td>
<td>ABCC2</td>
<td>rs2273697, rs3740066, rs56199535, rs56220353, rs56296335, rs717620</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)

Intermediate metabolizer (AS = 0.5)

Extensive metabolizer (As=1.0-2.0)

Ultrarapid metabolizer (AS >2.0)

Do not use codeine due to ineffectiveness “Strong”

normal dosing “Moderate”

normal dosing “Strong”

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 online 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/ I 5 days. Enter into RedCap

INGT Randomizes list using online randomization tool

Patient entered into RedCap and into PowerTrials

PGx lab notifies INGT of sample receipt

Patients entered into RedCap and into PowerTrials

INGT completes and emails IUH Research Registration /Grant Charge form

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

INGENIOUS IUH Workflow

Subjects reached Discuss study with subject and provide URL for online consent

Subject completes consent

Subject sent to closest IUH draw station

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

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

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

Refuse. Enter into RedCap

Subjects reached Discuss study with subject and provide URL for online consent

Subject completes consent

Subject sent to closest IUH draw station

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

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

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

Refuse. Enter into RedCap
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
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.
# 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>DPYD</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>
<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>
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, u
To account for medications in CYP2D6 genotyping studies, we developed a medication modified CYP2D6 activity score.
Omeprazole reduces the exposure to erlotinib

Kletzl et. al., Anticancer Drugs 2015
<table>
<thead>
<tr>
<th>CYP3A</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP2B6</th>
<th>CYP2C9</th>
<th>TPMT</th>
<th>DPYD</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Traffic Light" /></td>
<td><img src="image2" alt="Traffic Light" /></td>
<td><img src="image3" alt="Traffic Light" /></td>
<td><img src="image4" alt="Traffic Light" /></td>
<td><img src="image5" alt="Traffic Light" /></td>
<td><img src="image6" alt="Traffic Light" /></td>
<td><img src="image7" alt="Traffic Light" /></td>
</tr>
</tbody>
</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>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image8" alt="Traffic Light" /></td>
<td><img src="image9" alt="Traffic Light" /></td>
<td><img src="image10" alt="Traffic Light" /></td>
<td><img src="image11" alt="Traffic Light" /></td>
<td><img src="image12" alt="" /></td>
<td><img src="image13" alt="" /></td>
<td><img src="image14" alt="" /></td>
</tr>
</tbody>
</table>

- John Doe  March 2 2017

- M

- L

- L
Genomic guided therapy improves outcomes

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

Radovich et al., Oncotargets 2016
Plasma concentrations of active tamoxifen metabolites are highly variable, even after accounting for CYP2D6 genetics.

Plasna endoxifen concentration (nM)

P<0.0001

CYP 2D6 Genotype

Wt/Wt (N=51)  Wt/Vt (N=23)  Vt/Vt (N=3)

*  #  

Plasna endoxifen concentration (nM)

Jin et al, JNCI 2005
What are microRNAs?

• Small noncoding RNAs (~21 nucleotides long)

• Regulate gene expression by binding to messenger RNA

• Translational repression or messenger RNA cleavage

• At least 1881 microRNAs in human

• Predicted to control 20-90% of human genes, including all of the major drug metabolizing genes.

• Each microRNA can regulate multiple genes

• 100s of microRNA genes offer an enormous potential for regulatory circuitry
Human livers for studying developmental changes in hepatic miRNA expression

Collaboration with Andrea Gaedigk at CMH

- 30 fetal
- 30 pediatric
- 30 adult

miRNA expression by Taqman arrays
mRNA expression by RNA-seq
miR-431 is expressed in fetal livers, but decreases to undetectable postnatally.

Burgess et al., Clin Pharmacol Ther. 2015
Hepatic miR 497 increases postnataally

![Graph showing quantitative PCR (Ct #) vs. subject # for fetal, pediatric, and adult subjects.](Burgess et al., Clin Pharmacol Ther. 2015)
Principal component analysis of miRNA expression separates fetal livers from pediatric and adult fetal-blue (circled) pediatric-green adult-red.

