

Using the EHR for PGx

^
and LLMs

Marylyn D. Ritchie, PhD, FACMI

Vice Dean of Artificial Intelligence and Computing
University of Pennsylvania, Perelman School of Medicine

<http://ritchielab.org>



**Institute for
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PGx Implementation Barriers

- ▶ Prevalence of actionable PGx alleles and diplotypes



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

Abstract

IMPORTANCE Implementation of pharmacogenetic testing to guide drug prescribing has potential to improve drug response and prevent adverse events. Robust data exist for more than 30 gene-drug pairs linking genotype to drug response phenotypes; however, it is unclear which pharmacogenetic tests, if implemented, would provide the greatest utility for a given patient population.

OBJECTIVES To project the proportion of veterans in the US Veterans Health Administration (VHA) with actionable pharmacogenetic variants and evaluate how testing might be associated with prescribing decisions.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study included veterans who used national VHA pharmacy services from October 1, 2011, to September 30, 2017. Data analyses began April 26, 2018, and were completed February 6, 2019.

EXPOSURES Receipt of level A drugs based on VHA pharmacy dispensing records.

MAIN OUTCOMES AND MEASURES Projected prevalence of actionable pharmacogenetic variants among VHA pharmacy users based on variant frequencies from the 1000 Genomes Project and veteran demographic characteristics; incident number of level A prescriptions, and proportion of new level A drug recipients projected to carry an actionable pharmacogenetic variant.

RESULTS During the study, 7 769 359 veterans (mean [SD] age, 58.1 [17.8] years; 7 021 504 [90.4%] men) used VHA pharmacy services. It was projected that 99% of VHA pharmacy users would carry at least 1 actionable pharmacogenetic variant. Among VHA pharmacy users, 4 259 153 (54.8%) received at least 1 level A drug with 1 188 124 (15.3%) receiving 2 drugs, and 912 189 (11.7%) receiving 3 or more drugs. The most common incident prescriptions during the study were tramadol (923 671 new recipients), simvastatin (533 928 new recipients), citalopram (266 952 new recipients), and warfarin (205 177 new recipients). Gene-drug interactions projected to have substantial clinical impacts in the VHA population include the interaction of *SLCO1B1* with simvastatin (1 988 956 veterans [25.6%]), *CYP2D6* with tramadol (318 544 veterans [4.1%]), and *CYP2C9* or *VKORC1* with warfarin (7163 349 veterans [92.2%]).

Key Points

Question What is the potential impact of implementing pharmacogenetic testing for gene-drug interactions with a high level of evidence (level A)?

Findings This cross-sectional study of more than 7.7 million US veterans used variant frequencies from the 1000 Genomes Project and veteran demographic characteristics to estimate that 99% of veterans who use the Veteran Health Administration carry at least 1 actionable pharmacogenetic variant. Analysis of Veterans Health

Administration pharmacy records during a 6-year period suggested that 2.9

million veterans (37%) started treatment with at least 1 level A drug, with 25% of them receiving 2 level A drugs and 12% receiving 3 or more level A drugs.

Meaning Pharmacogenetic testing has the potential to inform pharmacotherapy decisions for most veterans.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

98-99% in this study



PharmCAT results in Penn Medicine BioBank

- ▶ 316,000 patients in Penn Medicine prescribed at least 2 drugs with CPIC A/B guidelines
- ▶ 98.8% of PMBB participants carry one or more PGx actionable alleles (treatment modification recommended)
- ▶ 13.3% (n=5785) patients prescribed medications that could be impacted by their genotype
 - 849 patients who carry CYP2C19 reduce function alleles were prescribed clopidogrel

98.8% in this study



Sony Tuteja, PharmD



Shefali Setia Verma PhD



Karl Keat

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Journal of
Translational Medicine

RESEARCH

Open Access



Evaluating the frequency and the impact of pharmacogenetic alleles in an ancestrally diverse Biobank population

Shefali S. Verma^{1†}, Karl Keat^{2†}, Binglan Li³, Glenda Hoffecker⁴, Marjorie Risman⁵, Regeneron Genetics Center, Katrin Sangkuhl³, Michelle Whirl-Carrillo³, Scott Dudek⁵, Anurag Verma⁴, Teri E. Klein^{3,6}, Marylyn D. Ritchie^{5†} and Sony Tuteja^{4††}

PharmCAT results in UK Biobank

ARTICLE

Frequencies of pharmacogenomic alleles across biogeographic groups in a large-scale biobank

100% in this study

Binglan Li,¹ Katrin Sangkuhl,¹ Ryan Whaley,¹ Mark Woon,¹ Karl Keat,² Michelle Whirl-Carrillo,¹ Marylyn D. Ritchie,^{3,4} and Teri E. Klein^{1,5,6,*}

Summary

Pharmacogenomics (PGx) is an integral part of precision medicine and contributes to the maximization of drug efficacy and reduction of adverse drug event risk. Accurate information on PGx allele frequencies improves the implementation of PGx. Nonetheless, curating such information from published allele data is time and resource intensive. The limited number of allelic variants in most studies leads to an underestimation of certain alleles.

