

# Building a pharmacogenomics program from the ground up: balancing research and clinical care

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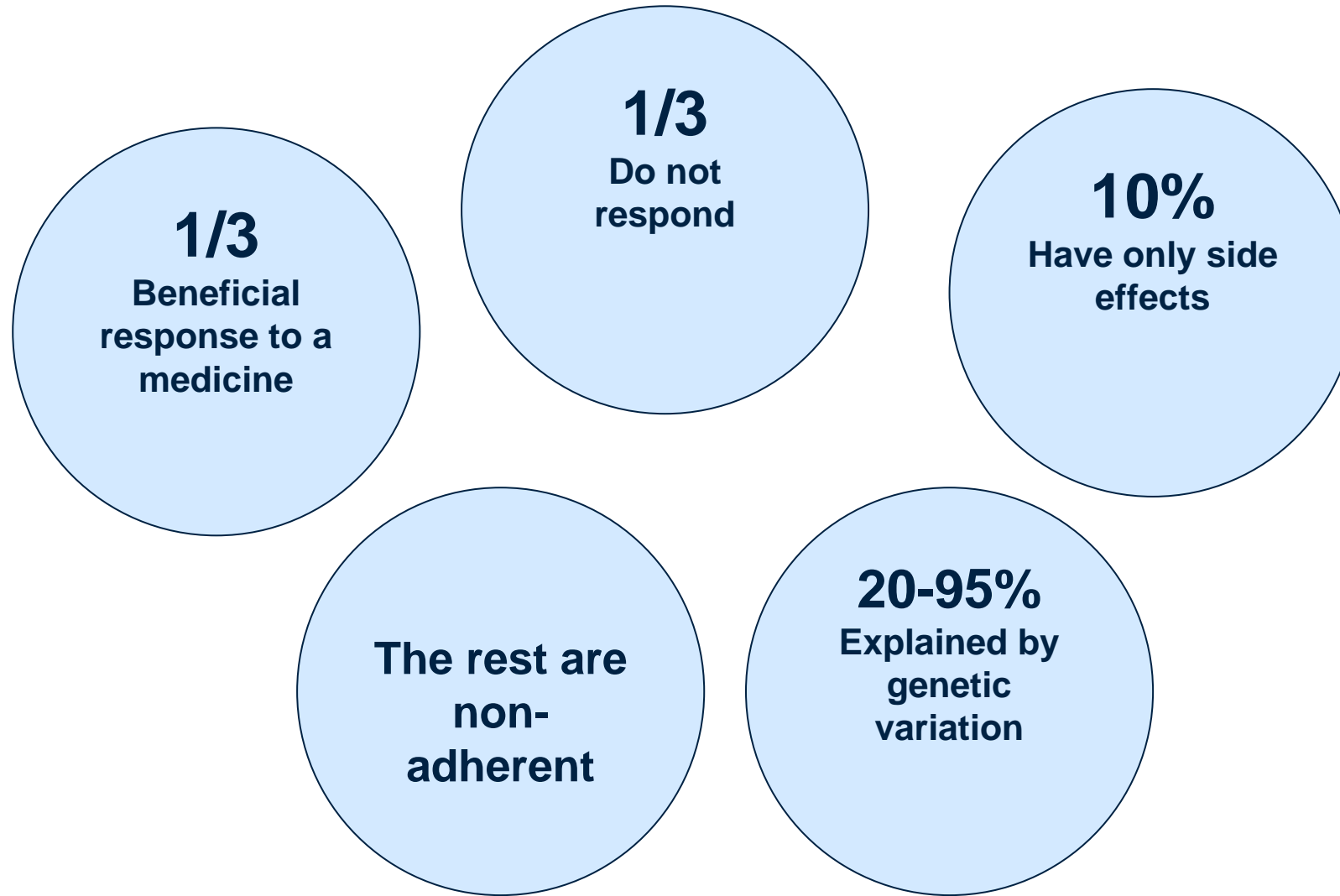
CPIC meeting October 5, 2023



# Outline

- Provide an overview of the PGx implementation strategy at Penn Medicine
- Describe current PGx implementation studies
- Discuss the outcomes of the PGx clinic

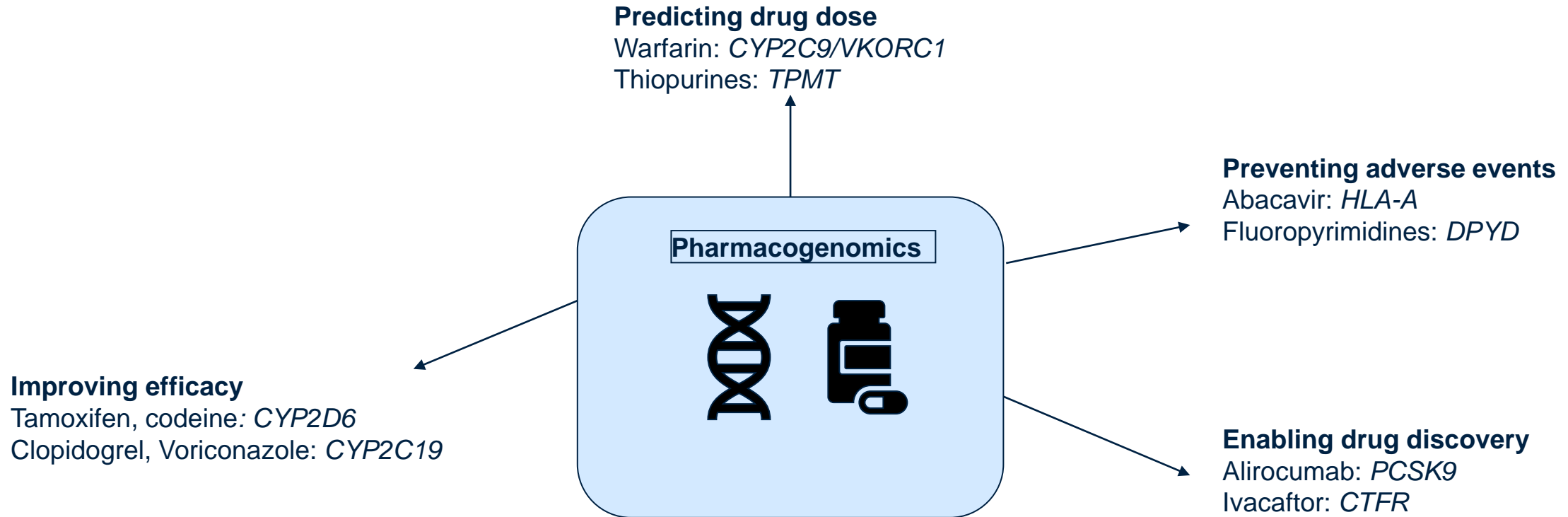
# Variability in drug response



<sup>1</sup> Maitland-van der Zee. European J Pharmacology 2000; 410: 121-30

<sup>2</sup> Roden DM. Circulation 2011;123:1661-1670

# Application of pharmacogenomics to clinical care and drug discovery



# What is the impact of pharmacogenomics?



Original Investigation | Genetics and Genomics

## Projected Prevalence of Actionable Pharmacogenetic Variants and Level A Drugs Prescribed Among US Veterans Health Administration Pharmacy Users

Catherine Chanfreau-Coffinier, PhD; Leland E. Hull, MD, MPH; Julie A. Lynch, RN, PhD; Scott L. DuVall, PhD; Scott M. Damrauer, MD; Francesca E. Cunningham, PharmD; Benjamin F. Voight, PhD; Michael E. Matheny, MD, MPH; David W. Oslin, MD; Michael S. Icardi, MD; Sony Tuteja, PharmD

