How/when will pharmacogenomics translate into improved clinical care?

David W. Haas, M.D.
Professor of Medicine. Pharmacology, Pathology, Microbiology & Immunology
Vanderbilt University School of Medicine
Objectives

• To consider the current status of pharmacogenetics (PGx) and clinical practice

• To consider challenges and strategies for implementing PGx testing in clinical practice

• To speculate on future directions
Welcome, David.

Thank you for subscribing to a U.S. Discovery Membership. Your tree and Ancestry’s family records help you discover your unique story. With your AncestryDNA test you will discover more about your ethnicity and your living relatives.
All of Us (the cohort formerly known as Precision Medicine Initiative)

The future of health begins with you

The All of Us Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.

https://allofus.nih.gov/
Commercial Labs Offering PGx Testing

Below are a list of laboratories that **offer** pharmacogenetic testing. This is not a sponsored list. We have no affiliations with these labs, and inclusion on this list is not an endorsement. If you know of a lab who offers pharmacogenetic testing but is not listed here, please let us know by emailing communitypharmpgx@gmail.com and we will update our list accordingly.

<table>
<thead>
<tr>
<th>Laboratory Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>AdmeraHealth</td>
</tr>
<tr>
<td>Alcala Labs</td>
</tr>
<tr>
<td>Ally Clinical Diagnostics</td>
</tr>
<tr>
<td>AltheaDx</td>
</tr>
<tr>
<td>ApolloGen</td>
</tr>
<tr>
<td>ARUP Laboratories</td>
</tr>
<tr>
<td>Assurance Laboratories</td>
</tr>
<tr>
<td>Assurex Health</td>
</tr>
</tbody>
</table>

[http://rxpgx.com/rxpgx-labs](http://rxpgx.com/rxpgx-labs)
US FDA-Approved Antiretrovirals (2018)

**NRTIs**
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

**NNRTIs**
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

**Protease Inh.**
- Amprenavir
- Atazanavir
- Darunavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

**Entry inhibitors**
- Enfuvertide
- Maraviroc
- Ibalizumab

**Integrase inhibitor**
- Dolutegravir
- Elvitegravir
- Raltegravir
- Bictegravir
Abacavir & HLA-B*5701
Performance of *HLA-B*\(^{*}5701\) Screening for Abacavir HSR

<table>
<thead>
<tr>
<th></th>
<th>Clinically Suspected HSR(^1)</th>
<th>Immunologically Confirmed HSR(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>HLA-B</em>(^{*}5701)</td>
<td><em>HLA-B</em>(^{*}5701)</td>
</tr>
<tr>
<td>HSR</td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>762</td>
</tr>
<tr>
<td>No HSR</td>
<td>Pos PV</td>
<td>Neg PV</td>
</tr>
<tr>
<td></td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Control Arm Data Only

Mallal et al; *NEJM* 2008
Atazanavir &
UGT1A1
Bilirubin-related ATV/r Discontinuation (A5257)

Efavirenz
&
CYP2B6
CYP2B6 and Efavirenz Discontinuation for CNS Side Effects – Vanderbilt (N = 563)

A  All

Cumulative treatment discontinuation

Number at risk
Extensive Metabolizer 260 238 230 229 225 222 220
Intermediate Metabolizer 231 210 207 202 199 195 192
Slow Metabolizer 72 64 62 59 57 55 53

Time to discontinuation in week

B  White

Cumulative treatment discontinuation

Number at risk
Extensive Metabolizer 185 172 165 165 164 163 162
Intermediate Metabolizer 126 115 113 109 109 108 107
Slow Metabolizer 24 20 19 17 16 16 16

C  Black

Cumulative treatment discontinuation

Number at risk
Extensive Metabolizer 58 53 52 52 49 47 46
Intermediate Metabolizer 95 87 86 85 82 79 77
Slow Metabolizer 45 41 40 39 38 36 34

D  White

Cumulative treatment discontinuation

Number at risk
Whites 24 20 19 17 16 16 16
Blacks 45 41 40 39 38 36 34

Leger et al. Pharmacogenet Genom 26:473; 2016
Dolutegravir & UGT1A1
# UGT1A1 Loss-of-Function Variants and Dolutegravir Pharmacokinetics