We applied the Pharmacogenomics Clinical Annotation Tool (PharmCAT) on an integrated 200K UK Biobank genetic dataset (N = 200,044). Based on PharmCAT results, we estimated PGx frequencies (alleles, diplotypes, phenotypes, and activity scores) for 17 pharmacogenes in five biogeographic groups: European, Central/South Asian, East Asian, Afro-Caribbean, and Sub-Saharan African. PGx frequencies were distinct for each biogeographic group. Even biogeographic groups with similar proportions of phenotypes were driven by different sets of dominant PGx alleles. PharmCAT also identified “no-function” alleles that were rare or seldom tested in certain groups by previous studies, e.g., *SLCO1B1**31 in the Afro-Caribbean (3.0%) and Sub-Saharan African (3.9%) groups.

Estimated PGx frequencies are disseminated via the PharmGKB (The Pharmacogenomics Knowledgebase: www.pharmgkb.org). We demonstrate that genetic biobanks such as the UK Biobank are a robust resource for estimating PGx frequencies. Improving our understanding of PGx allele and phenotype frequencies provides guidance for future PGx studies and clinical genetic test panel design, and better serves individuals from wider biogeographic backgrounds.



PGx Implementation Barriers

- ▶ Prevalence of actionable PGx alleles and diplotypes
- ▶ Cost
 - Testing, alternative treatment, reimbursement, new infrastructure, alternative treatment

What is the cost of NOT implementing PGx?

CANCER

Widow Files Suit Against OHSU After Husband Passes During Chemo

SARA E. TELLER — May 11, 2022

\$1 million to settle

- f A rare genetic condition that responds poorly
- 🐦 chemotherapy drug takes the life of a patient. H

David McIntyre had a reaction to Oregon Health & Science University (OHSU)'s chemotherapy drug which took his life. His widow then filed a wrongful death lawsuit against the university in 2019. OHSU promised to change an element of the chemo treatment and pay \$1 million to settle.



PGx Implementation Barriers

- ▶ Prevalence of actionable PGx alleles and diplotypes
- ▶ Cost
 - Testing, alternative treatment, reimbursement, new infrastructure, alternative treatment
- ▶ Lack of PGx knowledge in the health systems
 - Providers, decision makers

PGx education in health systems

- ▶ What is pharmacogenetics
- ▶ What do the clinical guidelines mean
- ▶ What to test
- ▶ When to test
- ▶ How to interpret the guideline in the context of the test
- ▶ How to change prescribing
- ▶ How to explain to patient

Can we leverage technology to close the gap?



Discrete PGx results in Precision Medicine tab

The screenshot shows the Epic Chart Review interface with the Precision Medicine tab selected. A red box highlights the Precision Medicine tab in the top navigation bar. Another red box highlights the Results table in the main content area. The Results table contains the following data:

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	

Below the table, the Result Information section shows a Flag: Abnormal ! and 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 DPYD-High risk medication alert

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: **intraVENOL**

Frequency: [] [] []

Duration: [] **Doses** Days

Starting: 1/28/2021 Ending: []

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

Quantity: [] [] [] Refill: []

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.

fluorouracil 500 mg/10 mL SOLN injection
Prescription: **New** Remove

High Override Reason...

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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Slide courtesy of Dr. Sony Tuteja

Electronic integration with external PGx lab

RightMed PGx16 Test

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 Lab, OneOme Lab

Priority: Routine, Routine, STAT

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

Specimen Src: SALIVA

Comments:

Next Required

Chart Review

09/29/2021 RIGHTMED PGX16 TEST Final result 70CA6 Genetic Results

Genomic Variant Results

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

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

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Slide courtesy of Dr. Sony Tuteja

Home

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



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:

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.

