VA PHASER: Pharmacogenomic testing for Veterans—A collaboration between VA and Sanford Health

University of Arizona Pharmacogenomics and Precision Medicine Symposium

January 17, 2020
The goal of pharmacogenetic testing (PGx) is to **reduce medication side effects**, **maximize medication benefits**, and **reduce opioid exposure** by using a patient’s genetic makeup to ensure the right dose of the right drug.

PGx impacts nearly **40 medications** commonly prescribed to Veterans.

**1 in 2 Veterans** is prescribed a medication under pharmacogenetic control.

Through a collaboration between VA and Sanford Health Care, PHASER will provide PGx to up to **250,000 Veteran patients over 4 years**.

PHASER will be a **leader in the field of precision medicine** by being the largest implementation of PGx in the US in an integrated health care system.
Mission of the U.S. Department of Veterans Affairs

“...to care for him who shall have borne the battle and for his widow and orphan...”
- Abraham Lincoln, 1865

Photo by Jeff Kubina
What is the U.S. Department of Veterans Affairs?

• Established in 1930
• Elevated to Cabinet level in 1989
• United States government’s 2nd largest department after the Department of Defense
• Three components:
  • Veterans Health Administration (VHA)
  • Veterans Benefits Administration (VBA)
  • National Cemetery Administration (NCA)
1,227 Sites of care throughout the U.S.**

- 168 Medical Centers
- 1,047 Outpatient Clinics
- 135 Community Living Centers
- 113 Domiciliary Rehabilitation Treatment Programs
- 60 Mobile Sites of Care
- 300 Readjustment Counseling (Vet) Centers
- 80 Mobile Vet Centers

**NOTE: The number of sites of care is NOT a total of the categories listed below, as several of the sites are also listed in multiple categories (e.g., there are 135 CLCs within the 168 medical centers)

Source: VSSC QES 1st Qtr FY16
Why perform pharmacogenetic testing in the VA?

*One-Drug Does Not Fit All*
Genetic Variation in Drug Metabolizing Genes Can Be used to Individualize Drug Dose

1 in 2 Veterans prescribed a medication under PGx control over 6 years: Analysis of 7.8 million Veterans using pharmacy benefits

New recipients = 2.9 million

Chanfreau-Coffinier et al JAMA Netw Open. 2019;2(6):e195345
PHASER Goals

• PHASER is a clinical program (i.e., not research) offered through the VA Specialty Care Services and the National Oncology Program Office

• Sanford Health is supporting
  • Pharmacogenetic testing in Sanford Imagenetics laboratory in Sioux Falls, SD
  • Funding to the VA for implementation of the program

• The goal is to test 250,000 Veterans nationwide over 4-5 years and integrate test results into routine patient care.

• PHASER is distinct from the VA Million Veterans Program (biorepository)
Current PHASER Pharmacogenetics Panel

Collaboration with Sanford Health and Sanford Imagenetics Laboratory

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alleles tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td><em>2</em>3<em>4</em>5<em>6</em>7<em>8</em>17</td>
</tr>
<tr>
<td>CYP2C9</td>
<td><em>2</em>3<em>5</em>6<em>8</em>11</td>
</tr>
<tr>
<td>CYP2D6</td>
<td><em>2</em>3<em>4</em>6<em>9</em>10*41</td>
</tr>
<tr>
<td>CYP3A5</td>
<td><em>3</em>6*7</td>
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<td><em>13</em>2A rs67376798</td>
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<tr>
<td>TPMT</td>
<td><em>2</em>3A<em>3B</em>3C*4</td>
</tr>
<tr>
<td>VKORC1</td>
<td>-1639 A</td>
</tr>
<tr>
<td>CYP2D6 copy number</td>
<td>within exon 9</td>
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</table>

Coming in February 2020: IFNL3, CYP4F2, CYP2C cluster
What medications are impacted by the panel?

