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

University of Arizona Pharmacogenomics and Precision Medicine Symposium

January 17, 2020

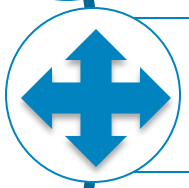
VA HEALTH CARE | Defining EXCELLENCE in the 21st Century

Veterans Health Administration

PHASER PROGRAM SUMMARY

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

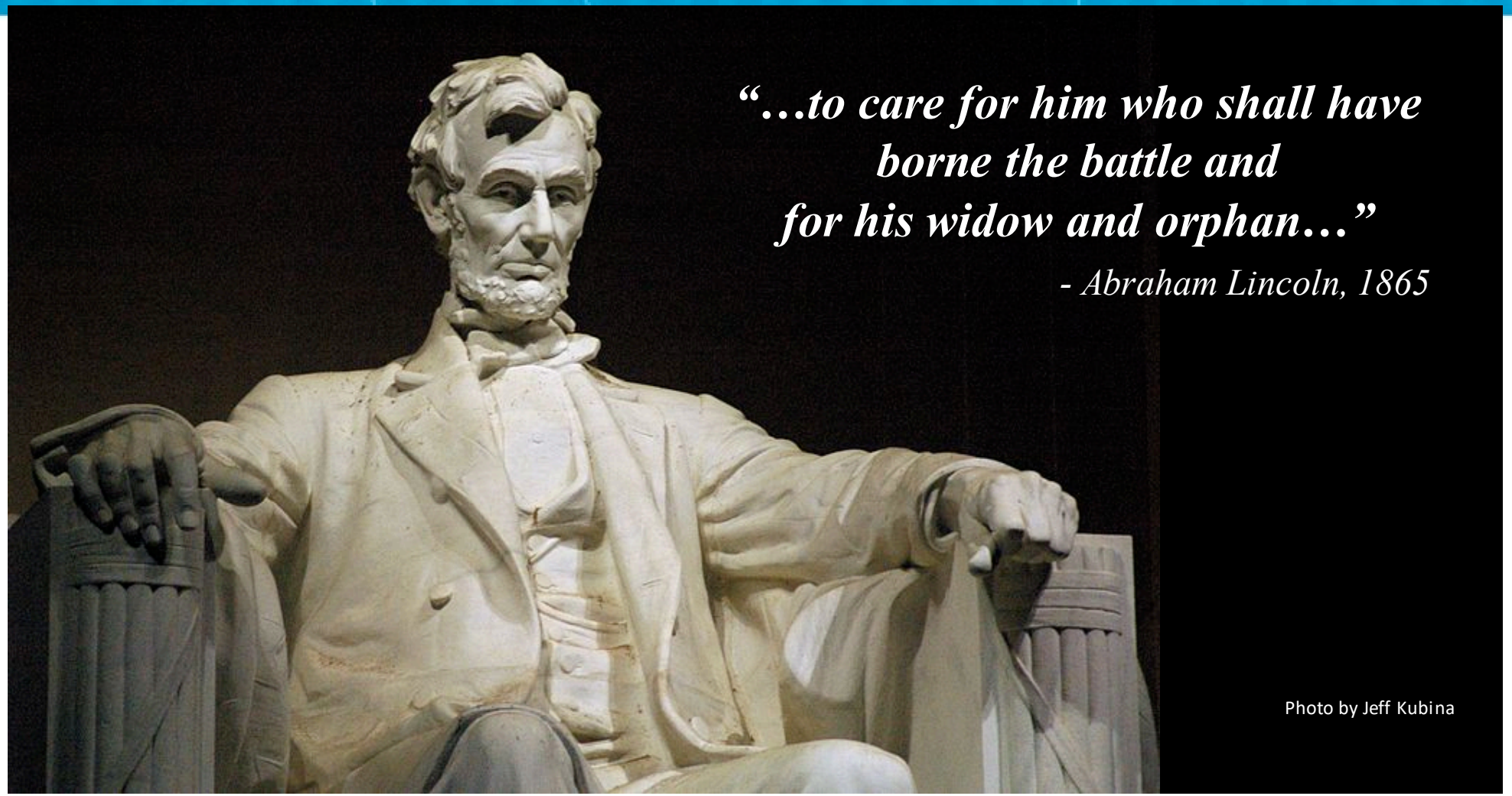


1 in 2 Veterans is prescribed a medication under pharmacogenetic control

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

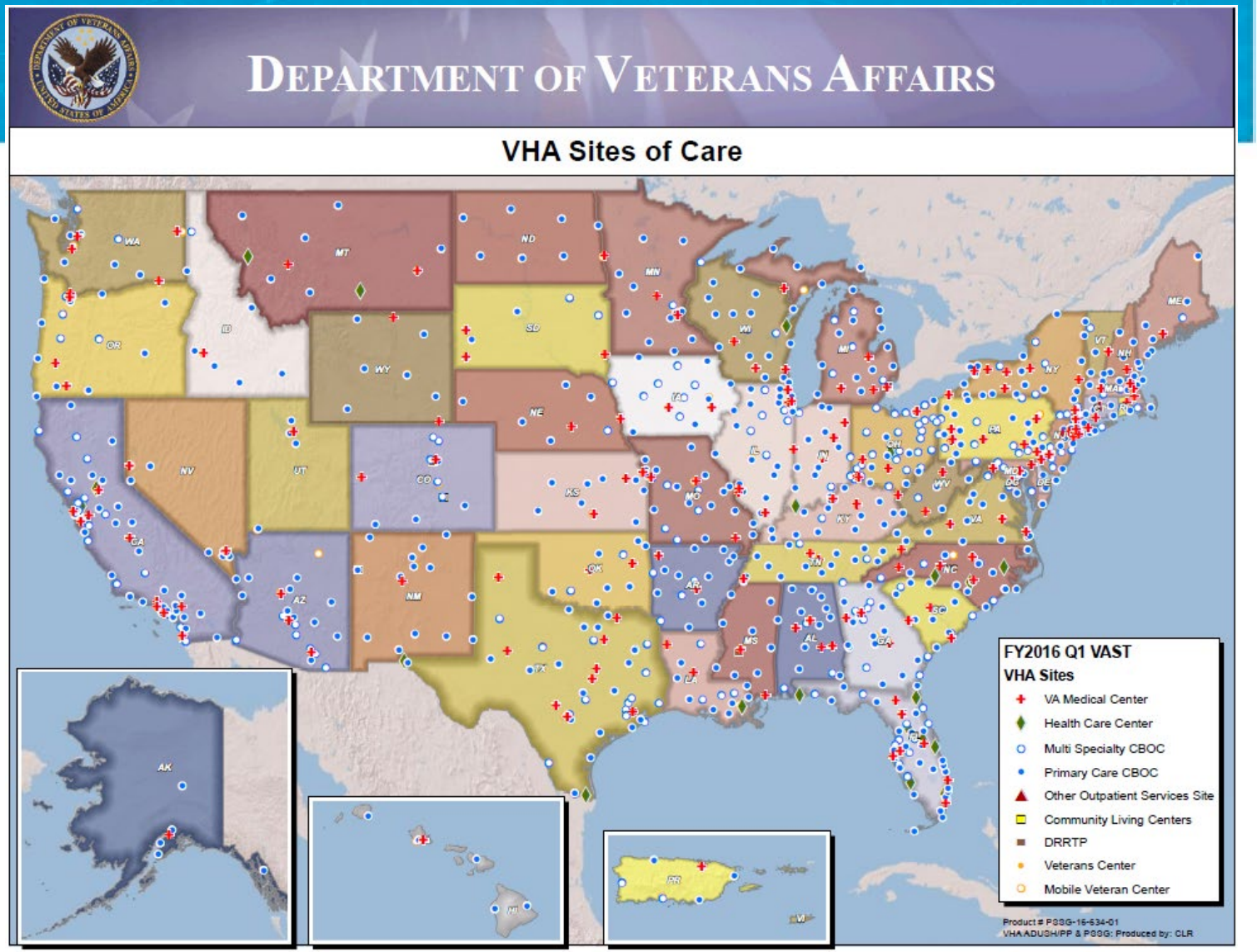


What is the U.S. Department of Veterans Affairs?