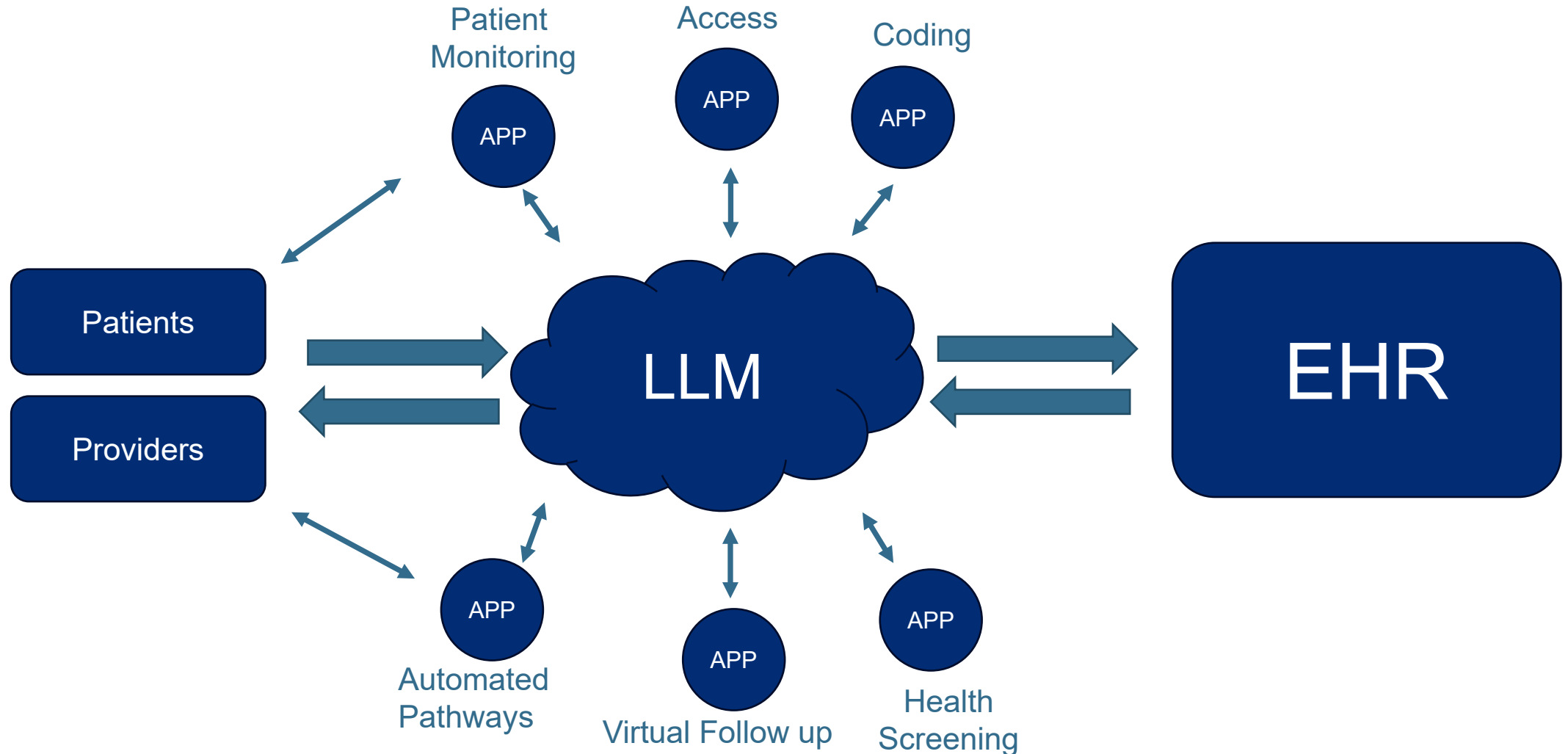
Resources

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

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

Slide courtesy of Dr. Sony Tuteja

Future state of EHR interfaces?



Generative AI and healthcare

The screenshot shows the top navigation bar of the Epic website with the Epic logo on the left and 'Software', 'About Us', and 'Newsroom' on the right. The main heading is 'Artificial Intelligence' in a large, bold, orange font. Below the heading is a paragraph: 'AI is improving healthcare and has great potential to do much more. AI is used in many forms, including generative AI and predictive models, throughout Epic's software today with more than 60 significant development projects underway.' This is followed by a sub-paragraph: 'Here's a peek at what's available today, how health systems are using it, and what's in store. We encourage Epic community members to reach out to their BFFs to learn more.' Below this text are six white cards arranged in a 2x3 grid. Each card features a colorful icon, a title, and a 'details →' link. The cards are: 1. 'Clinician Efficiency' with a 'DRAFT' document icon; 2. 'Insights from Data' with a line graph icon; 3. 'Revenue Cycle' with a piggy bank icon; 4. 'Population Health Tools' with a pie chart icon; 5. 'Patient Experience' with a speech bubble icon; 6. 'Capacity Management' with a square icon containing arrows and a small plant.