<table>
<thead>
<tr>
<th>Drug List</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Atomoxetine</td>
</tr>
<tr>
<td>Azathioprine</td>
</tr>
<tr>
<td>Capecitabine</td>
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<tr>
<td>Citalopram</td>
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<tr>
<td>Clomipramine</td>
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<tr>
<td>Clopidogrel</td>
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Who is eligible for PHASER?

• No inclusion criteria. Any Veteran can participate.

• We can send educational mailings to your patients ahead of an upcoming appointment.

• **PHASER testing is inappropriate in patients who have received bone marrow or liver transplantation**
What are the implementation barriers that we must address in order for PHASER to be successful?

Building on the shoulders of existing programs implementing pharmacogenomics
Successful pre-emptive pharmacogenomic testing US programs

• St. Jude’s Children’s Hospital
• Vanderbilt University
• University of Florida
• Mt. Sinai
• Mayo Clinic
Barriers to implementing pre-emptive pharmacogenetics in clinical practice

- Evidence base
  - Clinical validity
  - Clinical utility
  - Selecting appropriate PGx tests

- Guidelines directing clinical use of PGx test results

- Integrating genomic data into Electronic Health Record

- Physician/pharmacy awareness and education

- Implementing PGx into physician/pharmacy workflows

- Cost-consequences and reimbursement

- Scalability/translatability across and in-between facilities

*CLINICAL PHARMACOLOGY & THERAPEUTICS* VOLUME 101 NUMBER 3 | MARCH 2017
What is the evidence base supporting PGx informed prescribing?

CPIC – An evidenced based approach to developing PGx dosing guidelines
CPIC Summary

• Peer-reviewed, fully transparent, standards-based process to developing clinical guidelines based on all available evidence

• CPIC guidelines help clinicians understand HOW available genetic test results should be used to optimize drug therapy.
  • Not WHETHER tests should be ordered.
  • Meets PHASER use case

• All guidelines produced in a standard format
  • Published in *Clinical Pharmacology and Therapeutics*
  • Freely available on

- Retrospective clinical trials
- Clinical cohorts
- Prospective trials/studies

In vitro  PK/PD

Consensus assessment of actionability of drug-gene interaction

In vitro  PK/PD

Consensus assessment of actionability of drug-gene interaction
<table>
<thead>
<tr>
<th>CPIC Level</th>
<th>Clinical Context</th>
<th>Level of evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing</td>
<td>At least one moderate or strong action (change in prescribing) recommended.</td>
</tr>
<tr>
<td>B</td>
<td>Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing</td>
<td>Preponderance of evidence is weak with little conflicting data</td>
<td>At least one optional action (change in prescribing) is recommended.</td>
</tr>
<tr>
<td>C</td>
<td>There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics convincingly makes no difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.</td>
<td>Evidence levels can vary</td>
<td>No prescribing actions are recommended.</td>
</tr>
<tr>
<td>D</td>
<td>There are few published studies, clinical actions are unclear, little mechanistic basis, mostly weak evidence, or substantial conflicting data. If the genes are not widely tested for clinically, evaluations are not needed.</td>
<td>Evidence levels can vary</td>
<td>No prescribing actions are recommended.</td>
</tr>
</tbody>
</table>
Bi-directional interface with PGx laboratory to store data as computable elements

- Coordination between:
  - Local VAs
  - Reference Laboratory Network
  - Sanford Health Imagenetics Laboratory
  - VA Health Information Technology

Courtesy Mike Icardi, MD
Train-the-trainer model of information diffusion

Knowledge transfer:
- Scientific information
- Implementation guide(s)
- Health Informatics toolkit
  - Report cards
  - Best practices
  - Press Kit

Feedback on facilitators/barriers

PHASER Facility Leadership (Medical Director & Chief of Staff)

Local Site Champion (MD, PharmD)

Public Affairs Office

Oncology, Primary Care, Mental Health, Cardiology Services

Clinical Coordinator (RN, CRC)

Pharmacy Service

Nursing Staff

Laboratory/phlebotomy

CACs
Pre-test patient education

Pre-test Video

Website

Clinic Posters

Using genetics to find the best treatment: Information about the PHASER Program

Pharmacogenomics (PhG) is a science that studies how genes affect the way an individual responds to a drug. This science is helping doctors and other health professionals take an individualized approach to medicine. This is called personalized medicine. Pre-test patient education helps patients understand how their genes may affect their response to certain medications. This can lead to better health outcomes and improved treatment plans.