- 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



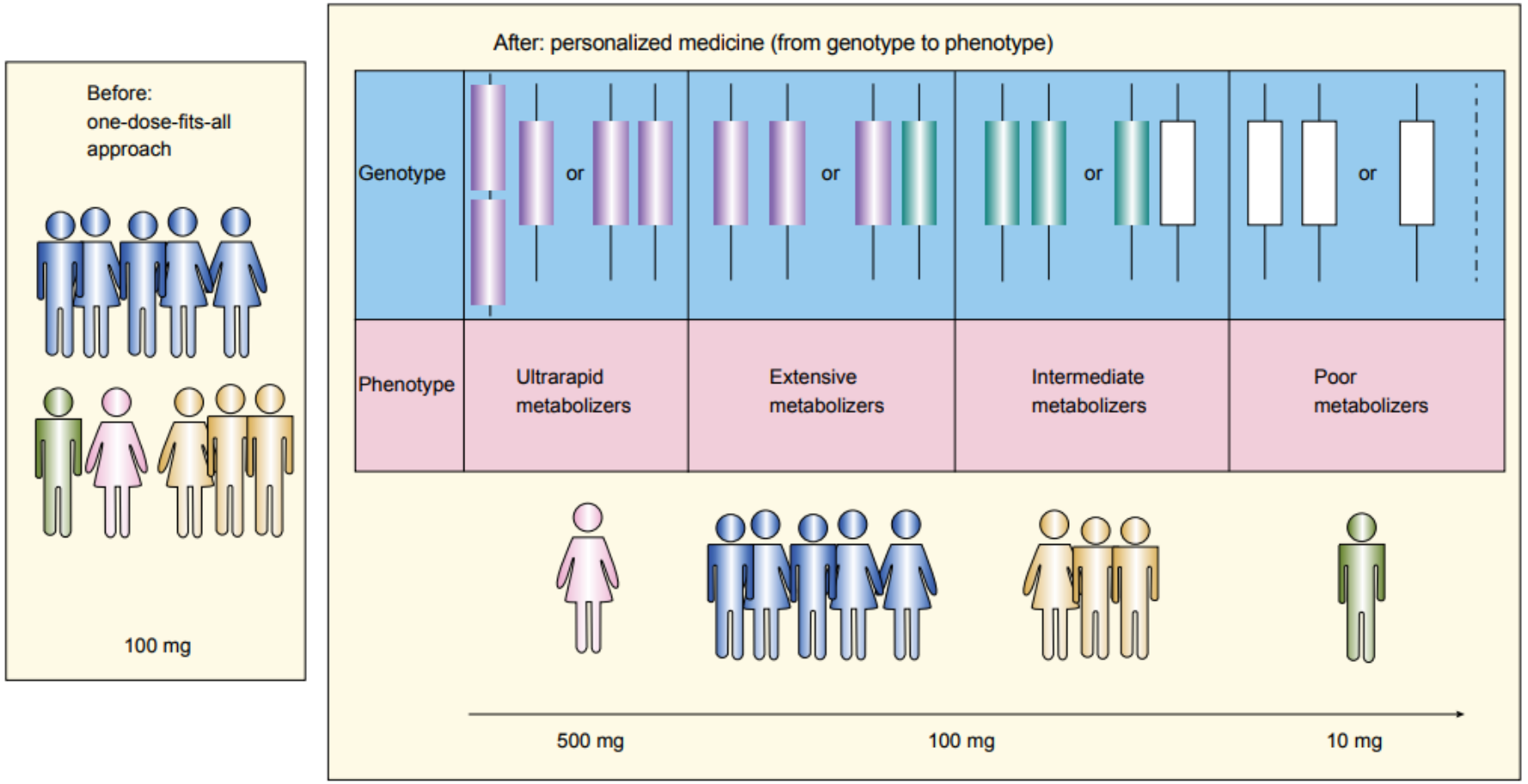
**NOTE: The number of sites of care is NOT a total of the categories listed below, as several of the sites are also listed in multiple categories (e.g., there are 135 CLCs within the 168 medical centers)

Source: VSSC, QFS 1st Qtr FY16

Why perform pharmacogenetic testing in the VA?

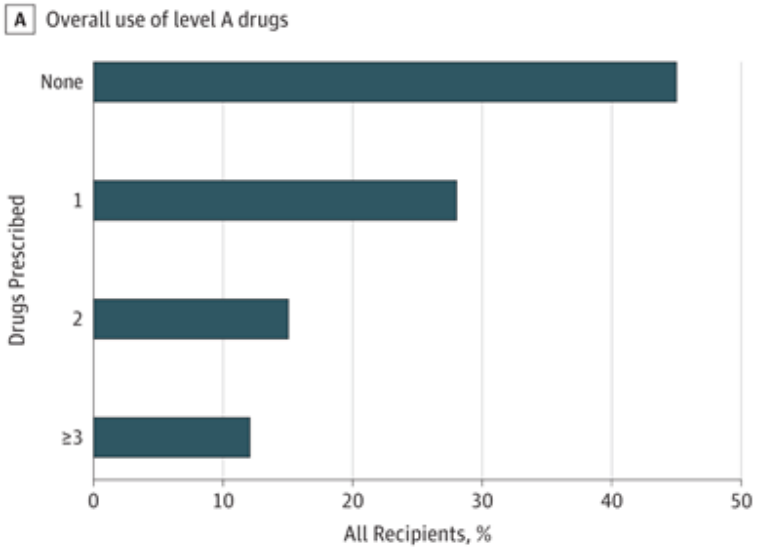
One-Drug Does Not Fit All

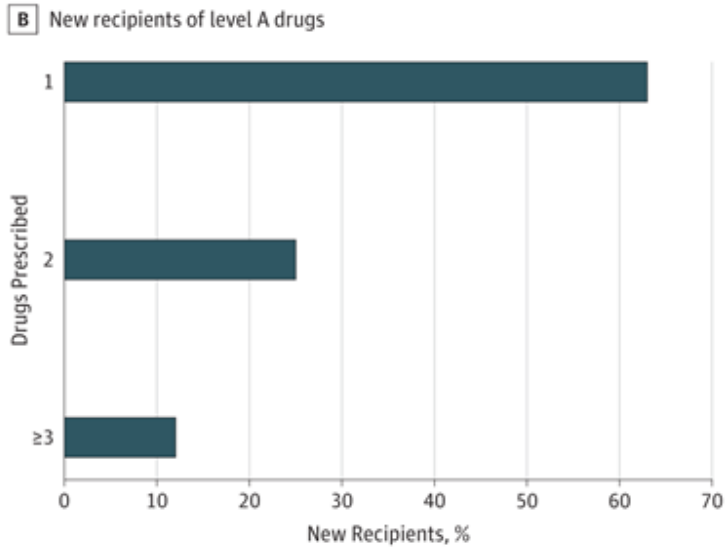
Genetic Variation in Drug Metabolizing Genes Can Be used to Individualize Drug Dose



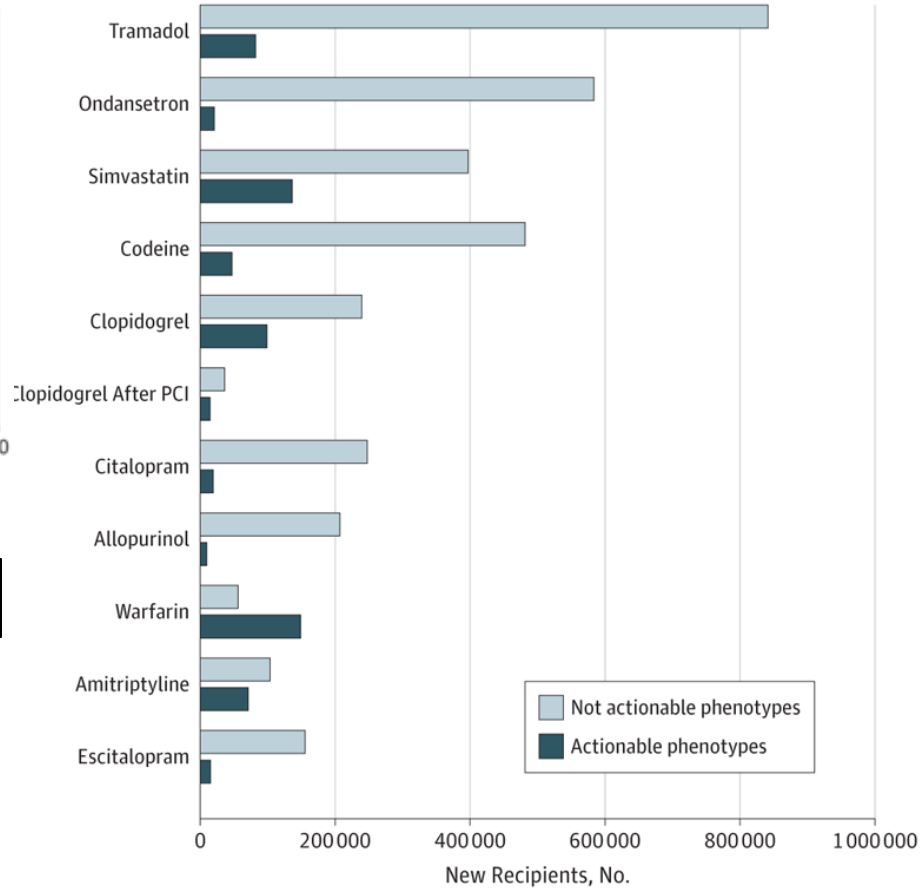
Xie, H., Frueh, F.W. *Personlized Medicine*. 2005; 2(4)

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

SANFORD imagenetics

Gene	Alleles tested
CYP2C19	*2*3*4*5*6*7*8*17
CYP2C9	*2*3*5*6*8*11
CYP2D6	*2*3*4*6*9*10*41
CYP3A5	*3*6*7
DPYD	*13*2A rs67376798
SLCO1B1	*1B*5*15*17
TPMT	*2*3A*3B*3C*4
VKORC1	-1639 A
CYP2D6 copy number	within exon 9

Coming in February 2020: *IFNL3*, *CYP4F2*, *CYP2C* cluster

What medications are impacted by the panel?