JAMA Network Open. 2019;2(6):e195345. doi:10.1001/jamanetworkopen.2019.5345

June 7, 2019

Out of 7.7 million veterans<sup>1</sup>:

- 99% have at least 1 level A variant
- 37% receive at least 1 level A drug
- 25% receive at least 2 level A drug

At Penn Medicine (3.3 million patients)<sup>2</sup>:

- 98% have at least 1 level A variant
- 21% receive at least 1 level A drug

<sup>1</sup> JAMA Network Open. PMID: 31173123

<sup>2</sup> J Transl Med. PMID: 36443877

# Elements needed to get PGx into clinical practice



Evidence for gene-drug pairs



Guidelines for translating results into prescribing decisions



Access to testing



Reimbursement for testing



Informatics infrastructure to incorporate user friendly clinical decision support tools



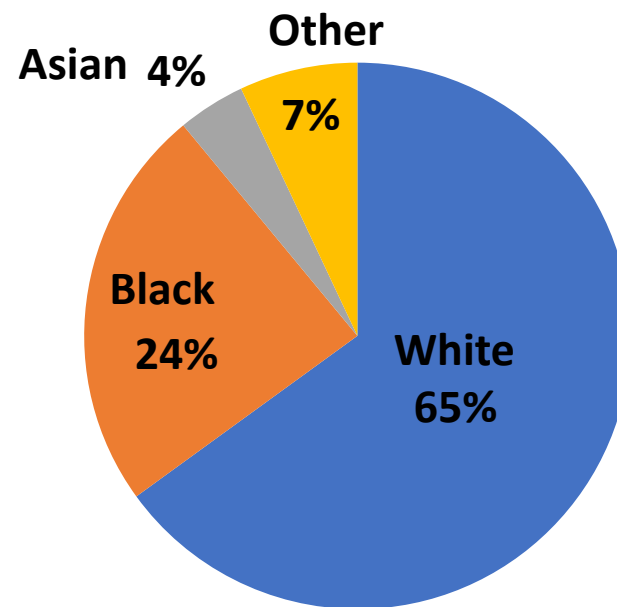
Provider knowledge regarding interpretation and application of PGx



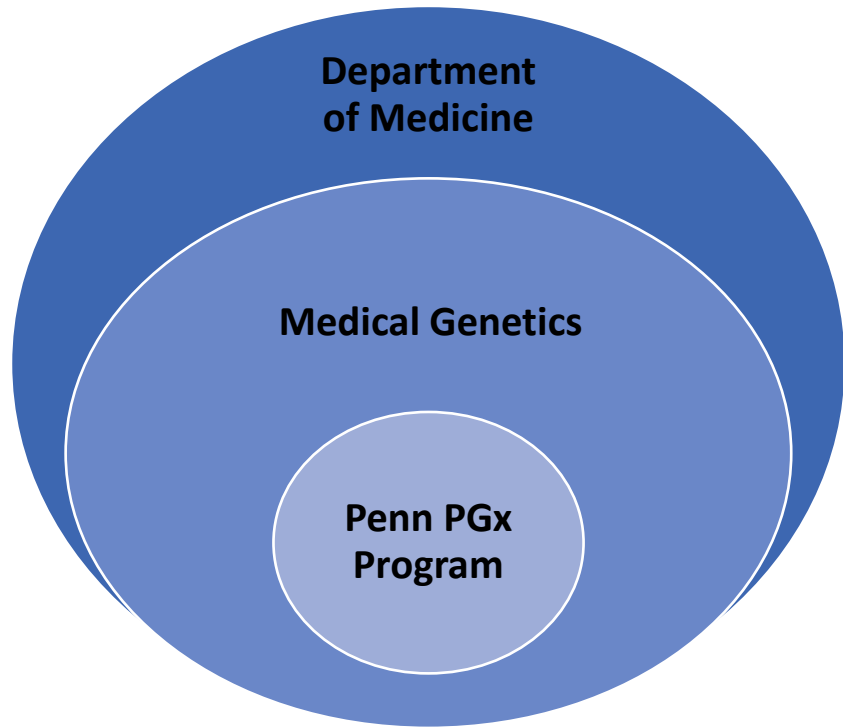
Incentives for clinicians to order tests



# Penn Medicine



6.5 million	Outpatient visits
337,000	ED visits
129,000	Adult admissions
7,478	Physicians
47,000	Employees