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Post-test patient education to support PHASER

Test Details

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>Alleles Tested</th>
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</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>*1/*2</td>
<td>Rapid Metabolizer</td>
<td>12, 13, 14, 15, 16, 17, 18, 19</td>
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<tr>
<td>CYP2C19</td>
<td>*1/*2</td>
<td>Intermediate Metabolizer</td>
<td>12, 13, 14, 15, 16, 17, 18, 19, 20</td>
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<tr>
<td>CYP2D6</td>
<td>*1/*2, *3/*4</td>
<td>Normal Metabolizer</td>
<td>12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22</td>
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<tr>
<td>CYP3A5</td>
<td>*1/*3</td>
<td>Poor Metabolizer</td>
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<td>CYP3A4</td>
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<td>Normal Metabolizer</td>
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<tr>
<td>ORNO</td>
<td>*1/*2</td>
<td>Normal Metabolizer</td>
<td>12, 13, 14, 15, 16, 17, 18, 19, 20</td>
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<tr>
<td>OCT1</td>
<td>*1/*2</td>
<td>Enhanced Transport</td>
<td>12, 13, 14, 15, 16, 17, 18, 19, 20</td>
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<tr>
<td>INNOL</td>
<td>*1/*2</td>
<td>Intermediate Metabolizer</td>
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<td>Intermediate Metabolizer</td>
<td>12, 13, 14, 15, 16, 17, 18, 19, 20</td>
</tr>
</tbody>
</table>

Post-test Video
Provider Training opportunities to support PHASER

Grand Rounds, morning-meeting, noon conference type sessions:
- Providers
- Nurses
- Pharmacists

Online CE module

Post-test videos

Pre-test Videos

What is pharmacogenomics (PGx)?

PHASeR - Overview and Videos
(VA 4527522)

Start Course
Passive clinical decision support systems (CDSS) to incorporate PGx during decision making

“Traffic light” PDF report based on CPIC guidelines

“On the fly” PGx interpretation

Gene: CYP2D6
Result: Ultrarapid metabolizer
Drugs Impacted:
- Codeine
- Desipramine
- Fluvoxamine
- Nortriptyline
- Ondansetron
- Paroxetine
- Tramadol

**Drugs impacted based on CYP2C19 and CYP2D6 results**
- Amitriptyline
- Clomipramine
- Doxepin
- Imipramine
- Trimipramine

Gene: CYP2C9
Result: Intermediate metabolizer
Drug Impacted:
- Phenytoin
Enabling deeper interpretation of PGx test results by linking to external databases

- Sophic Integrated Knowledge Environment
- PharmGKB
- Flockhart Table™
- Lexicomp
- VCF
- Rx
- ICDs
- Allergies

- GDx collaboration (Constance Murphy, Julie Lynch, Mike Icardi)
- SDS360 software
  - Cloud based re-interpretation
  - Leverage literature, ontologies, clinical data libraries
  - Ability to ‘socialize’ knowledge and interpretations
  - Customized views (pathology, oncology, pharmacy, etc.)
Interruptive CDSS incorporate PGx after decision making – Best for highest risk interactions

- Will allow for checking gene-drug interactions during ordering
- Alert provider to the potential nature and severity of interaction
- Offer alternatives (dose or drug selection)
- Can be overridden by provider with reasons
- If no interaction → no interruption in workflow

Current CROC examples
  - Metformin and CrCl check
  - ACEi/ARB and women of childbearing age check
Clinical Reminder Order Checks to Provide Clinical Decision Support at the Point of Prescription
National interfacility consultations with PHASER pharmacist

- Pre-test consultation (in reactive/diagnostic cases)
- Post-test consultation
- Medication reconciliation of active medications at time of PGx testing
- Comprehensive medication management in context of PGx