Drug List

Amitriptyline	Codeine	Imipramine	Ribavirin*	Trimipramine
Atomoxetine	Desipramine	Interferon, pegylated*	Sertraline	Tropisetron
Azathioprine	Doxepin	Mercaptopurine	Simvastatin	Voriconazole
Capecitabine	Escitalopram	Nortriptyline	Tacrolimus	Warfarin
Citalopram	Fluorouracil	Ondansetron	Tamoxifen	
Clomipramine	Fluvoxamine	Paroxetine	Thioguanine	
Clopidogrel	Fosphenytoin	Phenytoin	Tramadol	*coming soon

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

PLoS Med. 2007 Aug;4(8):e209
JAMA. 2016;316(15):1533-1535.
CLINICAL PHARMACOLOGY & THERAPEUTICS VOLUME 101 NUMBER 3 | MARCH 2017

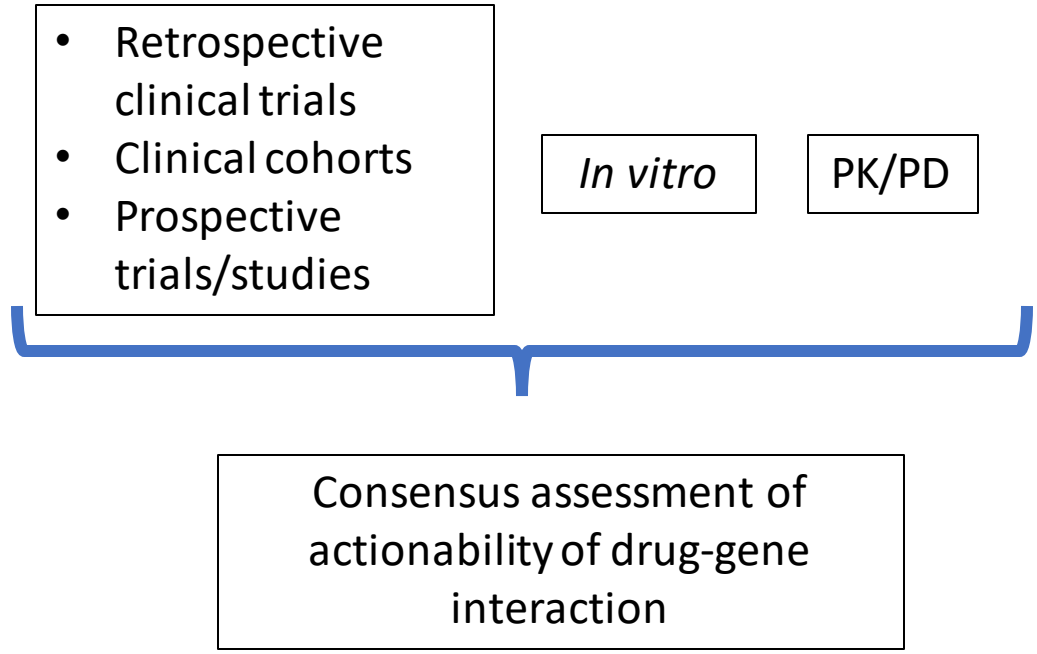
What is the evidence base supporting PGx informed prescribing?

CPIC – An evidenced based approach to developing PGx dosing guidelines

CPIC™
Clinical Pharmacogenetics Implementation Consortium

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



CPIC™ Clinical Pharmacogenetics Implementation Consortium

Level Definitions for CPIC Genes/Drugs

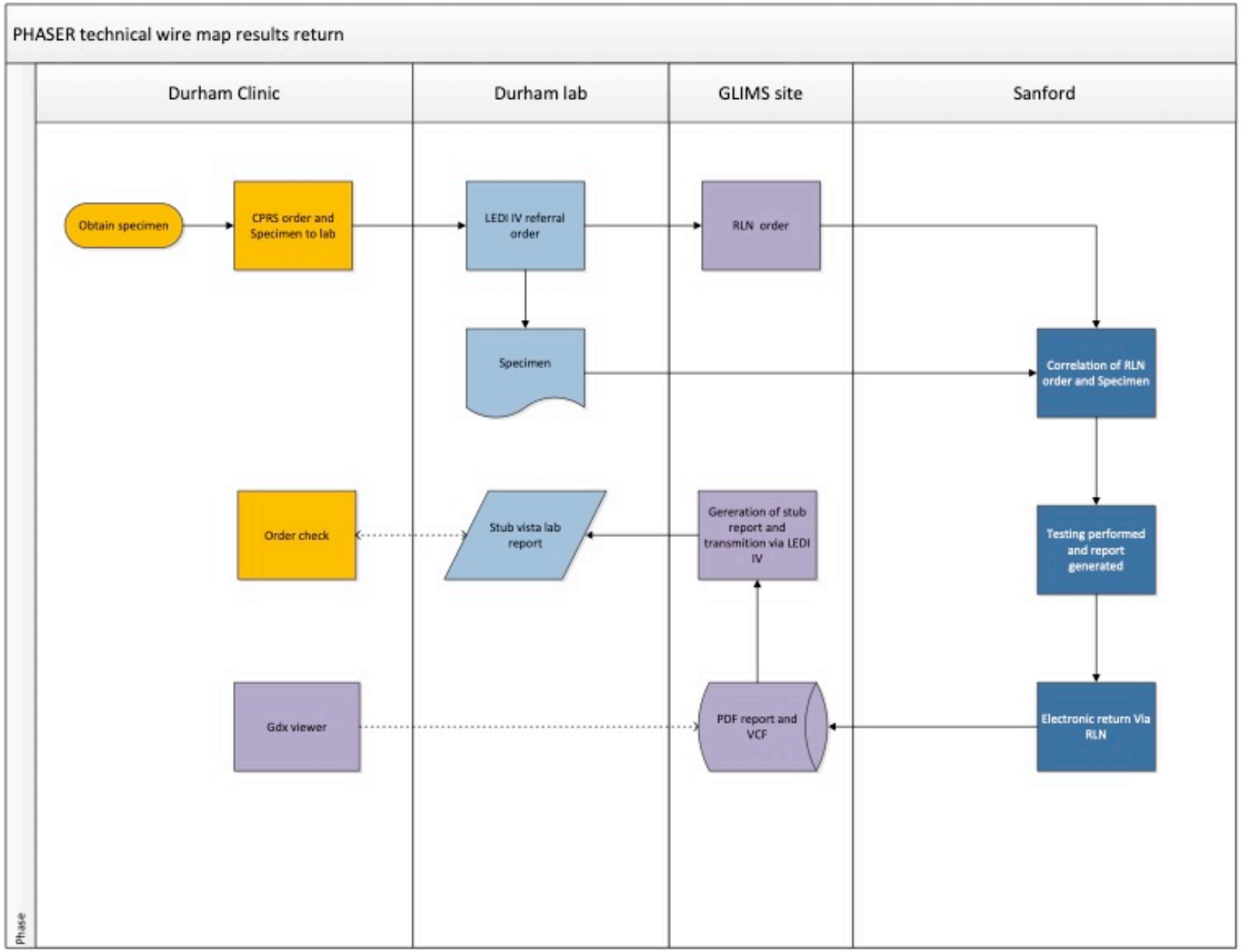
PHASER's focus

CPIC Level	Clinical Context	Level of evidence	Strength of Recommendation
A	Genetic information should be used to change prescribing of affected drug	Preponderance of evidence is high or moderate in favor of changing prescribing	At least one moderate or strong action (change in prescribing) recommended.
B	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	Preponderance of evidence is weak with little conflicting data	At least one optional action (change in prescribing) is recommended.
C	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.	Evidence levels can vary	No prescribing actions are recommended.
D	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.	Evidence levels can vary	No prescribing actions are recommended.

CPIC™
Clinical Pharmacogenetics Implementation Consortium

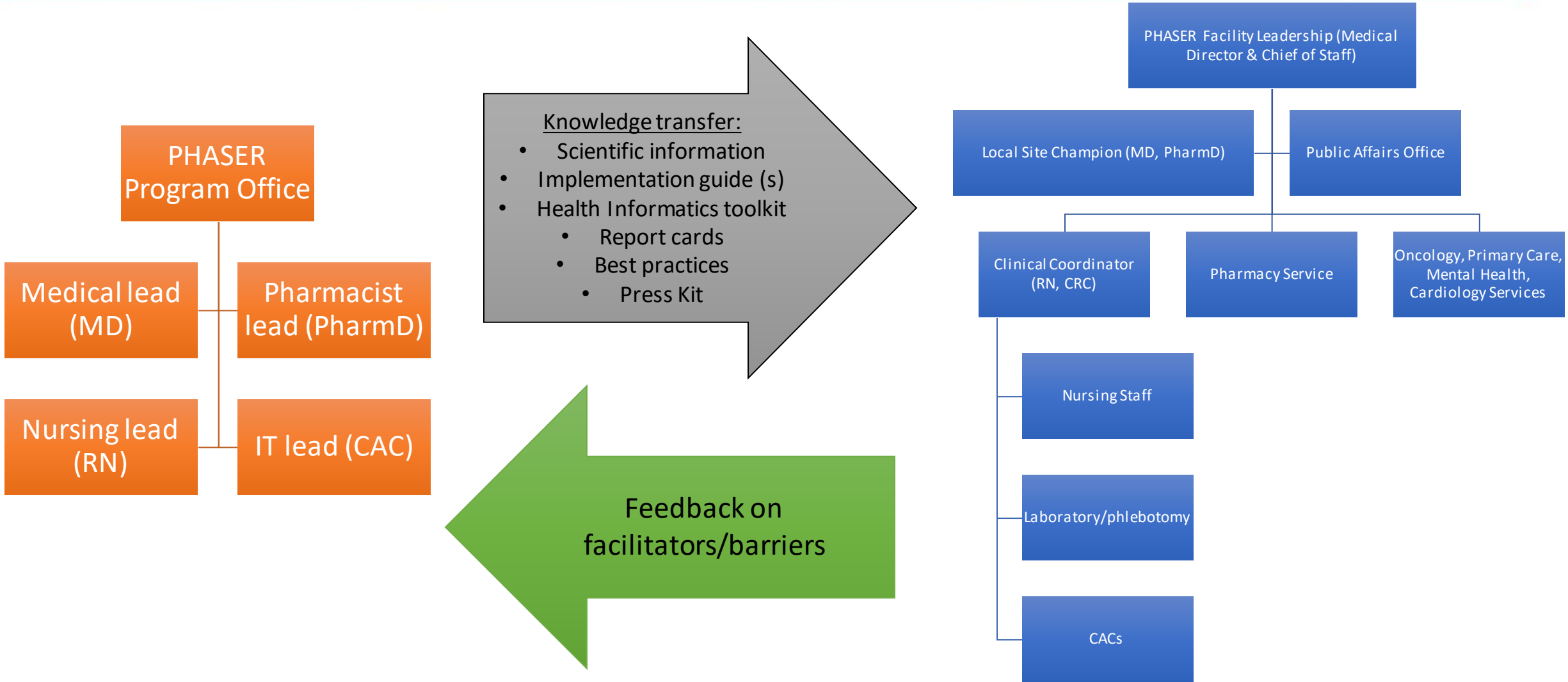
Bi-directional interface with PGx laboratory to store data as computable elements