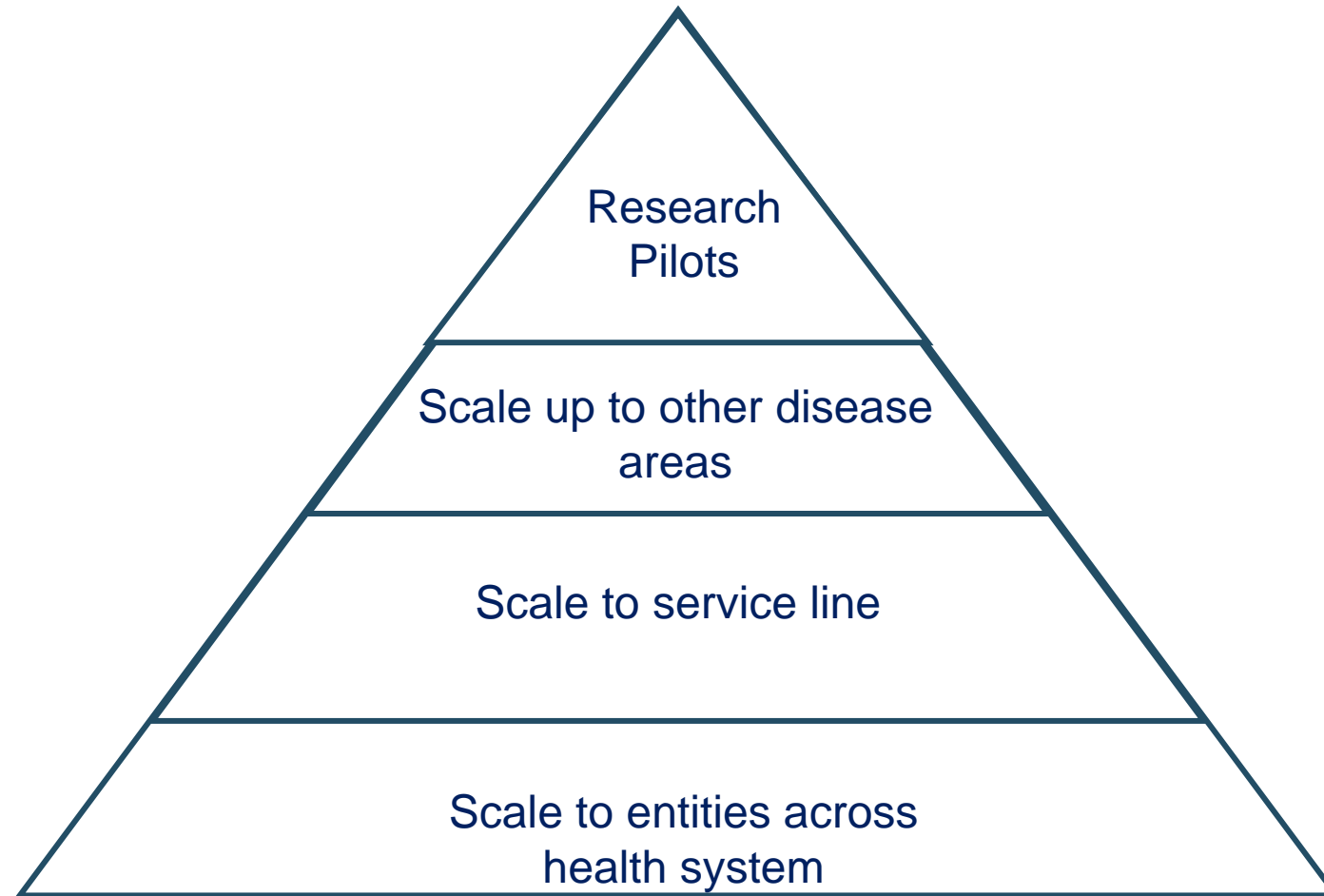


# Tackling roadblocks on the path to implementation

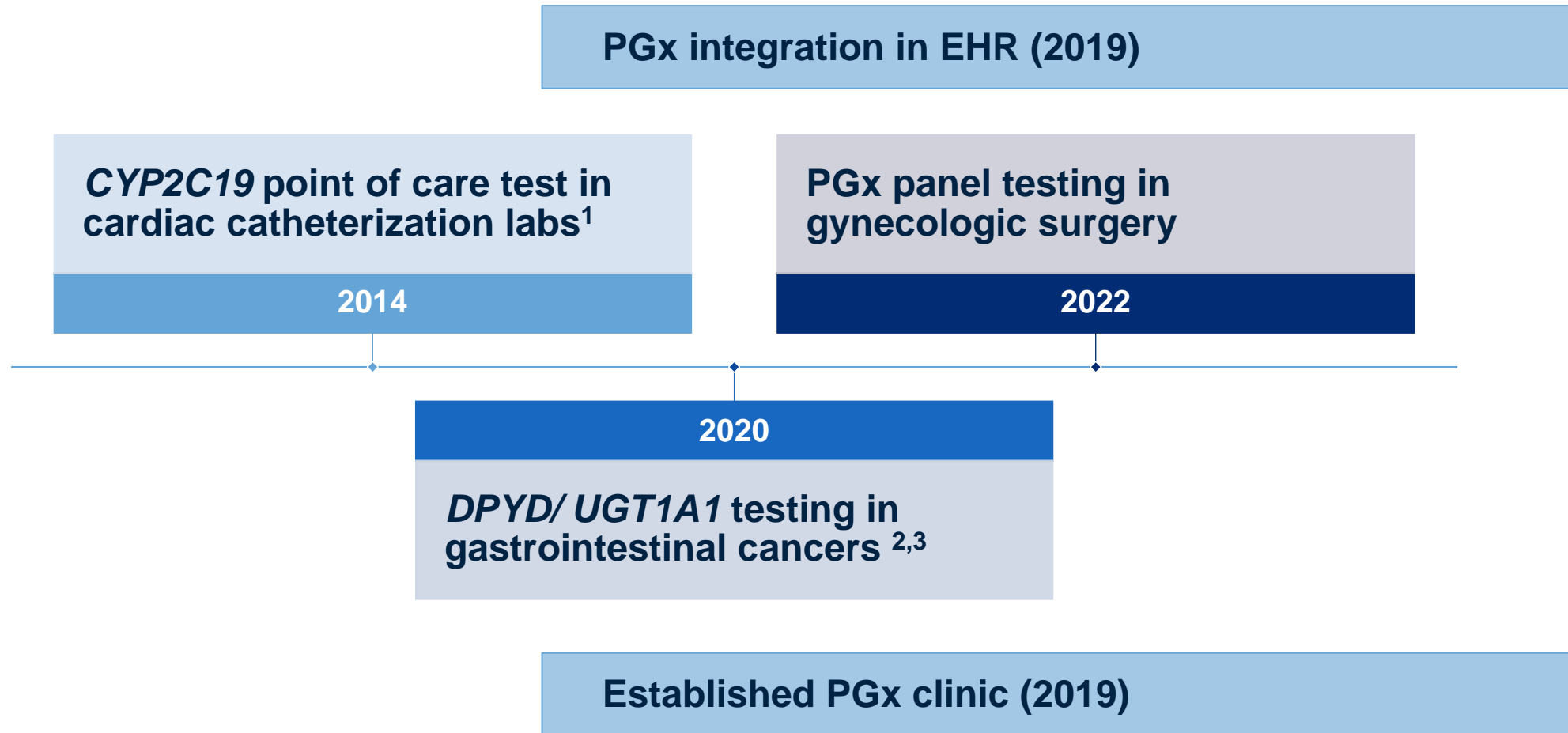
## Barriers

- ▶ Clinician skepticism
- ▶ Lack of clinician knowledge about PGx
- ▶ Lack of endorsement of PGx by medical organizations
- ▶ Lack of genotyped guided RCTs
- ▶ Laboratory support
- ▶ EHR infrastructure for returning PGx results

# Stepwise strategy for PGx implementation: a campaign of “wins”



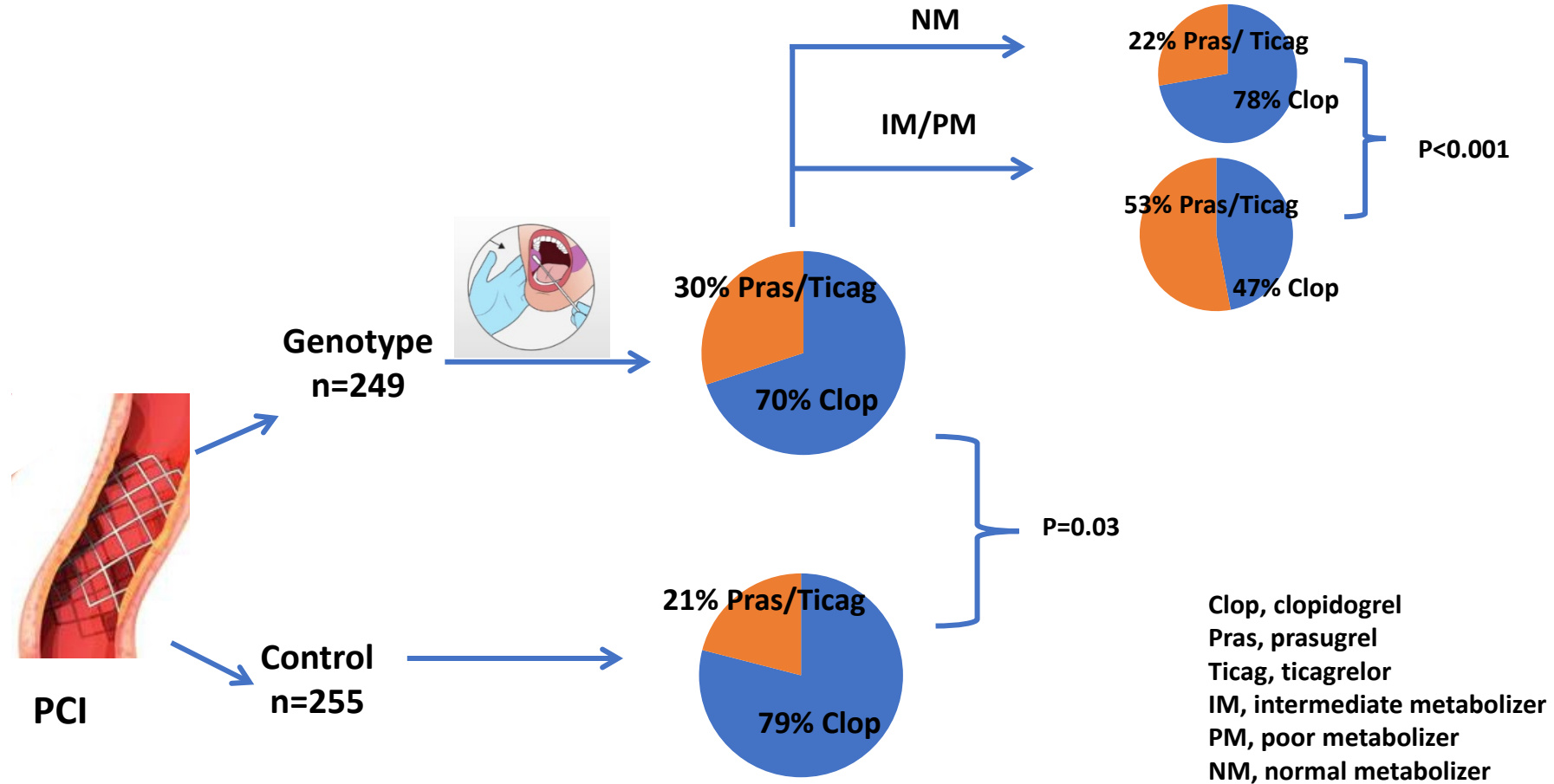
# Timeline of PGx research and clinical testing at Penn Medicine