Jill Bates, PharmD, MS, BCOP, FASHP
Pharmacy Program Manager
PHASER snapshot 2019
Overall characteristics since inception

Median turnaround time = 16 days
Patient characteristics

Race

- White: 314
- Black: 163
- Declined: 21
- Other: 0

Average age = 65 years
Provider characteristics

Bar graph showing the number of providers ordered tests within different ranges:
- 1-3: 60 providers
- 4-8: 10 providers
- 9-14: 2 providers
- 24-29: 3 providers
- >30: 4 providers

Pie chart showing the distribution of providers by specialty:
- Primary Care: 25
- Oncology/hematology: 23
- Mental Health: 16
- Pharmacy: 9
- Pulmonary: 5
- Cardiology: 4
- Other: 9

Specialties are color-coded as follows:
- Blue: Primary Care
- Brown: Oncology/hematology
- Light gray: Mental Health
- Yellow: Pharmacy
- Blue: Pulmonary
- Green: Cardiology
- Black: Other
Collect and analyze uptake and use of PGx data during implementation
Learning Health System

“Implementation”

PHASER
- Health/Bio Informatics
  - Reporting/Interpretation
    - Clinical Decision Support
  - Providers
  - Patients
  - Pharmacists
  - Nursing
  - Implementation
    - Clinical
    - Economic
    - MVP
- Education

VA/NIH
- Research
  - Discovery
  - Validation

“Research”
Data flow to support PHASER

Catherine Chanfreau, PhD
Director, PHASER data core
## Outcomes of interest for retrospective research

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Example(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process</strong></td>
<td>Steps in a process that lead to a health outcome</td>
<td>CROC acceptance vs. override</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>A biomarker associated with a health outcome</td>
<td>LDL for statins, INR for warfarin, cell counts for thiopurines.</td>
</tr>
<tr>
<td><strong>Health</strong></td>
<td>Health outcome which is attributable to PGx testing</td>
<td>New report of allergy/intolerance to medication, hospitalization for bleeding, cytopenia, etc.</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>Costs associated with intervention and health states experienced by patient</td>
<td>Cost of testing, PHASER infrastructure, costs of care related to PGx (i.e. meds, testing), utilization (hospitalization, visits, calls, consults)</td>
</tr>
<tr>
<td><strong>Behavior</strong> (individual and health system)</td>
<td>Change in patient/provider behavior</td>
<td>Adherence to medications, adherence to guidelines for specific medication classes, concordance of new prescriptions with PGx recommendations</td>
</tr>
</tbody>
</table>

Adapted from Peterson et al *Lancet* 2019
Using implementation science to optimize uptake

Goals: Use established frameworks to evaluate
- Program materials
- Resource utilization and costs
- Implementation processes
Leveraging VA’s Biorepository

The Clinical Pharmacogenetics Implementation Consortium Guideline for SLC01B1 and Simvastatin-Induced Myopathy: 2014 Update
LR Ramsey1, SG Johnson1, KE Caudle1, CE Holiday1, D Voors1, RA Wilks2,3, WD Maxwell5, HL McLeod5, BM Kraus6, JDM Roden4,5,6, DM Rosen6,6, Q Feng4,6, RM Cooper-D‘Hoff1, T L Gong1, TE Klein1, M Yudilov1, and M Nienaber6

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotype and Clopidogrel Therapy: 2013 Update
SA Scott1, E Sangkuhl2, CM Stein3, JHS Hulet4, JL Mega5, DM Roden2, TE Klein2, MS Sabatine4, JA Johnson5,6, and AR Budliger1,2

PHASER

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Discovery

Validation

MVP
Summary

• PHASER will be one of the largest implementations of pre-emptive PGx testing in clinical care in the US
• Integration of PGx testing across multiple, disparate health systems presents an opportunity to learn how to implement precision medicine at scale.
• In a learning health system approach, data mining will allow us to optimize implementation and adapt to new barriers/opportunities.
THANKS!
deepak.voora@va.gov

We are always looking for bright, motivated collaborators, post-doctoral fellows, and scientists excited to partner with PHASER