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



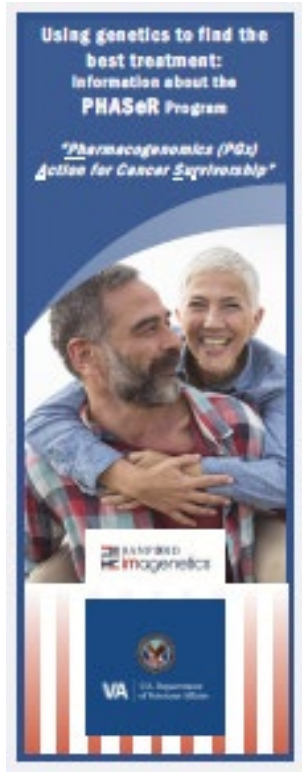
Courtesy Mike Icardi, MD

Train-the-trainer model of information diffusion



Pre-test patient education

Pre-appt. mailings



SANFORD imagenetics VA U.S. Department of Veterans Affairs

New program offering genetic testing for veterans to inform decisions about your medications

FREQUENTLY ASKED QUESTIONS (FAQS) for the "Pharmacogenomics Action for Cancer Survivorship" (PHASER) Program.

Sanford Health and the U.S. Department of Veterans Affairs have teamed up to offer genetic testing to current VA health care system patients at no cost to the patient. We want to help your doctor find appropriate medications for a number of common health concerns, including pain, depression, anxiety and blood clotting.

What is genetic testing?
Genetic testing finds differences in genes that are related to your health. There are many different genetic tests. Genetic tests look for changes in your genetic makeup (DNA) that are linked to certain conditions, physical traits, disease risk or how you respond to medication.

What type of genetic test does this program offer?
The type of genetic testing we're offering is a pharmacogenomic test. Pharmacogenomics, or PGx, determines how you respond to medication because of your genetics. Everyone responds to medicines differently, and sometimes these differences are due to gene changes. PGx testing uses your DNA to help your doctor determine prescription drugs that may work better for you. You can potentially reduce the trial-and-error process with certain medications, limit your side effects and get better drug responses by knowing the right drug at the right dose. This genetic test only provides information about your response to medicine. It does not provide information about the genetic risk of developing or recurring cancer, nor does it diagnose rare genetic diseases.

Who can get tested?
The genetic testing program launched in 2019 at the Durham VA Medical Center in Durham, North Carolina. The program plans to expand to all VA sites over time. Our goal is to test 250,000 U.S. veterans across 125 locations by 2022. Patients are not required to have a previous cancer diagnosis or any other diagnosis to participate.

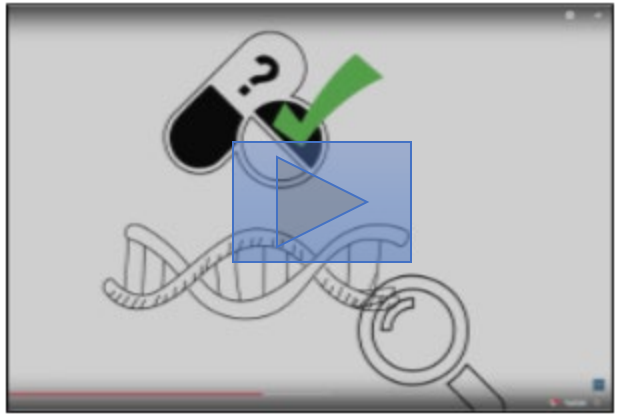
What will this cost?
This program comes at no cost for veterans or taxpayers due to a generous $25 million gift from philanthropist Denny Sanford and a matching fundraising effort from Sanford Health. Although the test itself will be provided at no cost to VA patients, standard co-payments for regular doctor visits and medications prescribed by their doctors are not covered.

How does this test help my doctor make better decisions when prescribing medications?
The test results will go back to your doctor with information on how your genetic profile may affect your body's response to several commonly prescribed medications. This information, along with other factors specific to you, can help your doctor when prescribing your medications.

What if new drugs come out or new information is learned in the future for the genes tested?
There's no need for additional testing if the new drug or information is related to the genes we looked at with this PGx test. We'll simply update your VA medical record with the new information.

Website

Pre-test Video



Clinic Posters

Post-test patient education to support PHASER

Post-test mailings

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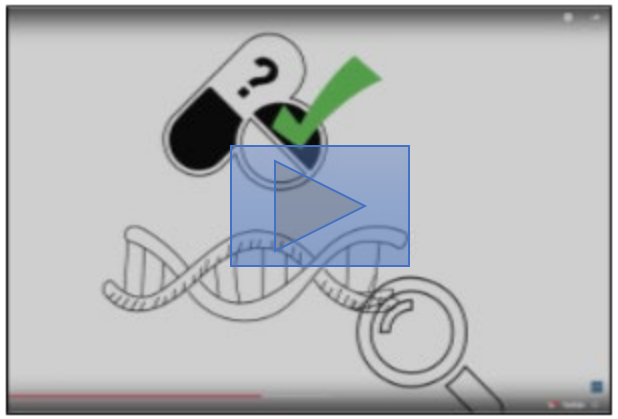
Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*1/*17	Rapid Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *17
CYP2C9	*1/*3	Intermediate Metabolizer	*2, *3
CYP2D6	*2/*10	Normal Metabolizer	*2, *3, *4, *4M, *6, *8, *9, *10, *17, *29, *41
CYP3A5	*3/*3	Poor Metabolizer	*3, *3C, *6, *7
DPYD	*1/*1	Normal Metabolizer	*2A, rs67376798 A, *13
SLCO1B1	*1/*5	Decreased Function	521T>C, 388A>G, -11187G>A
TPMT	*1/*3A or *3B/*3C	Intermediate or Poor Metabolizer	*2, *3A, *3B, *3C, *4
VKORC1 and CYP2C9	-1639G>A G/G, *1/*3	Intermediate Warfarin Sensitivity	-1639G>A

Post-test Video

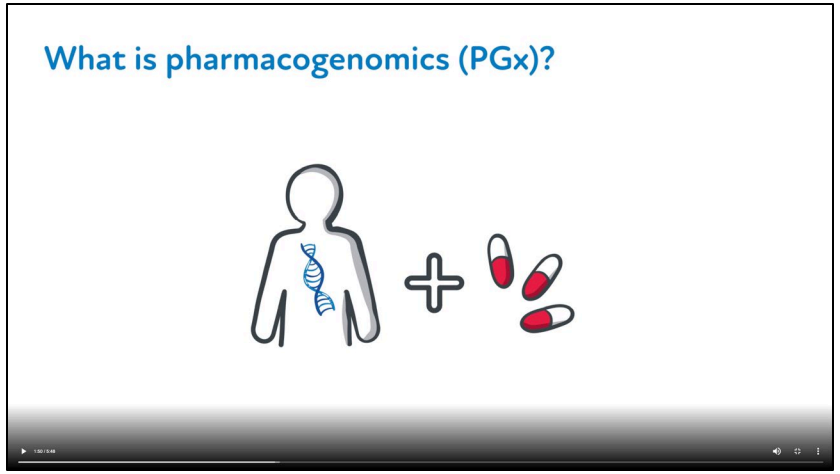


Provider Training opportunities to support PHASER

Grand Rounds, morning-meeting, noon conference type sessions:

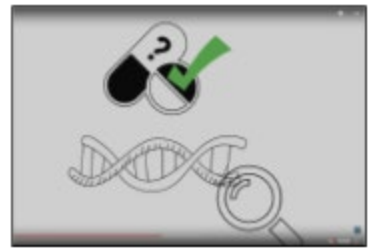
- Providers
- Nurses
- Pharmacists

Pre-test Videos



Online CE module

Post-test videos



Quarterly newsletter

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

"Traffic light" PDF report based on CPIC guidelines

SANFORD HEALTH

PATIENT INFORMATION
NAME: CARMEN RESEARCH3
MRN: F2717
DOB: 1/18/1979
SEX: Female

Potentially impacted Medications

CATEGORY	DRUG CLASS	STANDARD PRECAUTIONS	USE WITH CAUTION	CONSIDER ALTERNATIVES
Cardiovascular	Antiplatelets	Prasugrel (Effient) Ticagrelor (Brilinta) Vorapaxar (Zontivity)	Clopidogrel (Plavix)	
	Beta Blockers	Carvedilol (Coreg) Labetalol (Normodyne, Trandate) Metoprolol (Lopressor) Nebivolol (Bystolic) Propranolol (Inderal) Timolol (Timoptic)		
	Diuretics	Torsemide (Demadex)		
	Statins		Atorvastatin (Lipitor) Fluvastatin (Lescol) Lovastatin (Mevacor, Altoprev, Advicor) Pitavastatin (Livalo) Pravastatin (Pravachol) Rosuvastatin (Crestor)	Simvastatin (Zocor)