Epic Software About Us Newsroom

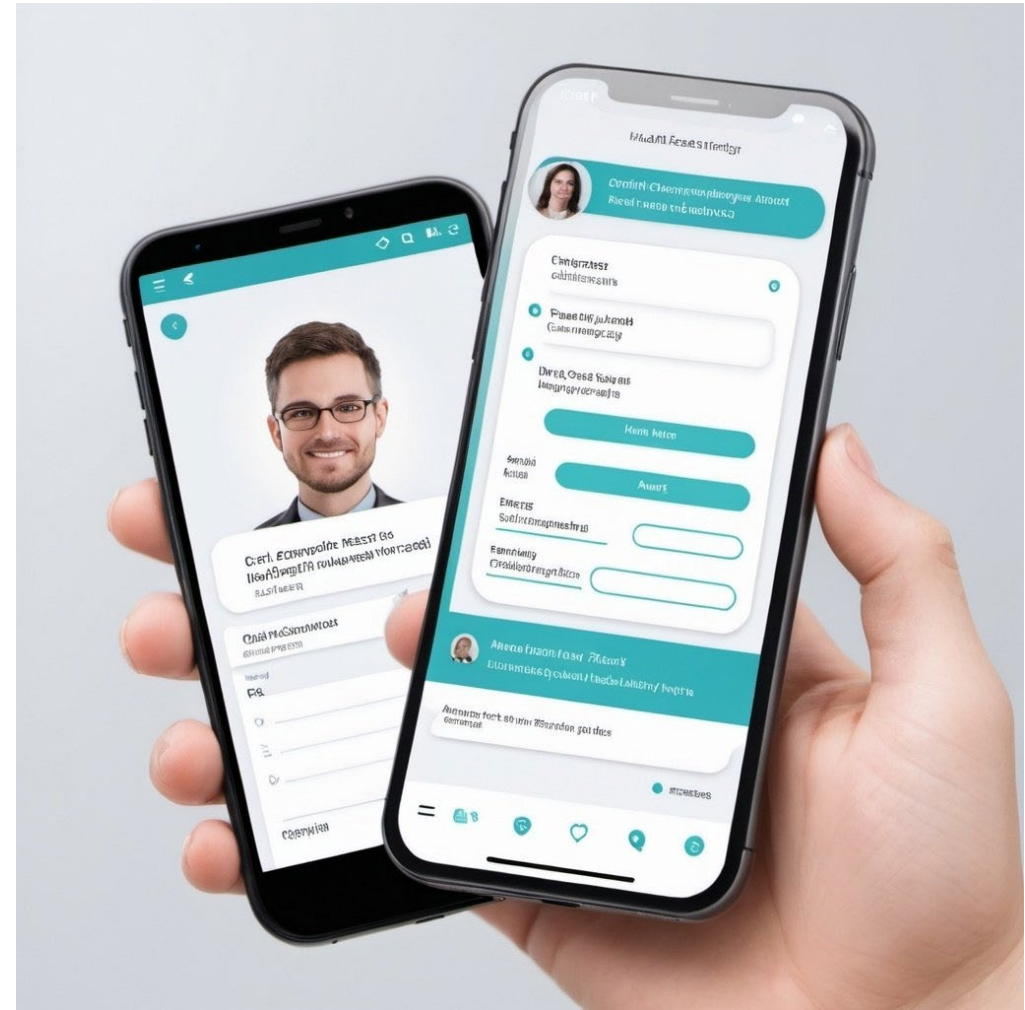