<sup>1</sup> PMID: 31928229

<sup>2,3</sup> PMID: 34996412, PMID: 35865463

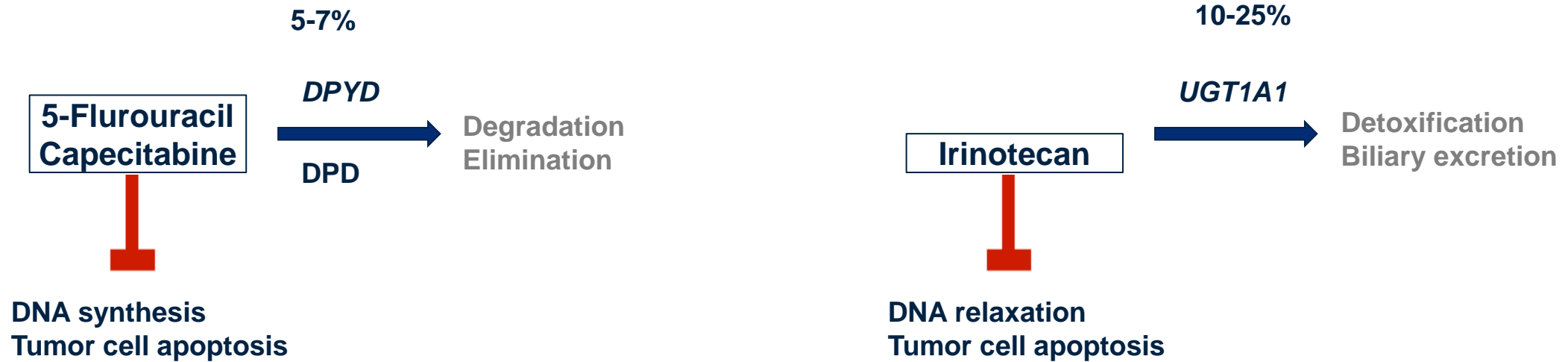
# CYP2C19- clopidogrel



## Benefits from the *CYP2C19* study

- ▶ Level of clinician engagement required for successful uptake of PGx
- ▶ Identified achievable intermediate outcomes to enable a “win” for PGx testing
- ▶ Established a workflow for returning PGx results to the EHR with CDS
- ▶ Helped facilitate transition to clinical use

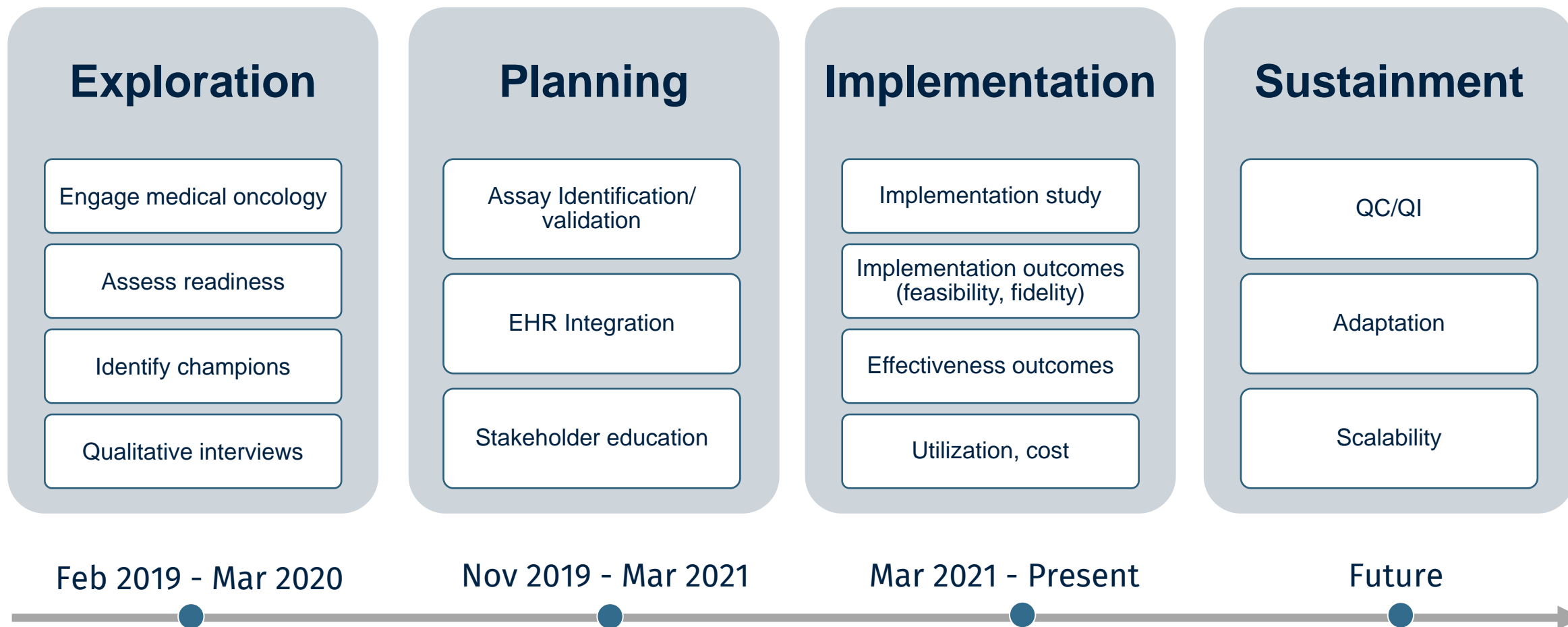
# *DPYD/ UGT1A1*- GI cancer therapies



*DPYD* variant carriers have greater dose-related toxicities

- Hematologic
- Gastrointestinal

# Implementation Science framework provides a roadmap



# Qualitative study helped identify workflow barriers for *PGx* testing in cancer care

1-on-1 semi-structured interviews with 25 oncology specialists

Barrier	Strategy
Long turnaround time (send-out)	Developed test with local partners
Difficulty accessing results	Discrete reporting in genomics module in Epic
Unclear dosing recommendations	Clinical decision support Train oncology pharmacists on PGx dosing
Limited evidence base	Educational initiatives on current guidance
Test costs	Testing covered by research funds



Kelsey Lau-Min, MD



# IMPACT GI: ImpleMenting PhArmagenetiC Testing in Gastrointestinal Cancers

- Pragmatic, non-randomized, open-label study across three Penn Medicine sites
- Goal: evaluate the feasibility of *DPYD/UGT1A1* testing in patients treated with fluoropyrimidines or irinotecan.