## Table 3. Association analysis between pharmacokinetic parameters and UGT1A1 predicted enzyme activity.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Geometric LS mean</th>
<th>Comparison</th>
<th>Geometric mean ratio (92% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal activity (n = 41)</td>
<td>Reduced activity (n = 40)</td>
<td>Low activity (n = 7)</td>
</tr>
<tr>
<td>CL/F (l/h)</td>
<td>1.09</td>
<td>0.936</td>
<td>0.749</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (μg × h/ml)</td>
<td>45.7</td>
<td>53.4</td>
<td>66.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax</td>
<td>3.45</td>
<td>3.89</td>
<td>4.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mixed effect model included predicted enzyme activity, sex and study as fixed effects and subject as a random effect.

**AUC<sub>0-t</sub>**: Area under the concentration–time curve; **CI**: Confidence interval; **CL/F**: Oral clearance; **LS**: Least squares; **PK**: Pharmacokinetic.

---

Chen et al. *Pharmacogenomics* 2014; 15, 9–16
Drug-drug interactions
Unexpected Interaction between Efavirenz and TB Therapy

Fig. 1. Influence of CYP2B6 c.516G→T genotypes and rifampin-containing antituberculous therapy on efavirenz plasma mid-dose concentrations. There was a significant
PGx of drug-drug interaction: Efavirenz and Isoniazid

What is CPIC?

The Clinical Pharmacogenetics Implementation Consortium (CPIC®) is an international consortium of individual volunteers and a small dedicated staff who are interested in facilitating use of pharmacogenetic tests for patient care.

One barrier to implementation of pharmacogenetic testing in the clinic is the difficulty in translating genetic laboratory test results into actionable prescribing decisions for affected drugs.

CPIC's goal is to address this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines (click here for all CPIC publications). CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpcpgx.org, where they are regularly updated.

CPIC started as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN) in 2009. CPIC guidelines are available on guidelines.gov, indexed in PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and referenced in ClinGen and PharmGKB.
# CPIC gene-drug pairs

<table>
<thead>
<tr>
<th># (N=355)</th>
<th>GENE (UNIQUE = 127)</th>
<th>DRUG (UNIQUE = 223)</th>
<th>GUIDELINE</th>
<th>CPIC LEVEL</th>
<th>PHARMGKB LEVEL OF EVIDENCE</th>
<th>PGX ON FDA LABEL</th>
<th>CPIC PUBLICATIONS (PMID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HLA-B</td>
<td>abacavir</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td>Testing required</td>
<td>• 22378157</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 24561393</td>
</tr>
<tr>
<td>2</td>
<td>HLA-B</td>
<td>allopurinol</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td></td>
<td>• 23232549</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 26094938</td>
</tr>
<tr>
<td>3</td>
<td>CYP2C19</td>
<td>amitriptyline</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td></td>
<td>• 23486447</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 27997040</td>
</tr>
<tr>
<td>4</td>
<td>CYP2D6</td>
<td>amitriptyline</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td>Actionable PGx</td>
<td>• 23486447</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 27997040</td>
</tr>
<tr>
<td>5</td>
<td>UGT1A1</td>
<td>atazanavir</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td></td>
<td>• 26417955</td>
</tr>
<tr>
<td>6</td>
<td>TPMT</td>
<td>azathioprine</td>
<td>Guideline</td>
<td>A</td>
<td>1A</td>
<td>Testing recommended</td>
<td>• 21270794</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• 23422873</td>
</tr>
</tbody>
</table>

https://cpicpgx.org/genes-drugs/
Challenges with Implementing PGx Testing in Clinical Practice
Challenges with Implementing PGx

**Limited Evidence**

- Few rigorous clinical trials
- May be difficult reach consensus on guidelines
- Associations may be inconsistent across studies

Challenges with Implementing PGx

Incorporating into Clinical Decision

- PGx just part of overall clinical picture
- Integrate with extrinsic factors (lifestyle) and intrinsic factors (comorbidities)
- Not well integrated into electronic medical records
- Limited decision support tools
- Avoidance of PGx drugs if alternatives

“Dave, I hear you’ve been going around saying that efavirenz is a bad drug for black people”

Judy Currier, circa 2007
Challenges with Implementing PGx

Who to PGx test?