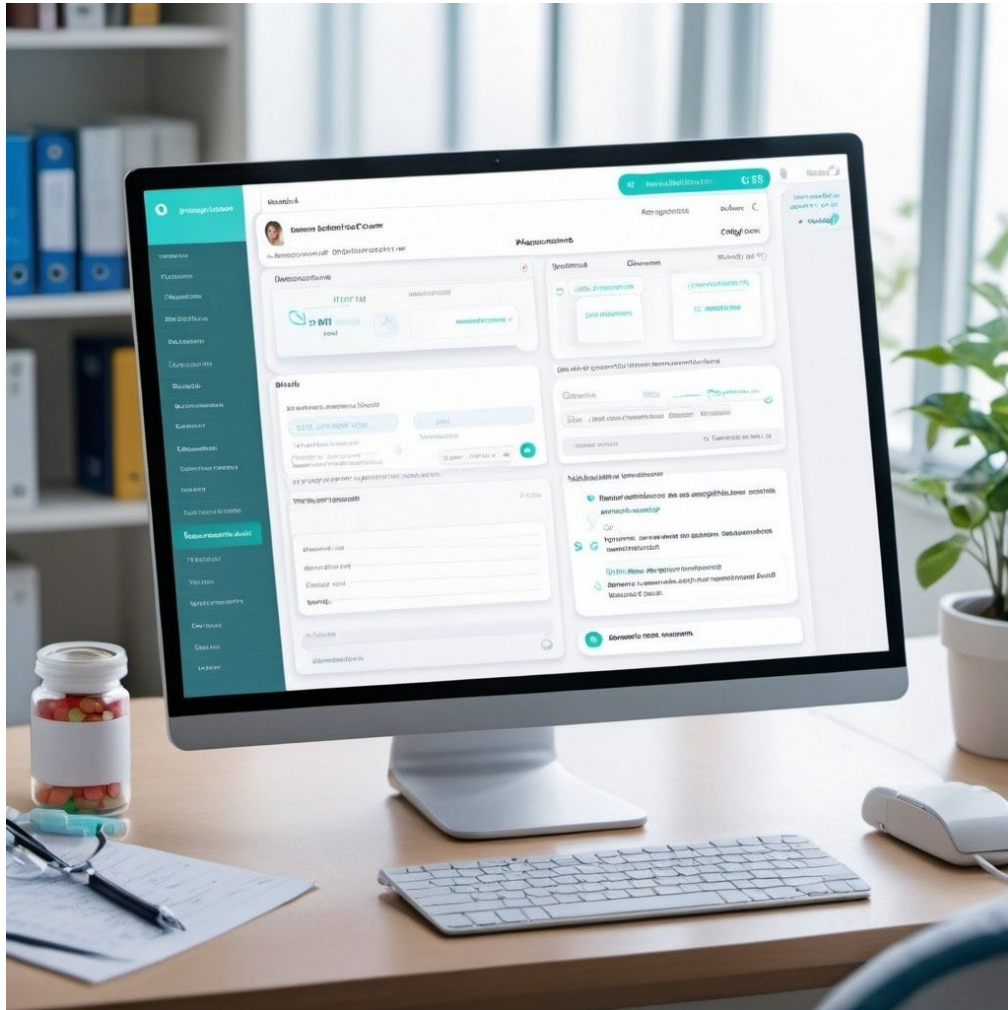
Artificial Intelligence