Implementation (primary)	Clinical effectiveness (secondary)
1. Determine <u>feasibility</u> , rate of PGx results returned prior to first dose of chemotherapy	1. Determine if providing PGx test results will decrease number of patients experiencing $\geq$ Grade 3 toxicity over first 6 cycles
2. Determine <u>fidelity</u> , level of acceptance by prescribers with genotype-based dosing guidelines	2. Determine if providing PGx test results will improve patient reported outcomes (PROs)
3. Determine <u>penetrance</u> , rates of testing among eligible patients	

Target enrollment: 300 patients



Lisa Varughese, PharmD

# Pharmacogenetic-guided Choice of post-Surgery analgesics (PRECISE)

- Randomized, controlled, study across two gynecology clinics (general and gyn-onc)
- Goal: Evaluate the feasibility of performing a multi-gene PGx panel test to provide tailored pain medication recommendations in patients undergoing major gynecologic surgery

Implementation (primary)	Clinical effectiveness (secondary)
<div>1. Determine <u>feasibility</u> of integrating PGx panel test in the EHR with a pharmacist PGx e-consult</div> <div>2. Determine the <u>fidelity</u> to genotype-guided pharmacotherapy recommendations</div>	<div>▪ Determine if PGx testing will:<ul style="list-style-type: none"><li>• Improve patient self-reported numeric pain scores</li><li>• Reduce total MME</li><li>• Decrease ADRs</li></ul></div>

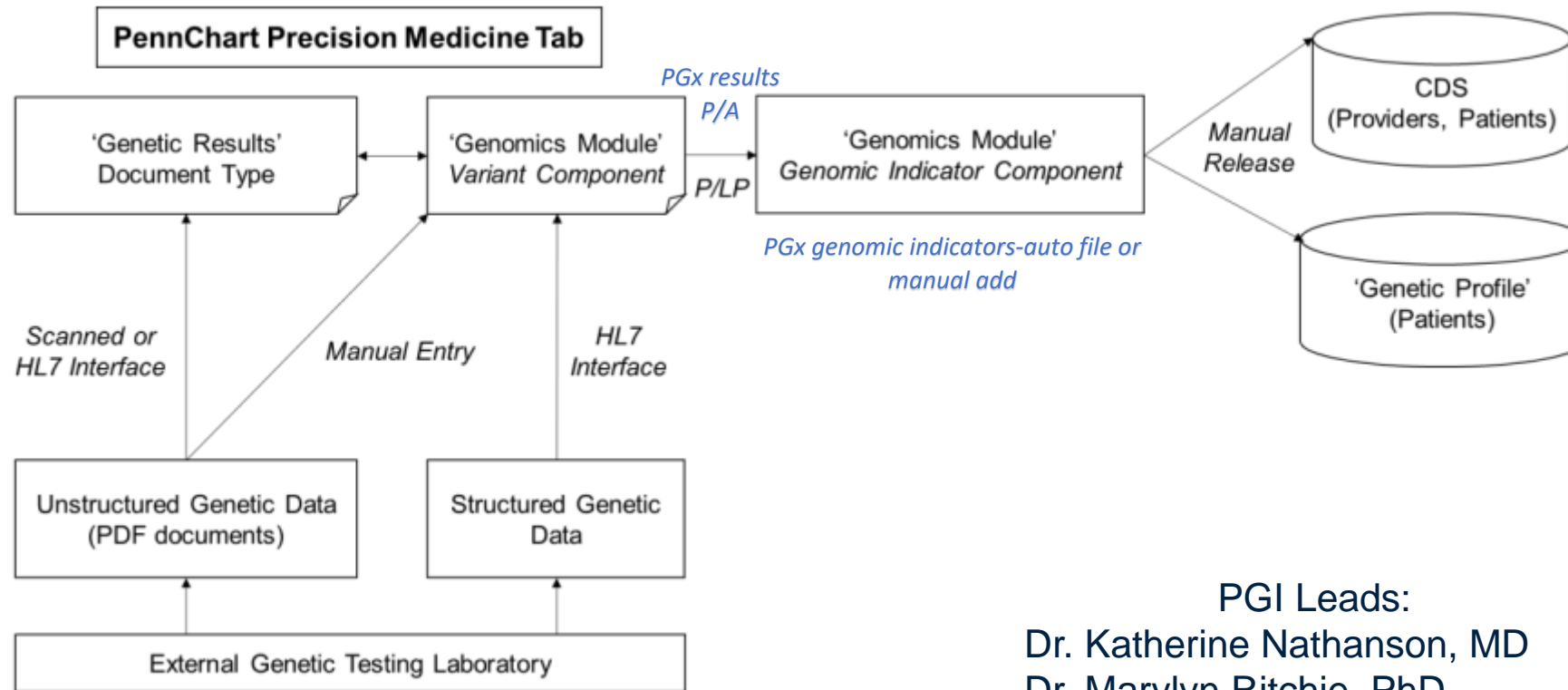
Target enrollment: 200 patients



Glenda Hoffercker, PharmD



# PennChart Genomics Initiative (PGI)



P/LP- pathogenic/ likely pathogenic  
P/A- present/absent

PGI Leads:  
Dr. Katherine Nathanson, MD  
Dr. Marylyn Ritchie, PhD

# Discrete PGx results in Precision Medicine tab

**Chart Review**

Encounters Labs Imaging Procedures Cardiology Medications Other Orders **Precision Medicine** Episodes

☒ Preview Refresh (8:38 AM) Select All Deselect All Review Selected Lab Flowsheet Flowchart Apply Default Sorting

Filters Hide Canceled

Medications and orders also exist

Date	Description
Recent	
07/28/2021	PGX:
Searched through 8/26/2018	

### Results

PGX: DPYD/UGT1A1 [PROC9049] (Accession 00000)

Component	Value	Ref Range & Units
DPYD ACTIVITY SCORE	1.5 !	2
DPYD PHENOTYPE	Intermediate !	Normal
UGT1A1 Genotype	*1/*1	*1/*1
UGT1A1 Phenotype	Normal	Normal
PGX REPORT SCAN	SEE MEDVIEW	

### Result Information

Flag: Abnormal ! Status: Final result (Collected: 7/28/2021 16:10)

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# PGx warnings at time of order entry

In-line warnings for patients with actionable results

fluorouracil 1 GM/20ML SOLN injection Accept Cancel

**Pharmacogenomic Warning**

This patient is predicted to have an increased risk of severe or life-threatening toxicity when treated with fluorouracil (5-FU) at the standard dose. Reduce starting dose by 50%. Closely monitor for toxicity with subsequent titration of 5-FU as clinically indicated.

Report: Common sizes:  
Vial: 20 mL

Product: **FLUOROURACIL 1 GM/20ML IV SOLN**

Sig Method: Specify Dose, Route, Frequency Use Free Text Taper/Ramp Combination Dosage

Dose:

Route:

Frequency:

Duration:  Doses Days

Starting:  Ending:

Dispense: Days/Fill: Full (0 Days) 30 Days 90 Days

Quantity:    Refill:

DPYD-High risk medication alert

Pop up Med Warning (priority set to high):

Medication Warnings

Warnings Report

New Warnings (1 unfiltered, 4 filtered) Show filtered (4)

**Pharmacogenomic Warning**

Patient is predicted to have an increased risk of severe toxicity when treated with 5-fluorouracil.