"On the fly" PGx interpretation

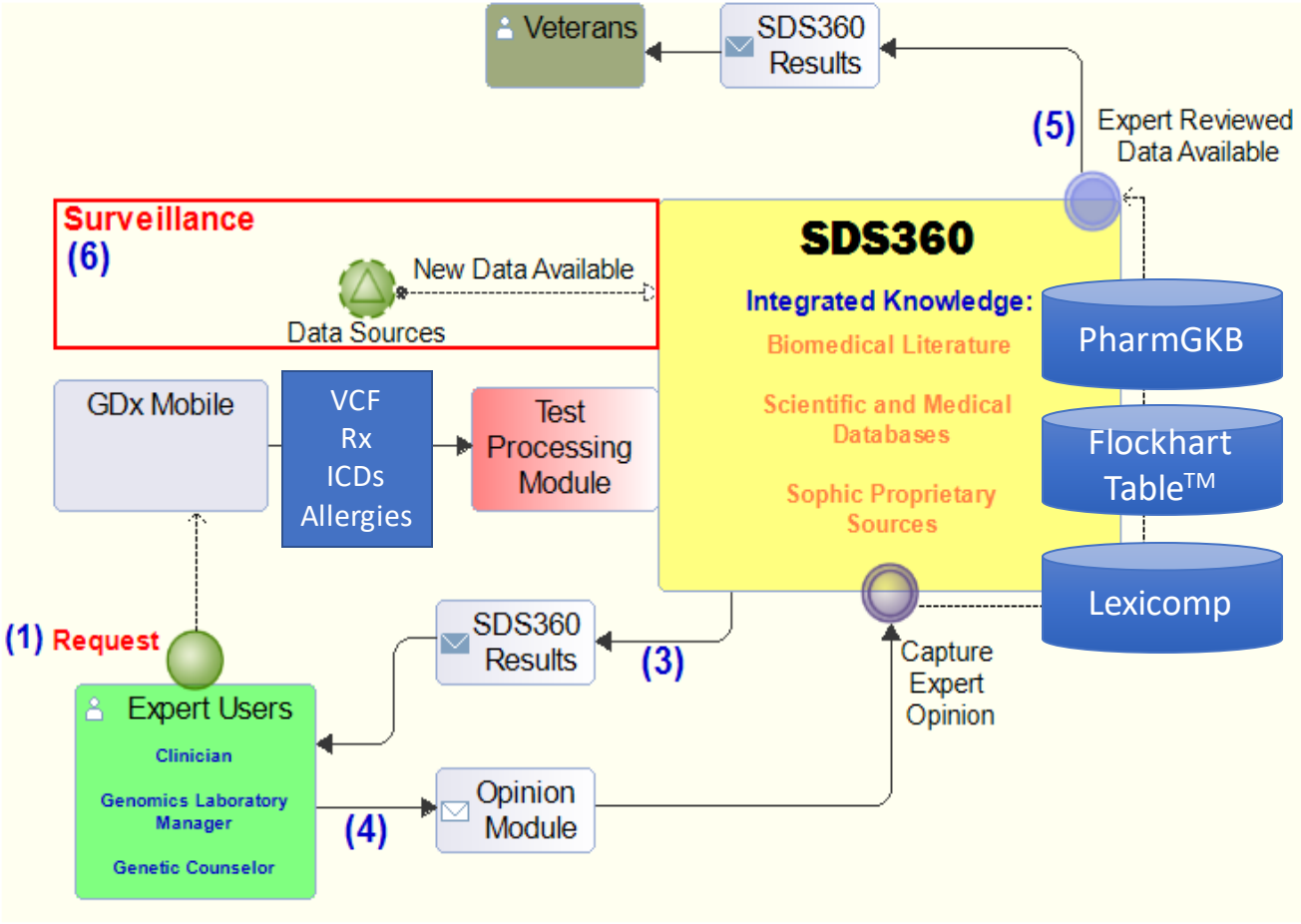
```
Gene: CYP2D6
  Result: Ultrarapid metabolizer
  Drugs impacted:
    - Codeine
    - Desipramine
    - Fluvoxamine
    - Nortriptyline
    - Ondanstron
    - Paroxetine
    - Tramadol

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

Gene: CYP2C9
  Result: Intermediate metabolizer
  Drug impacted:
    - Phenytoin
```

Translational software

Enabling deeper interpretation of PGx test results by linking to external databases

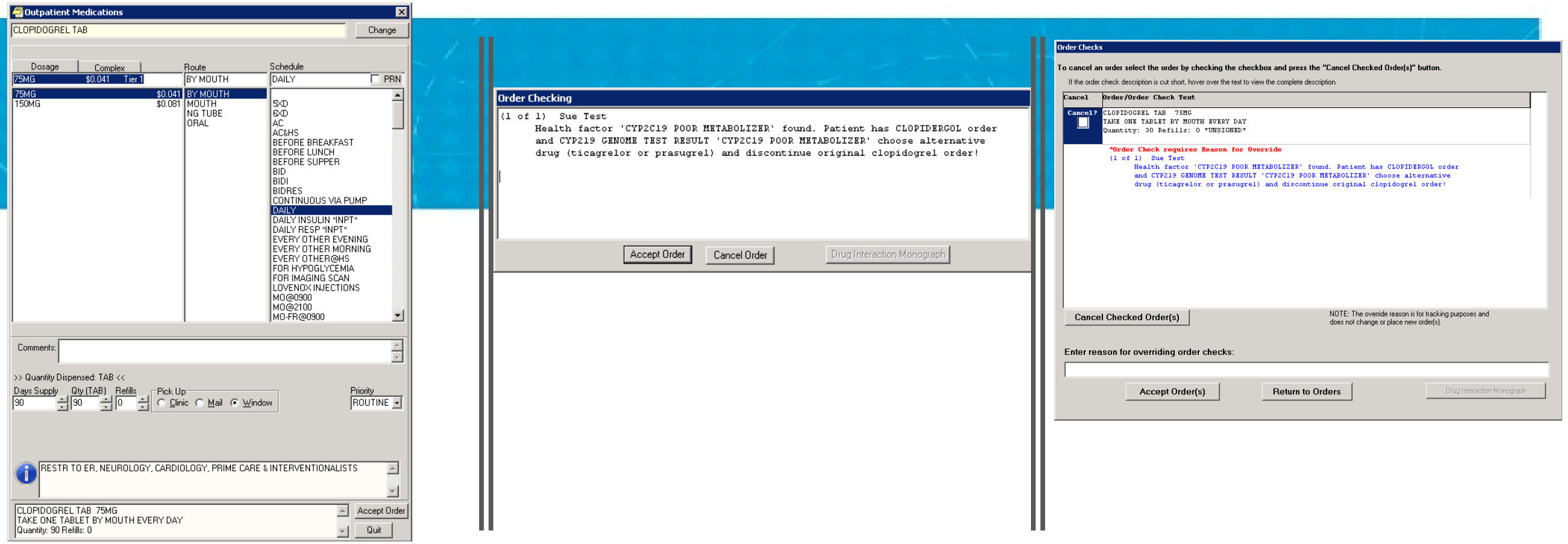


GDx collaboration (Constance Murphy, Julie Lynch, Mike Icardi) and SDS360 software

- Cloud based re-interpretation
- Leverage literature, ontologies, clinical data libraries
- Ability to 'socialize' knowledge and interpretations
- Customized views (pathology, oncology, pharmacy, etc.)

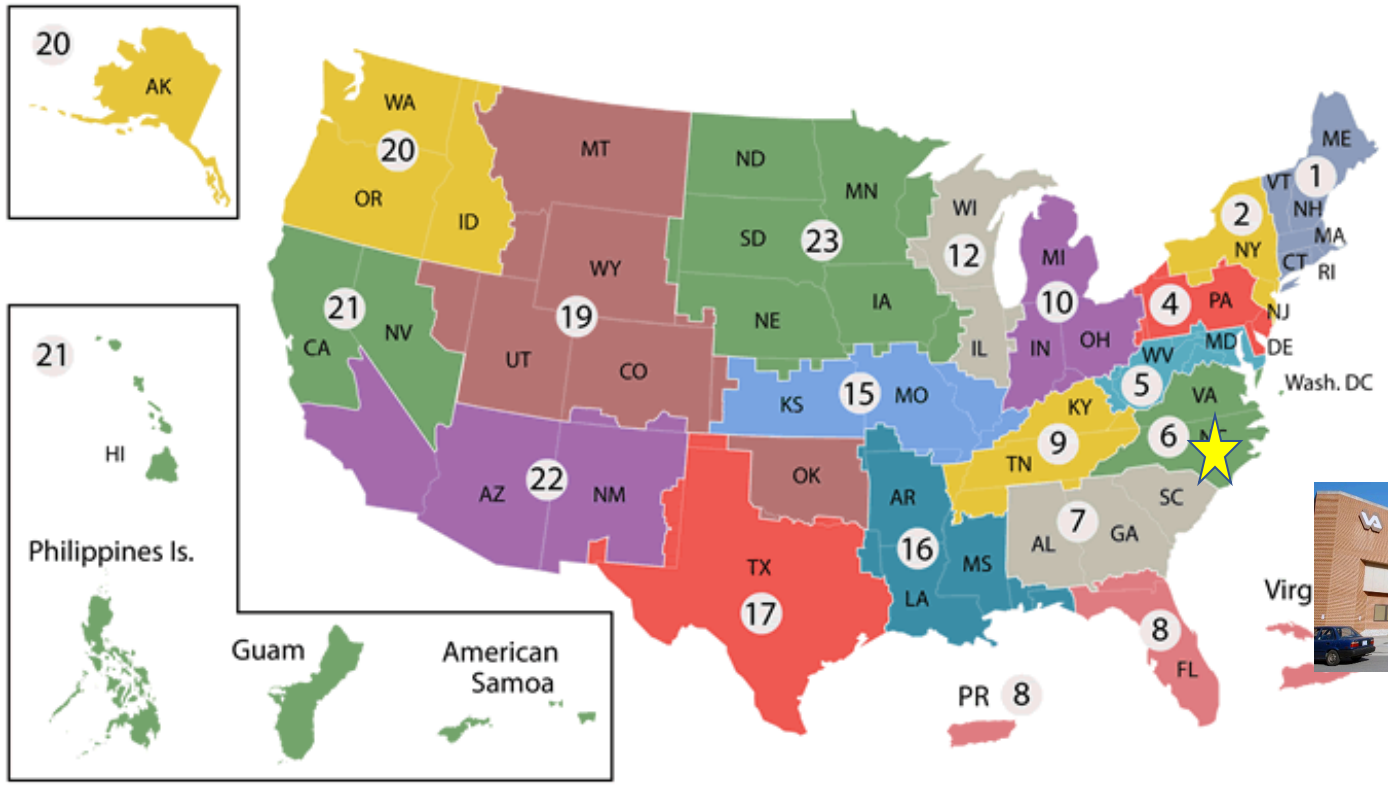
Interruptive CDSS incorporate PGx *after decision making* – Best for highest risk interactions