• Target population to test important for implementation
• Economic evaluation to inform implementation, which populations to test
• Benefit of widespread routine testing not known
Challenges with Implementing PGx

Likelihood of carrying actionable variant AND receiving drug

- Actionable variants very common
- Only matters if prescribed PGx-guided drug
- Many studies show high likelihood individuals with PGx variants will receive PGx-guided drug
Challenges with Implementing PGx

Economics of Implementing PGx Testing

• A 2015 systematic review evaluated economics of PGx testing in 80 studies
• Most assumed preemptive (not reactive) testing
• Was cost-effective in ~90% of studies

PGx and Fixed Dose Combination Tablets
Willingness to dose reduce efavirenz based on PGx testing

We are thinking about doing a research study that would involve replacing the 1 pill once a day with 2 or 3 pills once a day. This might make the person feel a little better, and would still control the person's HIV just as well. Do you think you would volunteer for such a study?

Consider another research study that would also involve replacing the 1 pill once a day with 2 or 3 pills once a day. This might make the person feel a little better, but with a small chance it might not control HIV as well. Do you think you would volunteer for such a study?

Willingness to Dose Reduce

N = 129

% of patients

N = 129

may feel better
may feel better but may not control HIV

Willing to change

yes
maybe
no
don't know

Strategies to Implement PGx in Clinical Practice
Strategies to Implement PGx

Preemptive (vs reactive) Genotyping

• Assures genetic data available when needed
• Testing multiple genes simultaneously greatly decreased cost
• For patients see providers only when ill, do reactive + preemptive testing
• May help identify patients preemptively at risk for future PGx-guided drug
Strategies to Implement PGx

Broad Public Health PGx Screening

• Analogous to newborn screening test
• Rare but devastating variants, deemed a public health benefit
• PGx variants far more common
• PGx testing not yet deemed public health benefit
Strategies to Implement PGx

US PGx implementation initiatives

• Piloting preemptive PGx testing
• Developing infrastructure and good practices for clinical uptake
• Clinical decision support (CDS) to identify patients most likely to benefit
## Some Preemptive PGx Initiatives in US

<table>
<thead>
<tr>
<th>Program</th>
<th>Target Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREDICT</strong> Vanderbilt University</td>
<td>3,000 patients scheduled for cardiac cath</td>
</tr>
<tr>
<td><strong>Right Drug, Right Dose, Right Time</strong> Mayo Clinic Biobank</td>
<td>1,013 patients multivariable prediction to identify high risk of starting statin within 3 yrs</td>
</tr>
<tr>
<td><strong>CLIPMERGE PGx</strong> Mount Sinai</td>
<td>1,500 subjects on or likely to start PGx drug</td>
</tr>
<tr>
<td><strong>PG4KDS</strong> St. Jude Children’s Research Hospital</td>
<td>1,559 patients enrolled as of August 2013</td>
</tr>
<tr>
<td><strong>Personalized Medicine</strong> Univ. Florida and Shands Hospital</td>
<td>800 patients receiving cardiac cath</td>
</tr>
<tr>
<td><strong>1200 Patients Project</strong> University of Chicago</td>
<td>1,200 adults with access to outpatient care, on 1–6 medications</td>
</tr>
<tr>
<td><strong>eMERGE Network</strong> 10 sites across US</td>
<td>9,000 patients likely to be prescribed PGx-guided drugs within 1–3 yrs</td>
</tr>
</tbody>
</table>