AI is improving healthcare and has great potential to do much more. AI is used in many forms, including generative AI and predictive models, throughout Epic's software today with more than 60 significant development projects underway.

Here's a peek at what's available today, how health systems are using it, and what's in store.
We encourage Epic community members to reach out to their BFFs to learn more.

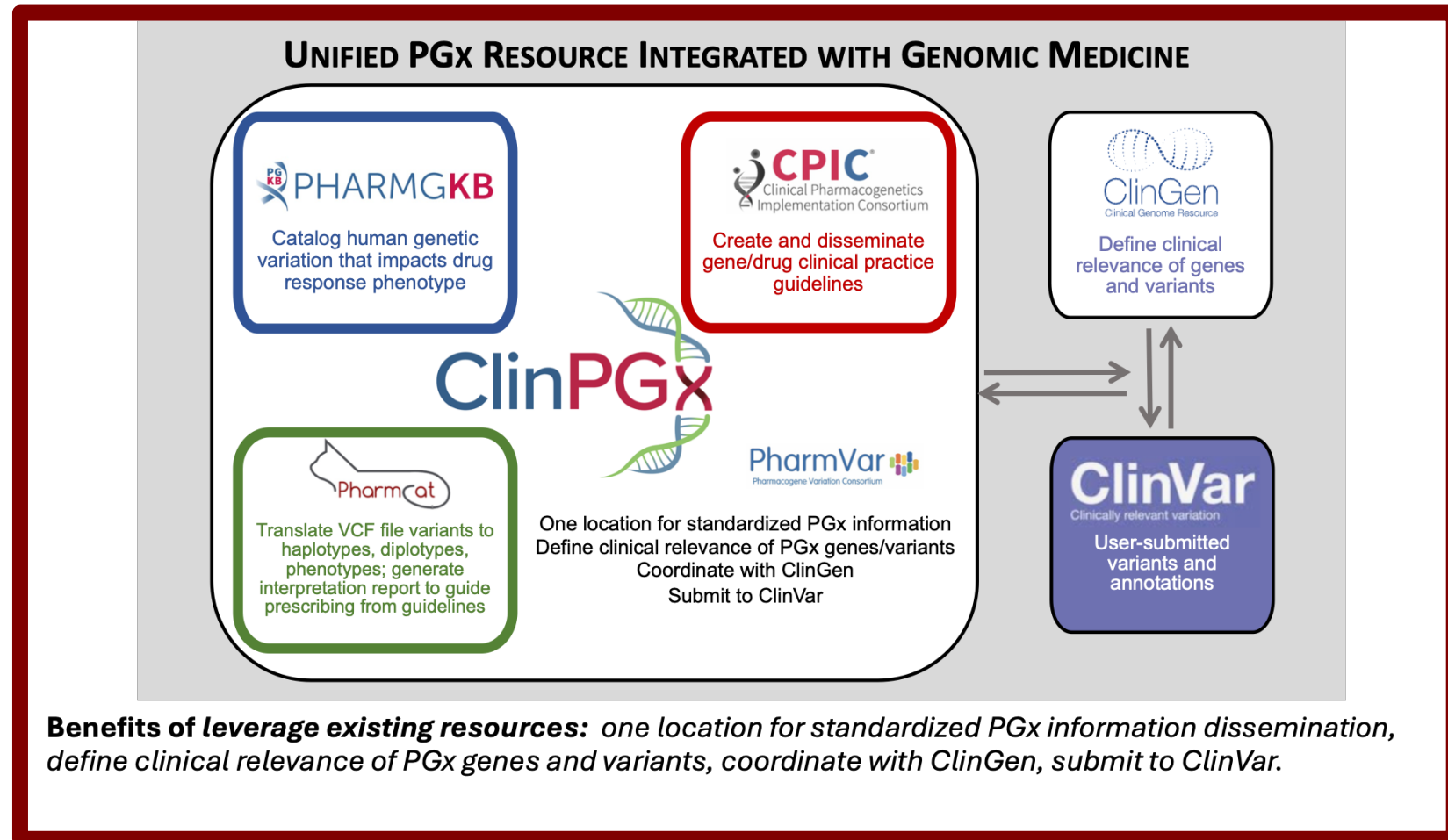
- Clinician Efficiency**
details →
- Insights from Data**
details →
- Revenue Cycle**
details →
- Population Health Tools**
details →
- Patient Experience**
details →
- Capacity Management**
details →