**High**

fluorouracil 500 mg/10 mL SOLN injection Remove

Prescription New

Immediately override all warnings:

Benefits exceed risks Duplicate appropriate Will monitor closely Has previously tolerated Override All Warnings...

Override and Accept Cancel

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# PGx infrastructure build in the EHR

## ► 50 Genomic Indicators for 13 genes

- *DPYD* (3)
- *UGT1A1* (3)
- *CYP2B6* (5)
- *CYP2C9* (5)
- *CYP2C19* (5) → Poor metabolizer, intermediate metabolizer, normal metabolizer, Rapid metabolizer, ultrarapid metabolizer
- *CYP2D6* (5)
- *CYP3A5* (3)
- *HLA-A* \*31:01 (2)
- *HLA-B* \*15:02, \*57:01, \*58:01 (6)
- *IFNL4* (2)
- *NUDT15* (4)
- *SLCO1B1* (3)
- *TPMT* (4)
- In progress (*VKORC1*, *CYP4F2*, *CYP2C* cluster)

## ► Clinical decision support

- 83 inline warnings with pharmacotherapy recommendations created for 31 CPIC Level A or B medications

## Home





Welcome to the PennChart Genomics Initiative (PGI) at the University of Pennsylvania. PGI is a multidisciplinary collaborative that aims to optimize the electronic health record (EHR). The PGI team has successfully developed the EHR infrastructure supporting genomic medicine and is now among the most advanced in the nation. In response to repeated requests from other institutions for details about how to optimize their respective EHR platforms to easily order genetic testing directly through the EHR, as well as receive and store genetic test results in a standardized way, we have developed this website to facilitate the sharing of this information, making it accessible to other institutions globally.

On this website, you will find:

<https://www.med.upenn.edu/pgi/>

## Videos

- **Optimizing Genomic Medicine in the Electronic Health Record**  - In this video, Katherine Nathanson, MD depicts the integration of genomics into the electronic health record at Penn Medicine via the PennChart Genomics Initiative. She covers the importance of optimizing genetics in the EHR, barriers to implementation of genomic medicine, and how to set up a genomic medicine friendly EHR.
- **Customizing the Electronic Health Record for Delivery of Pharmacogenetics**  - Sony Tuteja, PharmD, MS, BCPS, FAHA discusses pharmacogenetic variants that impact medical care for patients, specifically the types of medications they are prescribed. She describes how pharmacogenetic implementation was tested and implemented at Penn Medicine, including setting up an infrastructure that facilitates standardization and the inclusion of clinical decision support aids for clinicians.

## Resources

You will be required to use your Epic login to access resources.

- **Penn Overview Tutorials** - these videos will depict:

# Electronic integration with external PGx lab

RightMed PGx16 Test

Accept Cancel

! Ethnicity: American Indian or Alaska Native, Ashkenazi or Sephardi Jewish, Asian, Black or African American, Hispanic or Latino, Native Hawaiian or Other Pacific Islander, White or Caucasian, Unknown / not provided

Institution/account: Penn PGx, Penn Research, Penn Proactive Genomics

Billing type: Insurance, Institutional, Patient

Shipping: Ship to patient, Kit provided onsite

! Primary reason for the request: The patient has a history of medication failure. The patient is starting a new medication, with no previous history. The patient has a new diagnosis, with no pharmacological treatment history to treat that diagnosis. The patient has a history of, or is currently experiencing, adverse side effects from his/her current medication(s). The patient is on multiple medications, raising the risk for adverse drug reactions. The patient has not complied with his/her current medication regimen due to adverse drug reactions. Dosing increases on current medications have had a sub-therapeutic response. The patient is taking a medication with pharmacogenetic biomarkers in the FDA labeling. Unspecified

! The test results are necessary to: Make more informed decisions about which medications to prescribe and/or avoid for this patient, or make more informed de ... Identify possible alternative medications which may be subject to less impact from genetic variability and yield more consistent ... Identify the predicted severity of any potential gene-drug interactions. Manage this patient's cardiovascular or thrombotic risk. Unspecified

Release to patient: Auto Release, Hold for Manual Release

Status: Normal, Standing, Future

Class: OneOme Ld, OneOme Lab

Priority: Routine, Routine, STAT

Lab: Resulting Agency: ONEOME GENET, Collection Date: , Collection Time:

! Specimen Src: SALIVA

Comments: Insert SmartText

! Next Required

Accept Cancel

Chart Review Admin Data Rooming Immunizations Plan Infusion Verify Wrap-Up ACP

Chart Review

Encounters Labs Imaging Procedures Cardiology Medications Other Orders Precision Medicine Episodes Letters

Preview Refresh (2:21 PM) Select All Deselect All Review Selected Lab Flowsheet Flowsheet Apply Default Sorting Route Load Remaining More

Filters Hide Canceled Clear Filter

Date	Description	Status	Accession	Scan Doc Description
09/29/2021	RIGHTMED PGX16 TEST	Final result	70CA6	Genetic Results

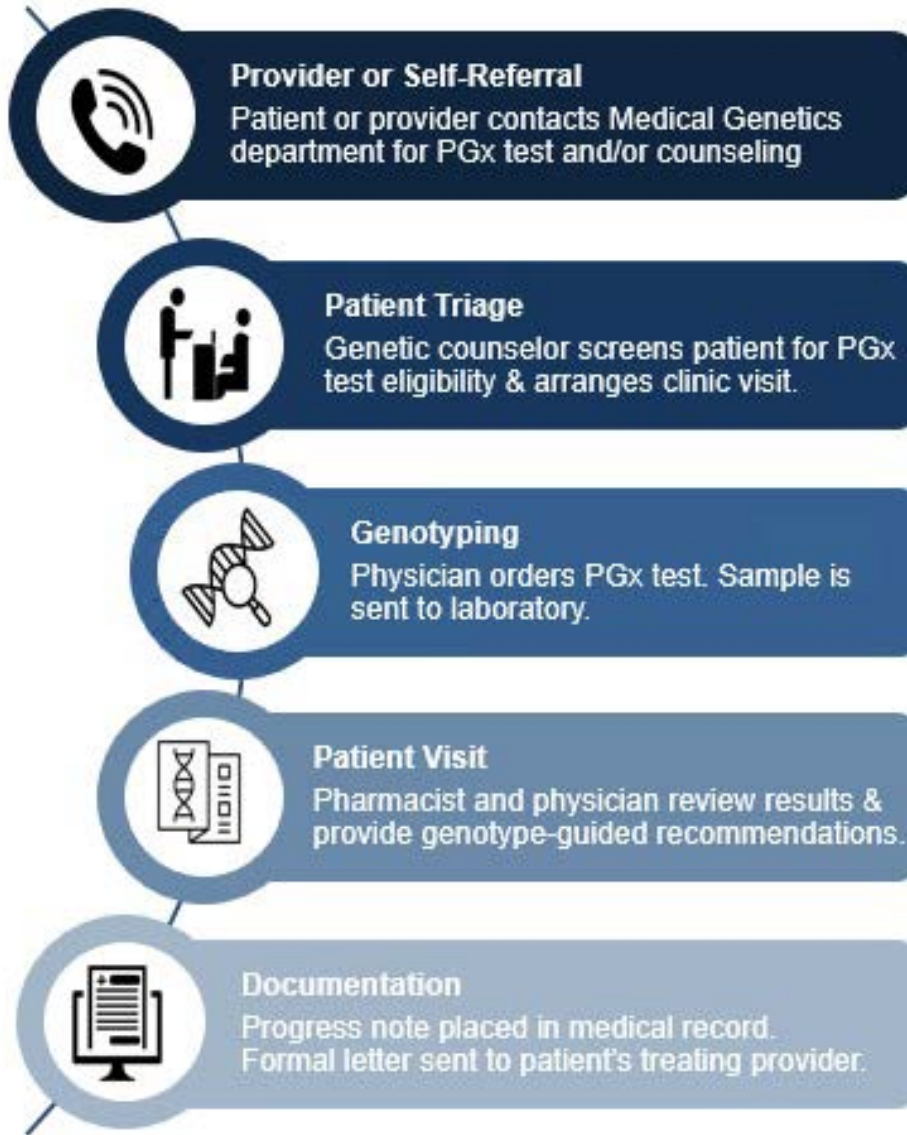
Genomic Variant Results Expand All Collapse All