Vanderbilt’s PREDICT re-launched in Jan 2018

PREDICT: Personalized Medicine Initiative
## Vanderbilt’s PREDICT (PDX) test

<table>
<thead>
<tr>
<th>CPT</th>
<th>CDM</th>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81225</td>
<td>76008002</td>
<td>CYP2C19</td>
<td><strong>Antiplatelet</strong> <em>(e.g., clopidogrel); antidepressant; antiepileptic; proton pump inhibitors; anti-pain (analgesic)</em></td>
</tr>
<tr>
<td>81226</td>
<td>66000878</td>
<td>CYP2D6</td>
<td>Antidepressant; beta blockers, antiarrhythmic; antihistamine, anti-pain, opioids, antipsychotic</td>
</tr>
<tr>
<td>81400</td>
<td>76008028</td>
<td>SLC01B1</td>
<td><strong>Statins</strong></td>
</tr>
<tr>
<td>81401</td>
<td>66000829</td>
<td>CYP3A5</td>
<td><strong>Immunosuppressant</strong> <em>(e.g., tacrolimus)</em></td>
</tr>
<tr>
<td>81401</td>
<td>66000829</td>
<td>TPMT</td>
<td><strong>Thiopurines</strong> <em>(purine antimetabolites widely used in the treatment of acute lymphoblastic leukemia, autoimmune disorders (e.g., Crohn's disease, rheumatoid arthritis), and organ transplant recipients)</em></td>
</tr>
<tr>
<td>81227</td>
<td>66000845</td>
<td>CYP2C9</td>
<td><strong>Anticoagulant</strong> <em>(e.g. warfarin)</em></td>
</tr>
<tr>
<td>81355</td>
<td>66000852</td>
<td>CYP2C9/VKORC1</td>
<td><strong>Anticoagulant</strong> <em>(e.g. warfarin)</em></td>
</tr>
<tr>
<td>81479</td>
<td>66000894</td>
<td>CYP4F2</td>
<td><strong>Anticoagulant</strong> <em>(e.g. warfarin)</em></td>
</tr>
</tbody>
</table>

**Total: $**

**32 SNPs**

**8 genes**
Vanderbilt’s PREDICT (PDX) test

Will insurance pay for it?

• Once patient receives PREDICT test, a claim is submitted to insurance. If denied, patient is responsible.

Where can patients find results?

• In “My Health at Vanderbilt” under the “Genes Affecting my Medicines” section of “My Results”
## Table 1 Gene–drug pairs implemented into clinical practice at institutions participating in the IGNITE Pharmacogenetics Working Group

<table>
<thead>
<tr>
<th>Institution</th>
<th>Gene–drug pairs implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Florida&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel; CYP2D6-codeine, tramadol; TPMT-thiopurines; CYP2D6/CYP2C19-SSRIs; CYP2C19-PPIs; CYP2C19-voriconazole (in development)</td>
</tr>
<tr>
<td>Vanderbilt University&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel; SLCO1B1-simvastatin; CYP2C9/VKORC1-warfarin; CYP3A5-tacrolimus; TPMT-thiopurines</td>
</tr>
<tr>
<td>Indiana University&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel, voriconazole, PPIs, citalopram; CYP2D6-opioids, SSRIs, aripiprazole, atomoxetine; SLCO1B1-simvastatin; CYP2C9/VKORC1/CYP4F2-warfarin; CYP3A5-tacrolimus; TPMT-thiopurines; CYP2D6/CYP2C19-TCAs; DPYD-5-fluorouracil, capecitabine, tegafur; G6PD-rasburicase; ITPA-thioguanine; CYP2B6-efavirenz</td>
</tr>
<tr>
<td>Sanford Health&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel; CYP2C9/VKORC1-warfarin; CYP2D6/CYP2C19-SSRIs, TCAs; CYP2D6-opioids; CYP3A5-tacrolimus; SLCO1B1-simvastatin; TPMT-thiopurines; DPYD-capecitabine, fluorouracil, tegafur</td>
</tr>
<tr>
<td>University of Maryland&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel</td>
</tr>
<tr>
<td>Mount Sinai&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CYP2C19-clopidogrel; CYP2C9/VKORC1-warfarin; SLCO1B1-simvastatin; CYP2D6-codeine, tramadol; CYP2D6/CYP2C19-TCAs (in development); CYP2D6/SSRIs (in development)</td>
</tr>
<tr>
<td>Duke University&lt;sup&gt;b&lt;/sup&gt;</td>
<td>SLCO1B1-statins</td>
</tr>
<tr>
<td>University of North Carolina at Chapel Hill</td>
<td>CYP2C19-clopidogrel</td>
</tr>
<tr>
<td>Nemours Children’s Health System</td>
<td>CYP2C19-PPIs</td>
</tr>
<tr>
<td>University of Illinois at Chicago</td>
<td>CYP2C19-clopidogrel; CYP2C9/VKORC1-warfarin</td>
</tr>
<tr>
<td>Mission Health System</td>
<td>HLA-B*1502-carbamazepine</td>
</tr>
<tr>
<td>St. Luke’s Mountain States Tumor Institute</td>
<td>DPYD-fluorouracil, capecitabine; TPMT-thiopurines</td>
</tr>
<tr>
<td>University of Pittsburgh</td>
<td>CYP2C19-clopidogrel</td>
</tr>
<tr>
<td>University of Pennsylvania</td>
<td>CYP2C19-clopidogrel</td>
</tr>
<tr>
<td>H. Lee Moffitt Cancer Center &amp; Research Institute</td>
<td>CYP2C19-voriconazole; CYP2D6-opioids; TPMT-thiopurines</td>
</tr>
<tr>
<td>University of Alabama, Birmingham</td>
<td>CYP2C19-clopidogrel</td>
</tr>
</tbody>
</table>