Use LLMs to enable provider & patient education

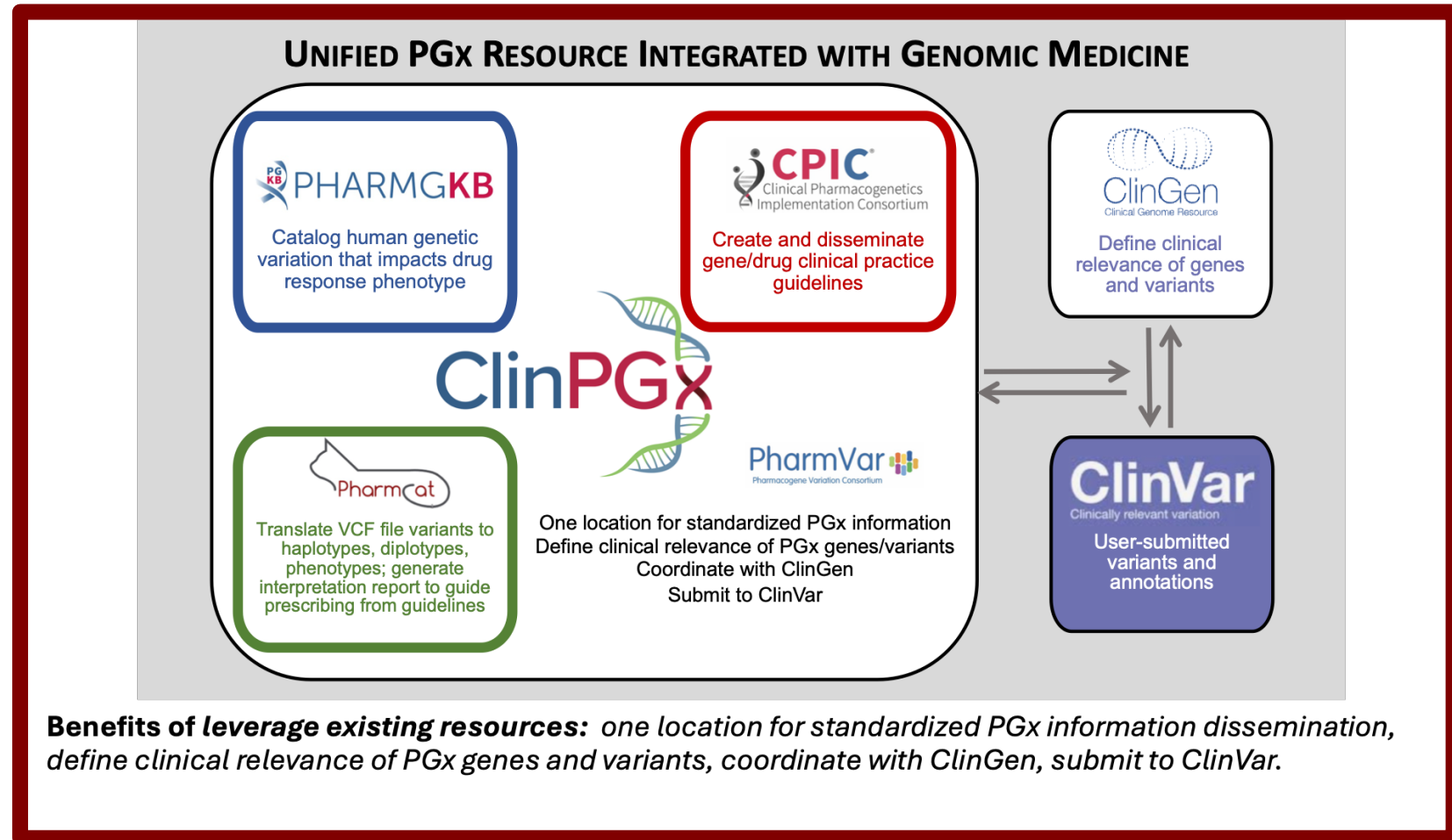


Images generated by OpenArt.ai

Use LLMs to interact with ClinPGx



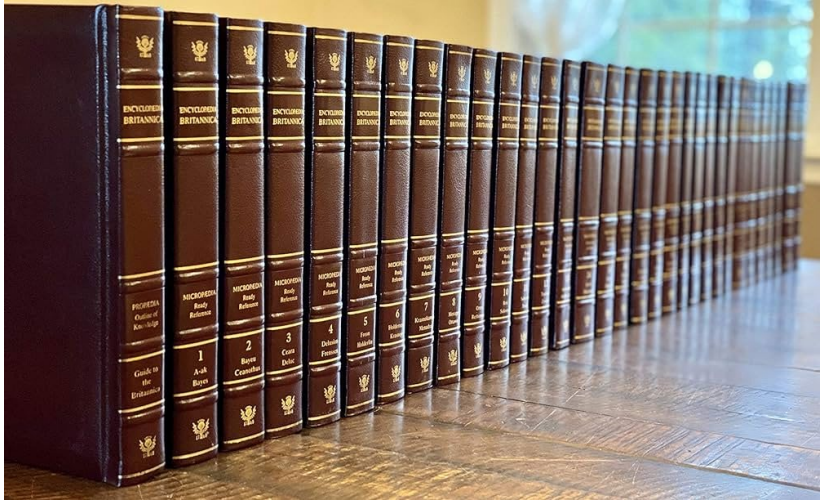
Use LLMs to interact with ClinPGx



Disruptors



<https://www.geeksforgeeks.org/what-is-internet-definition-uses-working-advantages-and-disadvantages/>