- 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

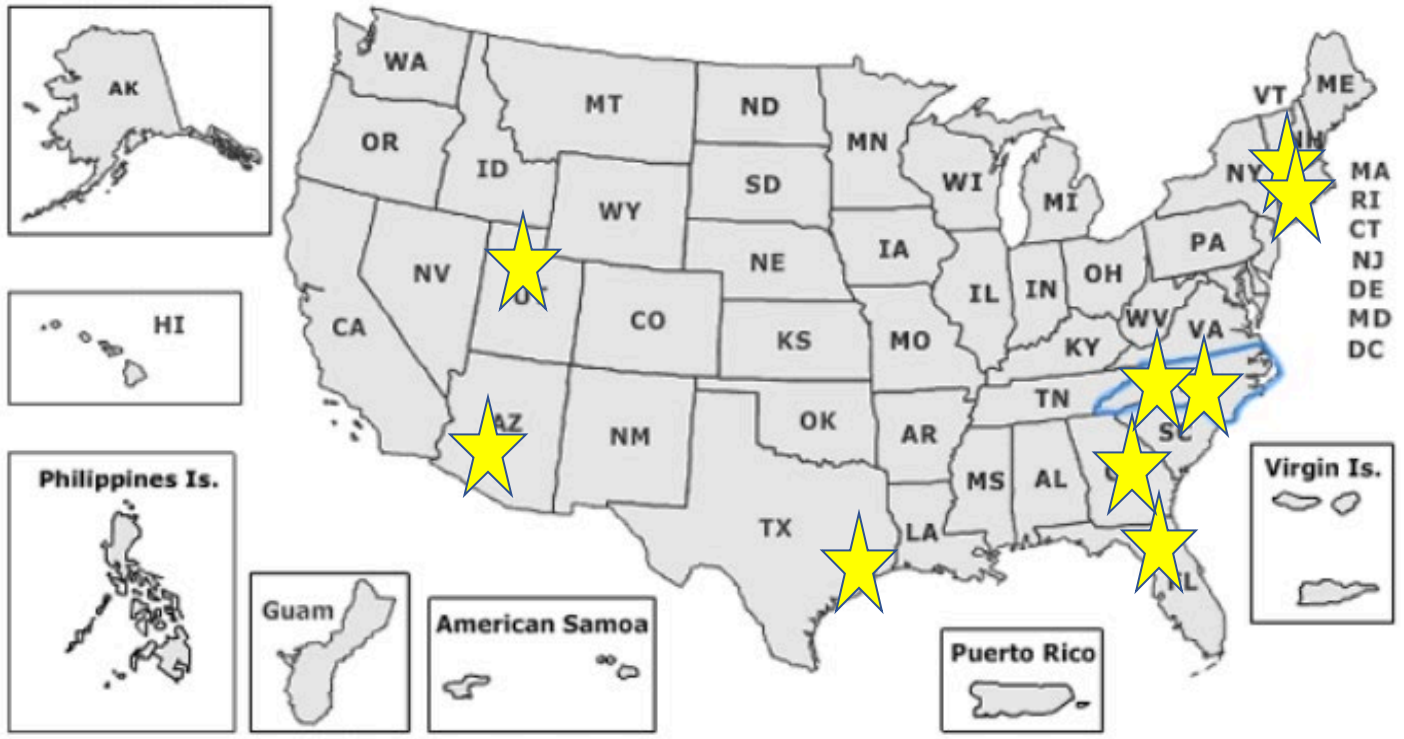
National interfacility consultations with PHASER pharmacist



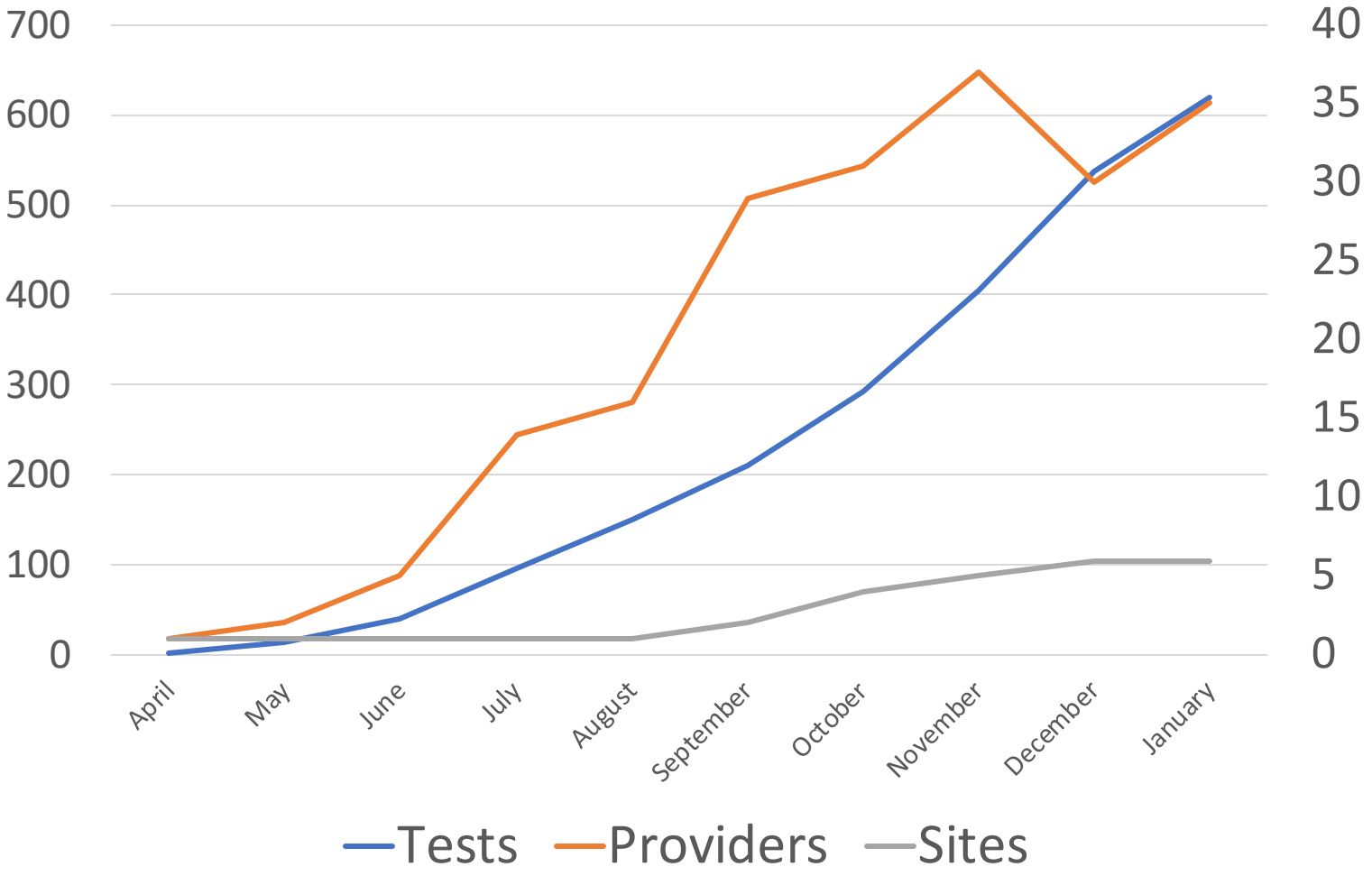
- Pre-test consultation (in reactive/diagnostic cases)
- Post-test consultation
- Medication reconciliation of active medications at time of PGx testing
- Comprehensive medication management in context of PGx