Strategies to Implement PGx

Evolving technologies

• Single marker genotyping
• Multiplex marker platforms
• Next-Gen sequencing
PGx and the World

Global HIV rates (2014)

- People living with HIV: 36.9m
- New HIV infections: 2.0m
- AIDS-related deaths: 1.2m

Source: UNAIDS
Credit: Rebecca Robinson/LSHTM
Objectives

• To consider the current status of pharmacogenetics (PGx) and clinical practice

• To consider challenges and strategies for implementing PGx testing in clinical practice

• To speculate on future directions
Acknowledgements

Key scientific foundation
• Grant Wilkinson
• Alastair Wood
• Richard Kim
• Jonathan Haines
• Ellen Clayton
Acknowledgements (1)

• Funding
  • NIAID R01 AI120790
  • NIAID RO1 AI077505
  • Tennessee CFAR (P30 AI110527)
  • NIAID - ACTG (UM1 AI068636)
  • NCATS - VICTR (UL1 TR000445)

• Collaborators and colleagues.
Acknowledgements (2)

DNA Resources Core/VANTAGE
- Cara Sutcliffe
- Paxton Baker
- Melissa Potter

Univ. Penn
- Marylyn Ritchie
- Yuki Bradford
- Anurag Verma
- Sudha Venturi

Univ. Cape Town
- Gary Maartens
- Helen McIllleron
- Phuml Sinxadi

VU ACTG Clinical Research Site
- Beverly Woodward
- Huso Erdem
- Fred Nicotera
- Brenda Jackson
- Becky Basham
- Joan Gottesman
- Michael Leonard
- Latifa DaSilva
- Tracey Watkins

CEPAC Group
- Ken Freedberg
- Bruce Schackman
- Cynthia Li
- Sanghee S. Park
Acknowledgements (3)

Vanderbilt Collaborators
• Tim Sterling
• Todd Hulgan
• Simon Mallal
• Elizabeth Phillips
• Bryan Shepherd

Trainees
• Ben Grady
• Emily Holzinger
• Paul Leger
• Phumla Sinxadi
• Tailah Almeida

VUMC Mass Spec Core
• Richard Caprioli
• Brian Hachey

A5128 Team
• Kris Coughlin
• Evelyn Hogg

ACTG Collaborators
• Eric Daar (UCLA)
• Trip Gulick (Cornell)
• Richard Haubrich (UCSD)
• Jeff Lennox (Emory)
• Heather Ribaudo (Harvard)
• Greg Robbins (Harvard)