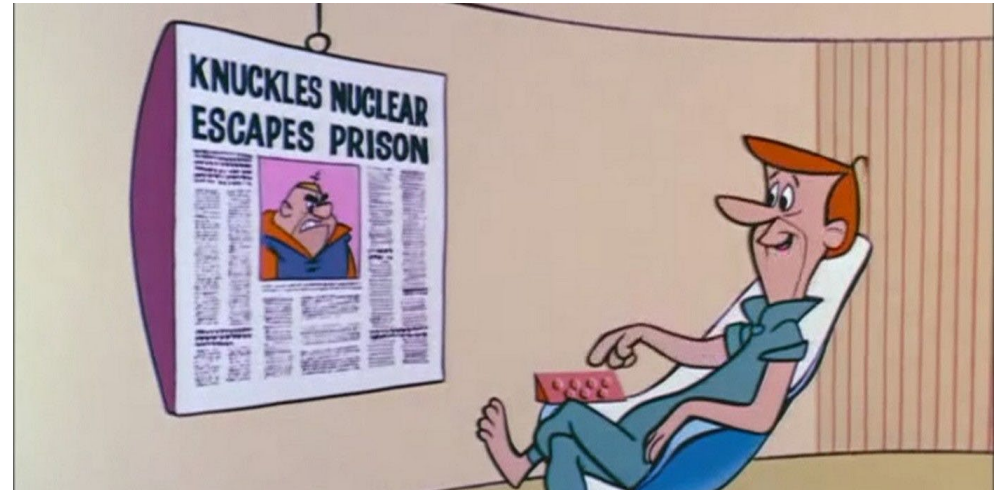
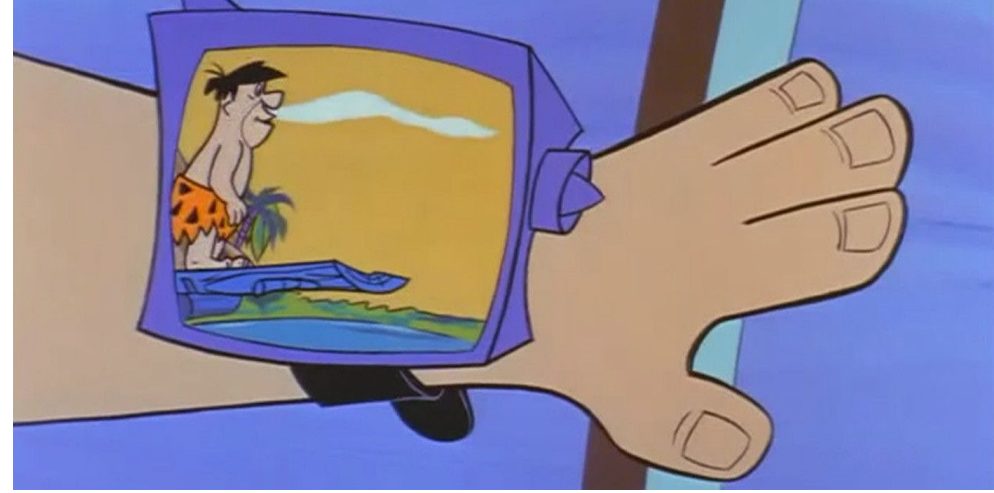
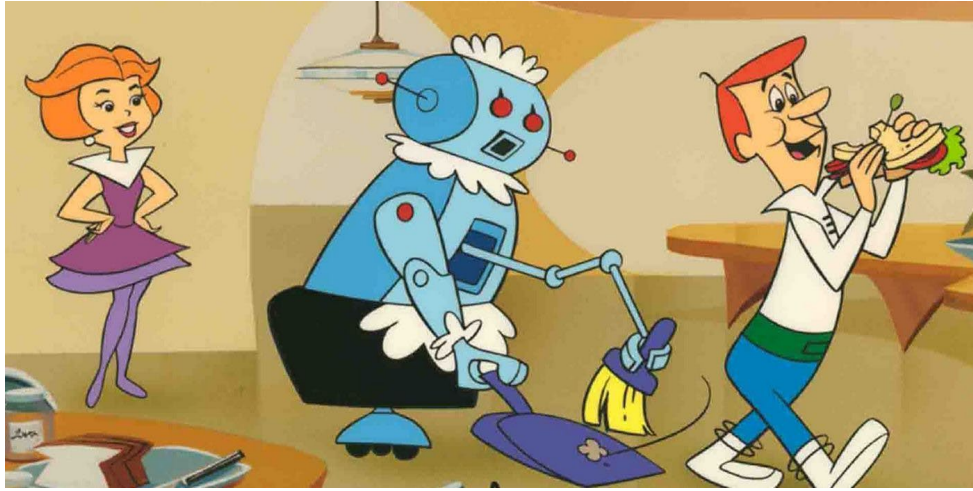


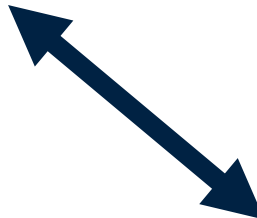
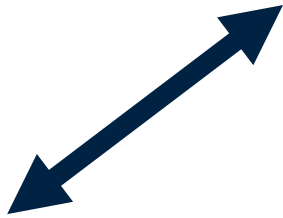
Disruptors



Affymetrix







Looking ahead

- ▶ You will see changes with ClinPGx, but we are gaining (not losing) any of the functionality of the current projects such as PharmGKB, CPIC, or PharmCAT
- ▶ You have an opportunity to influence and communicate what would be helpful
 - Send emails to feedback@pharmgkb.org for all of these projects
 - These resources are for you and if there is certain functionality desired, let us know
- ▶ We will be developing more patient/lay person forward tools/information
- ▶ Stay involved – join/follow the ClinPGx Blog <https://blog.clinpgx.org>
- ▶ There will be a ClinPGx meeting in 2025 – stay tuned for date/location

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- ▶ Volunteers along the walk from the hotel
- ▶ April Blankenship and Rasika Venkatesh – mic runners
- ▶ AV staff
- ▶ Speakers and moderators
 - Especially Paul and Wanpen Anderson for sharing their story
- ▶ Poster presenters
- ▶ All of you

- ▶ NHGRI for their support of PGx

See you at ClinPGx 2025!