Jill Bates, PharmD, MS, BCOP, FASHP
Pharmacy Program Manager

PHASER snapshot 2019

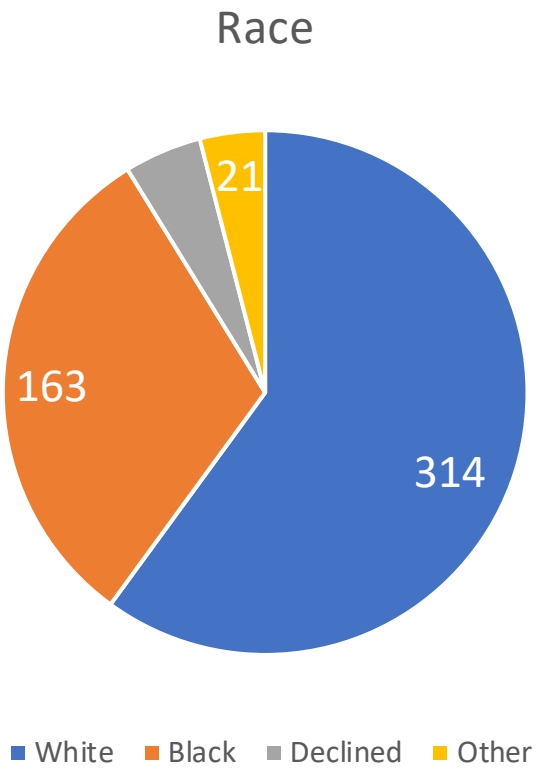


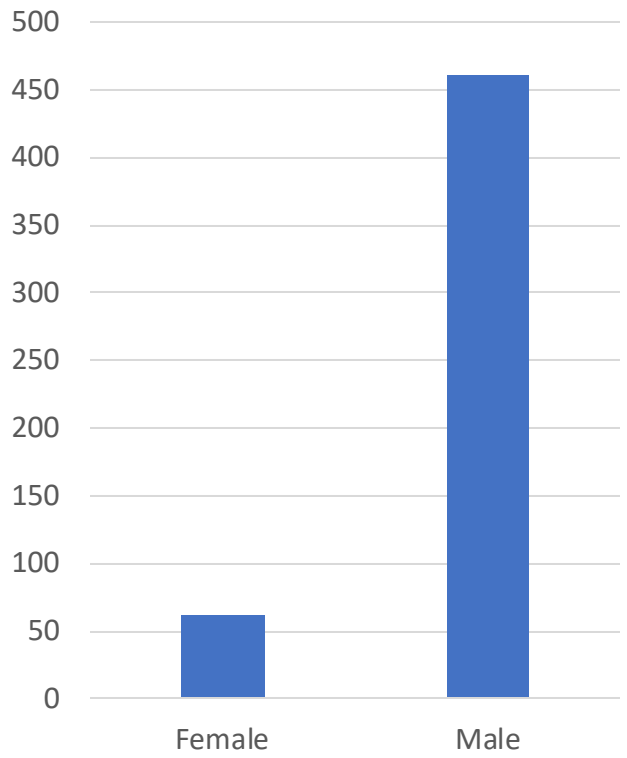
Overall characteristics since inception



Median turnaround time = 16 days

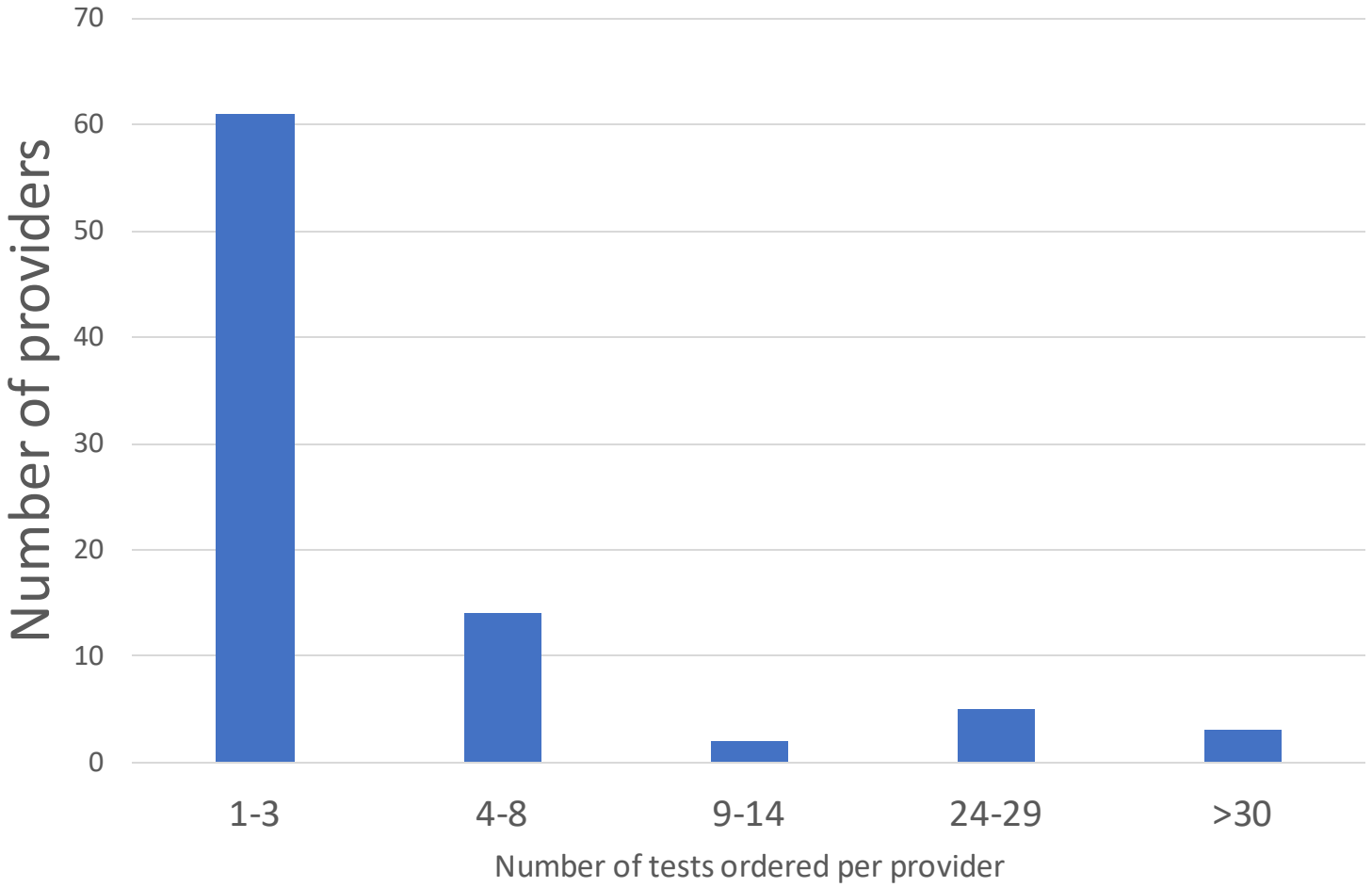
Patient characteristics

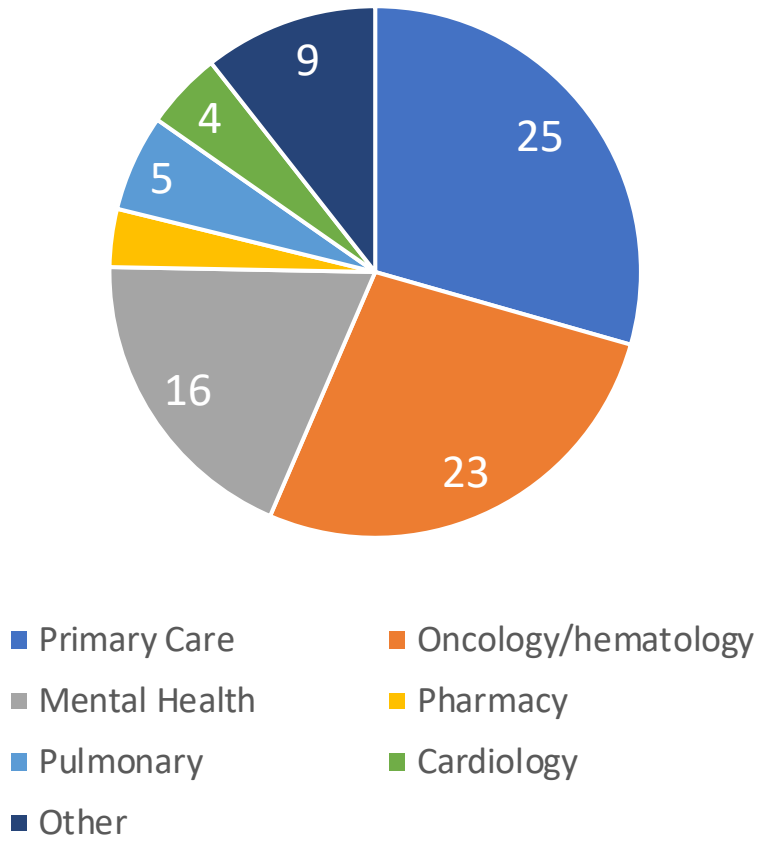




Average age = 65 years

Provider characteristics

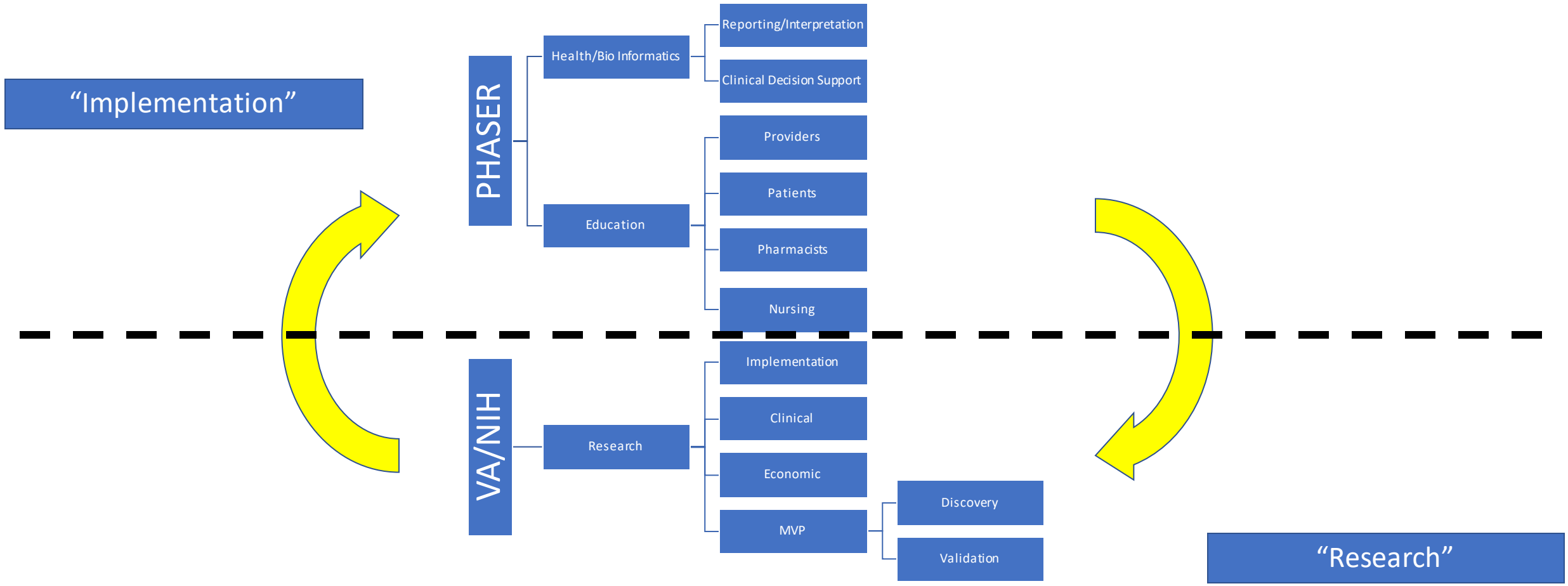




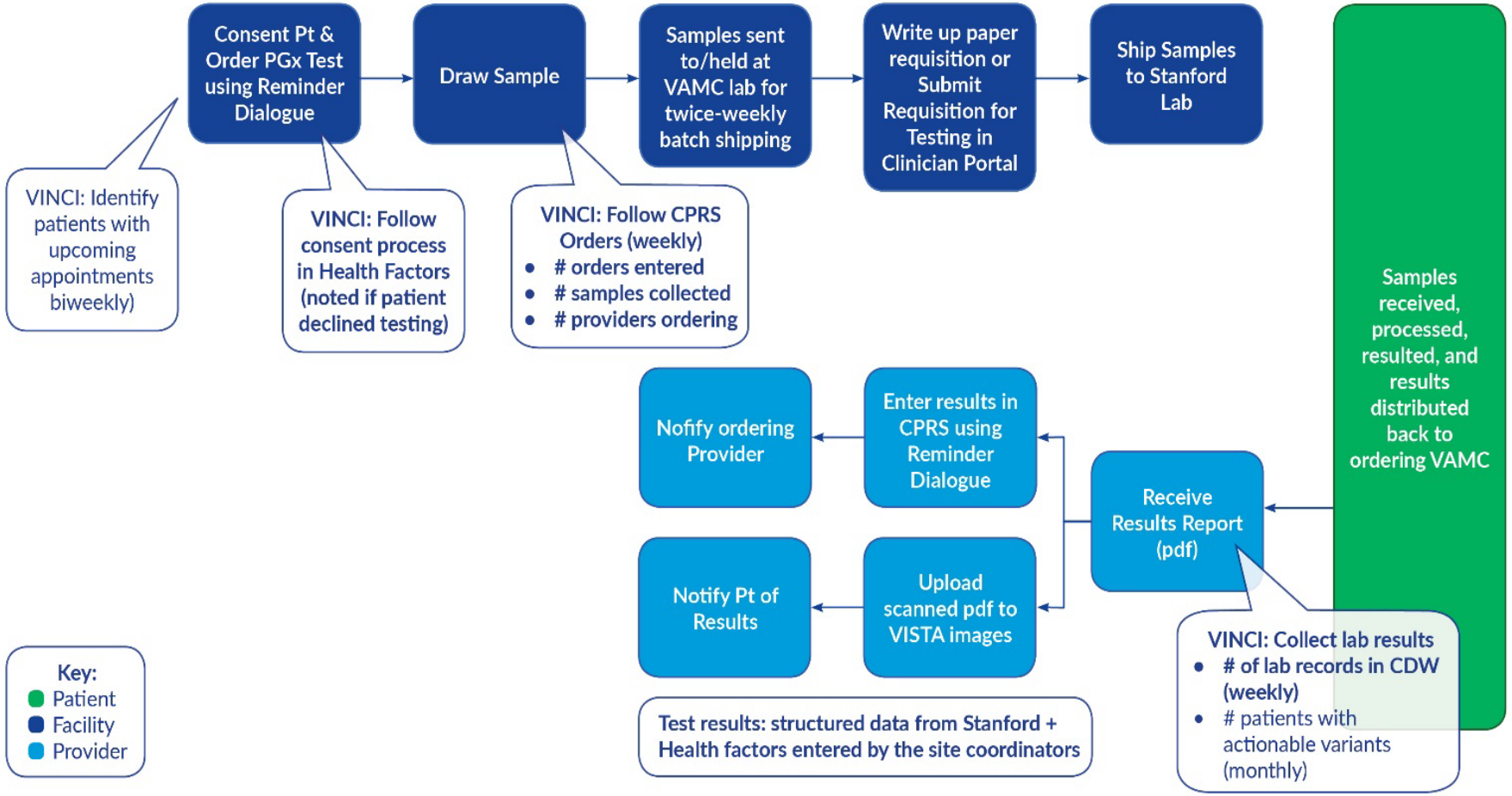
PHASER Outcomes and Research Opportunities

Collect and analyze uptake and use of PGx data during implementation

Learning Health System



Data flow to support PHASER



VA Informatics and Computing Infrastructure

Catherine Chanfreau, PhD
Director, PHASER data core

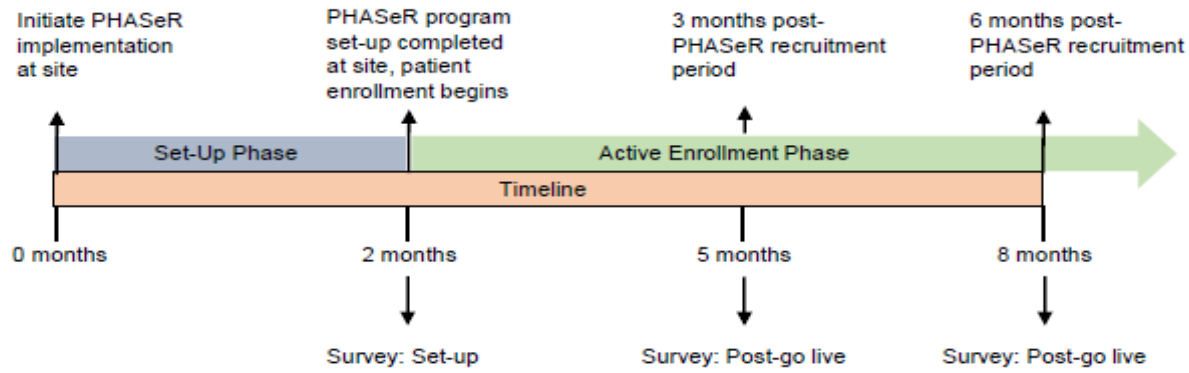
Outcomes of interest for retrospective research

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

Adapted from Peterson et al *Lancet* 2019

Using implementation science to optimize uptake

Summary of survey collection time points at each VA site



Key Personnel	Set-up	Post-go live
Site champs/coordinator	x	x
VA lab	x	x
Sanford lab (Linda Berg)	x	x
CAC/LIM	x	
Provider (active – consented patients)		x
Provider (inactive – attended in-services but have not consented patients)		x