RIGHTMED PGX16 TEST  
Collected: 9/29/2021 Status: Final result Dx: Heartburn Order: 375159

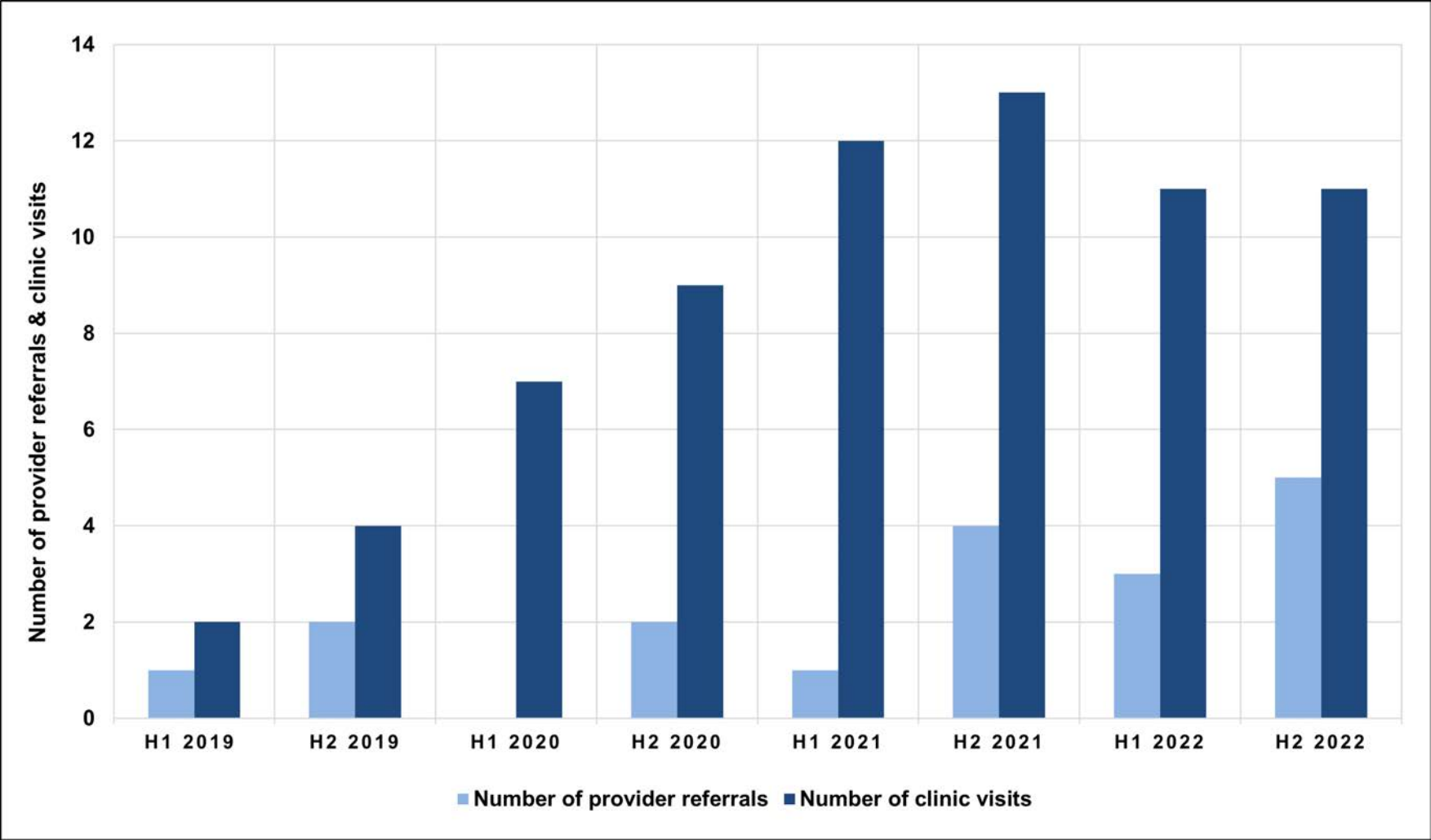
Pharmacogenomic Genotype CYP2B6	Type: Pharmacogenomic Genotype
Genotypes: CYP2B6 *1/*1	
Pharmacogenomic Genotype CYP2C Cluster	Type: Pharmacogenomic Genotype
Genotypes: CYP2C Cluster rs12777823 GG	
Pharmacogenomic Genotype CYP2C19	Type: Pharmacogenomic Genotype
Genotypes: CYP2C19 *17/*17	
Pharmacogenomic Genotype CYP2C9	Type: Pharmacogenomic Genotype
Genotypes: CYP2C9 *1/*3	
Pharmacogenomic Genotype CYP2D6	Type: Pharmacogenomic Genotype
Genotypes: CYP2D6 *2/*5	
Pharmacogenomic Genotype CYP3A5	Type: Pharmacogenomic Genotype
Genotypes: CYP3A5 *3/*3	
Pharmacogenomic Genotype CYP4F2	Type: Pharmacogenomic Genotype
Genotypes: CYP4F2 *1/*1	
Pharmacogenomic Genotype DPYD	Type: Pharmacogenomic Genotype
Genotypes: DPYD *1/*2A	
Pharmacogenomic Genotype HLA-A	Type: Pharmacogenomic Genotype
Genotypes: HLA-A Negative	
Pharmacogenomic Genotype HLA-B	Type: Pharmacogenomic Genotype
Genotypes: HLA-B Negative	

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# Establishment of a multi-disciplinary PGx clinic



# Growth of clinic volume and referrals



# Patient demographics

	N=69
Age, years	48 ± 16
Female sex, n (%)	40 (58%)
Ethnicity, n (%)	
White	58 (84%)
Other	6 (9%)
Unknown	5 (7%)
Referral Method, n (%)	
Self-referred	32 (46%)
Preventative genomics screening program	20 (29%)
Psychiatrist	7 (10%)
Primary care	6 (9%)
Reason for consult, n (%)	
Current or historical ADRs	26 (38%)
Preventative genomic screening	20 (29%)
History of medication nonresponse	11 (16%)