Burgess et al., Clin Pharmacol Ther. 2015
miRNAs are up- and down-regulated by rifampin in primary human hepatocytes

<table>
<thead>
<tr>
<th>miRNA</th>
<th>p-value</th>
<th>Fold-change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Up-regulated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-886-3p</td>
<td>0.0006</td>
<td>2.3</td>
</tr>
<tr>
<td>miR-26b</td>
<td>0.0007</td>
<td>1.3</td>
</tr>
<tr>
<td>miR-21</td>
<td>0.0020</td>
<td>1.4</td>
</tr>
<tr>
<td>miR-218</td>
<td>0.0028</td>
<td>1.8</td>
</tr>
<tr>
<td>miR-29c</td>
<td>0.0029</td>
<td>1.2</td>
</tr>
<tr>
<td>miR-25</td>
<td>0.0045</td>
<td>1.3</td>
</tr>
<tr>
<td>miR-194</td>
<td>0.0056</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Down-regulated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miR-27a</td>
<td>0.0015</td>
<td>-3.0</td>
</tr>
<tr>
<td>miR-135a</td>
<td>0.0025</td>
<td>-18.9</td>
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<tr>
<td>miR-149</td>
<td>0.0028</td>
<td>-1.6</td>
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<tr>
<td>miR-671-3p</td>
<td>0.0034</td>
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<td>miR-95</td>
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<td>miR-1303</td>
<td>0.0042</td>
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<td>miR-200b#</td>
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<tr>
<td>miR-331-5p</td>
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<tr>
<td>miR-1180</td>
<td>0.0082</td>
<td>-12.6</td>
</tr>
</tbody>
</table>

Ramamoorthy et al., 2013
Drug Metab Disp
SNPs in 3'UTRs are predicted to affect many miRNA binding sites

<table>
<thead>
<tr>
<th>CYP Gene</th>
<th>Sites (SNPs)</th>
<th># of miRNAs lost</th>
<th># of miRNAs gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1A2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1B1</td>
<td>10</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>2A6</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2B6</td>
<td>15</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>2C9</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3A4</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3A5</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>HNF4A</td>
<td>5</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

Ramamoorthy et al., Drug Metab Dispos. 2012
rs#11574744 reduces the effect of the miRNAs on luciferase activity in pIS-HNF4A

Ramamoorthy et al., Drug Metab Dispos. 2012
rs#11574744 was observed only in African Americans

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th># of subjects genotyped</th>
<th>Minor allele frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian – Chinese</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Asian – Japanese</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>Caucasian</td>
<td>151</td>
<td>0</td>
</tr>
<tr>
<td>African American</td>
<td>94</td>
<td>3.4%</td>
</tr>
<tr>
<td>African American</td>
<td>451</td>
<td>4.6%</td>
</tr>
</tbody>
</table>

Ramamoorthy et al., Drug Metab Dispos. 2012
Subjects with the rs#11574744 tended to have lower CYP2D6 activity (DM/DX ratio)

African Americans phenotyped with dextromethorphan; MAF 4.6%

Ramamoorthy et al., Drug Metab Dispos. 2012
High throughput assay to functionally test genetic variants in miRNA binding sites

1. PCR
2. NEBuilder
3. Transformation
4. Scale-up
5. Transfection
6. cDNA synthesis
7. Barcoded Primers
8. PCR
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

Next Generation Sequencing (Ion Proton)
Results of the high throughput assay correlate well with traditional luciferase assays.
High throughput assay results are reproducible

\[
R^2 = 0.7496
\]
A dinucleotide variant in CYP2B6 is predicted to create a miRNA-1275 binding site.
A SNP in a miRNA binding site in the CYP2B6 3’UTR alters the miRNA targeting
A variant in the CYP2B6 3’UTR is associated with in vivo efavirenz metabolism
Evidence supports the implementation of pharmacogenetic testing for a variety of drug tools are available for their implementation. Factors in addition to the genetic test results must be considered when implementing the testing. Many additional variants need to be evaluated for potential use in pharmacogenetics.
Acknowledgments

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Lang Li
Yunlong Liu

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NIH-NHGRI (IGNITE)
NIH-NCI

Genetics
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