Goals: Use established frameworks to evaluate

- Program materials
- Resource utilization and costs
- Implementation processes

Olivia Dong, PhD

Leveraging VA's Biorepository

The Clinical Pharmacogenetics Implementation Consortium Guideline for *SLCO1B1* and Simvastatin-Induced Myopathy: 2014 Update

LB Ramsey[1], SG Johnson[2,3], KE Caudle[1], CE Haidar[1], D Voora[4], RA Wilke[5,6], WD Maxwell[7], HL McLeod[8], RM Krauss[9], DM Roden[10,11], Q Feng[10,11], RM Cooper-DeHoff[12], L Gong[13], TE Klein[13], M Wadelius[14] and M Niemi[15,16]

Clinical Pharmacogenetics Implementation Consortium Guidelines for *CYP2C19* Genotype and Clopidogrel Therapy: 2013 Update

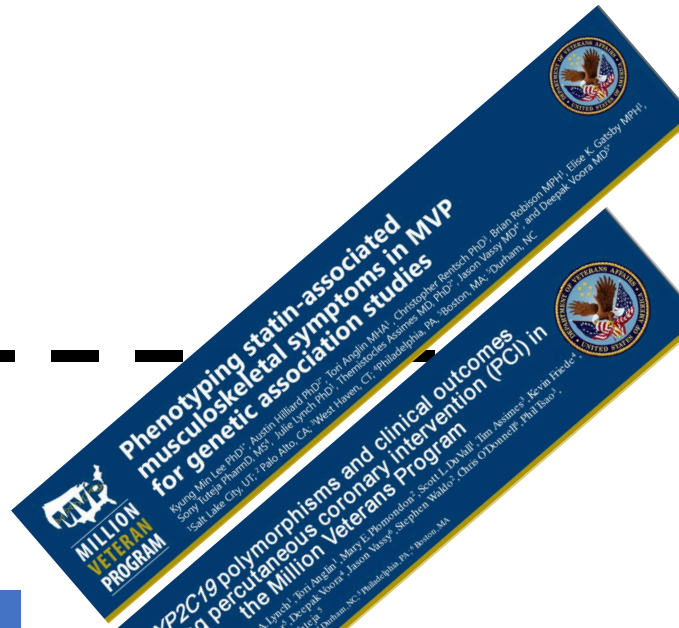
SA Scott[1], K Sangkuhl[2], CM Stein[3], J-S Hulot[4,5], JL Mega[6], DM Roden[7], TE Klein[2], MS Sabatine[6], JA Johnson[8,9,10] and AR Shuldiner[11,12]

PHASER

- Health/Bio Informatics
  - Reporting
  - Clinical Decision Support
- Education
  - Providers
  - Patients
  - Pharmacists
  - Nursing

VA

- Research
  - Implementation
  - Clinical
  - Economic
  - MVP
    - Discovery
    - Validation



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!

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