# Clinical Impact of PGx testing

***All patients had at least one actionable PGx allele***

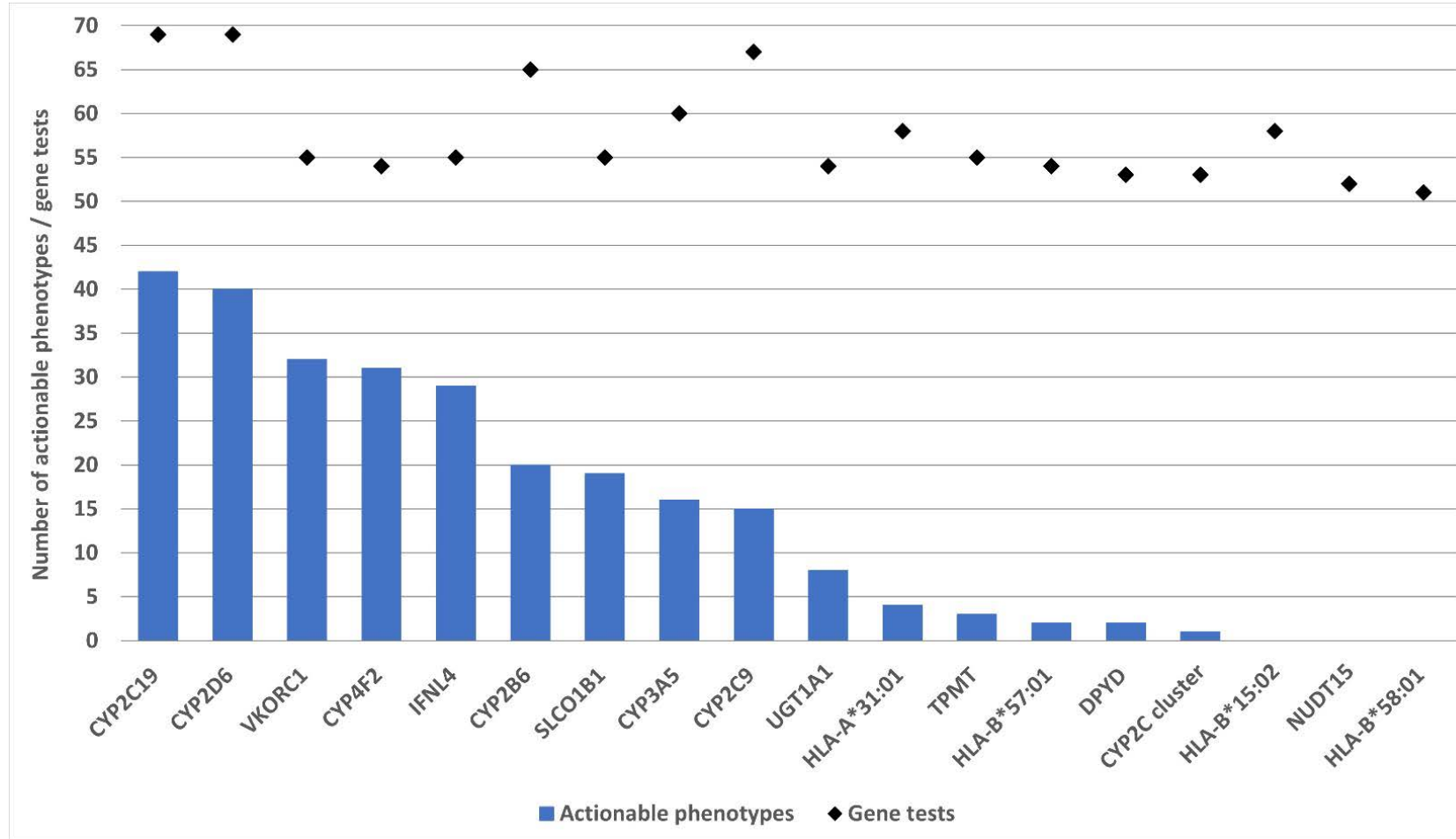
## **Actionable alleles**

Average per patient, mean $\pm$ SD	4 $\pm$ 1.8
$\geq 3$ actionable alleles	51 (74%)

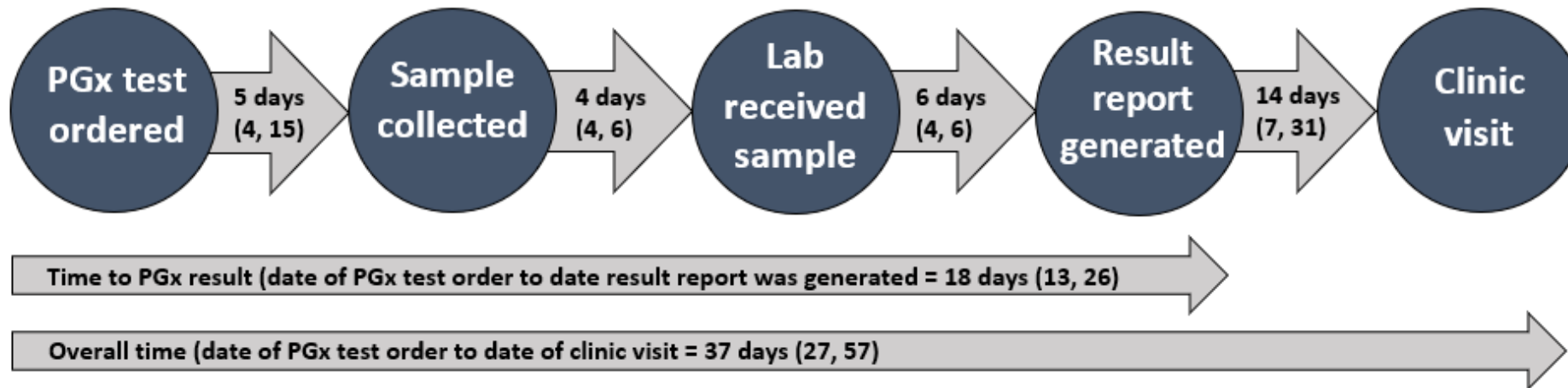
## **Drug-gene interactions**

current medication	17 (25%)
historical medication	12 (17%)
<i>CYP2C19/CYP2D6</i> - SSRI	8
<i>CYP2D6</i> - opioids	4
<i>CYP2C19/CYP2D6</i> -TCAs	4
<i>CYP2C19</i> – proton pump inhibitor	3
<i>SLCO1B1</i> - statins	3
<i>CYP2C9</i> - NSAIDS	2
Other	4

# Most common PGx alleles identified



# Timeframe for testing and clinic visits



## Next Steps for PGx clinic

- ▶ PGx e-consult services
- ▶ Advertise the clinic internally to Penn providers to increase referrals
- ▶ New PGx pharmacist

# Summary

- ▶ Implementation science provided a roadmap for PGx implementation and provides a set of process outcomes that can help demonstrate early “wins”
- ▶ Investment in EHR infrastructure was critical
- ▶ Patient needs/demands was the impetus for the PGx clinic
- ▶ Strategy of wins will help scale PGx across the health system

# Acknowledgements



## Penn PGx Program

Glenda Hoffecker, PharmD

Mari Cayabyab, PharmD

Lisa Varughese, PharmD

Jean De Dieu Ndayishimiye, PharmD

Archna Bajaj, MD

Stephanie Asher, MS, LCGC

Victoria Wittner, MPH

Daniel Rader, MD

## PennChart Genomics Initiative

Katherine Nathanson, MD

Marylyn Ritchie, PhD

Jeff Landgraf

Joe Bleznuck

## Funding

**Penn Center for Precision  
Medicine**

NHLBI

NHGRI

VA HSR&D

## GI Oncology

Ursina Teitelbaum, MD

Kelsey Lau-Min, MD, MSCE

Ryan Massa, MD (PPMC)

Nandi Reddy, MD (LGH)

Randy Oyer, MD (LGH)

## Obstetrics and Gynecology

Mary Deagostino-Kelly, MD

Lakeisha Mulugeta-Gordon, MD,

Stefan Gysler, MD

## Cardiology

Jay Giri, MD, MPH

William Matthai, MD,

Daniel Kolansky, MD

## Laboratory Partners

Penn Lab Medicine

Children's Hospital of Philadelphia,

Center for Applied Genomics

OneOme

# Questions?

