Using the EHR for PGx ^ and LLMs

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PGx Implementation Barriers

- Prevalence of actionable PGx alleles and diplotypes

JAMA Network Open

Original Investigation | Genetics and Genomics

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

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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 (7 163 349 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 pharmacogenic 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

Verma *et al. Journal of Translational Medicine* (2022) 20:550
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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 Li[3], Glenda Hoffecker[4], Marjorie Risman[5], Regeneron Genetics Center, Katrin Sangkuhl[3], Michelle Whirl-Carrillo[3], Scott Dudek[5], Anurag Verma[4], Teri E. Klein[3,6], Marylyn D. Ritchie[5†] and Sony Tuteja[4*†]

U24HG010862

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

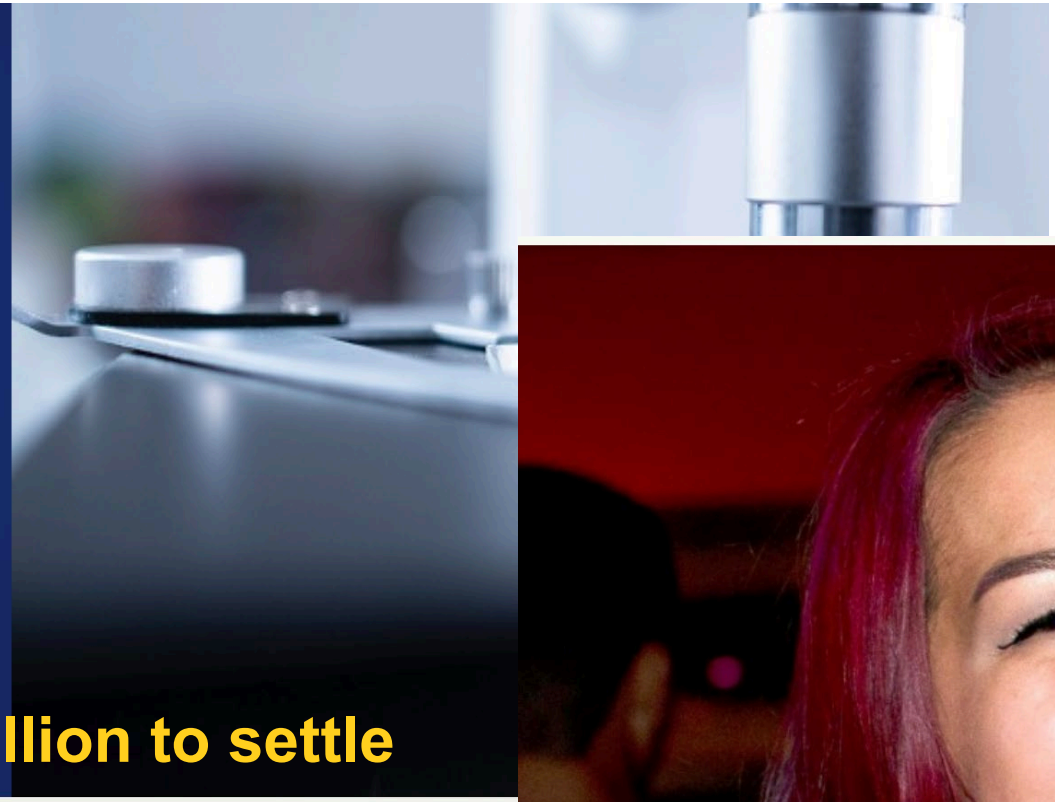
- Prevalence of actionable PGx alleles and diplotypes
- Cost
  - Testing, alternative treatment, reimbursement, new infrastructure, alternative treatment

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

A rare genetic condition that responses 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

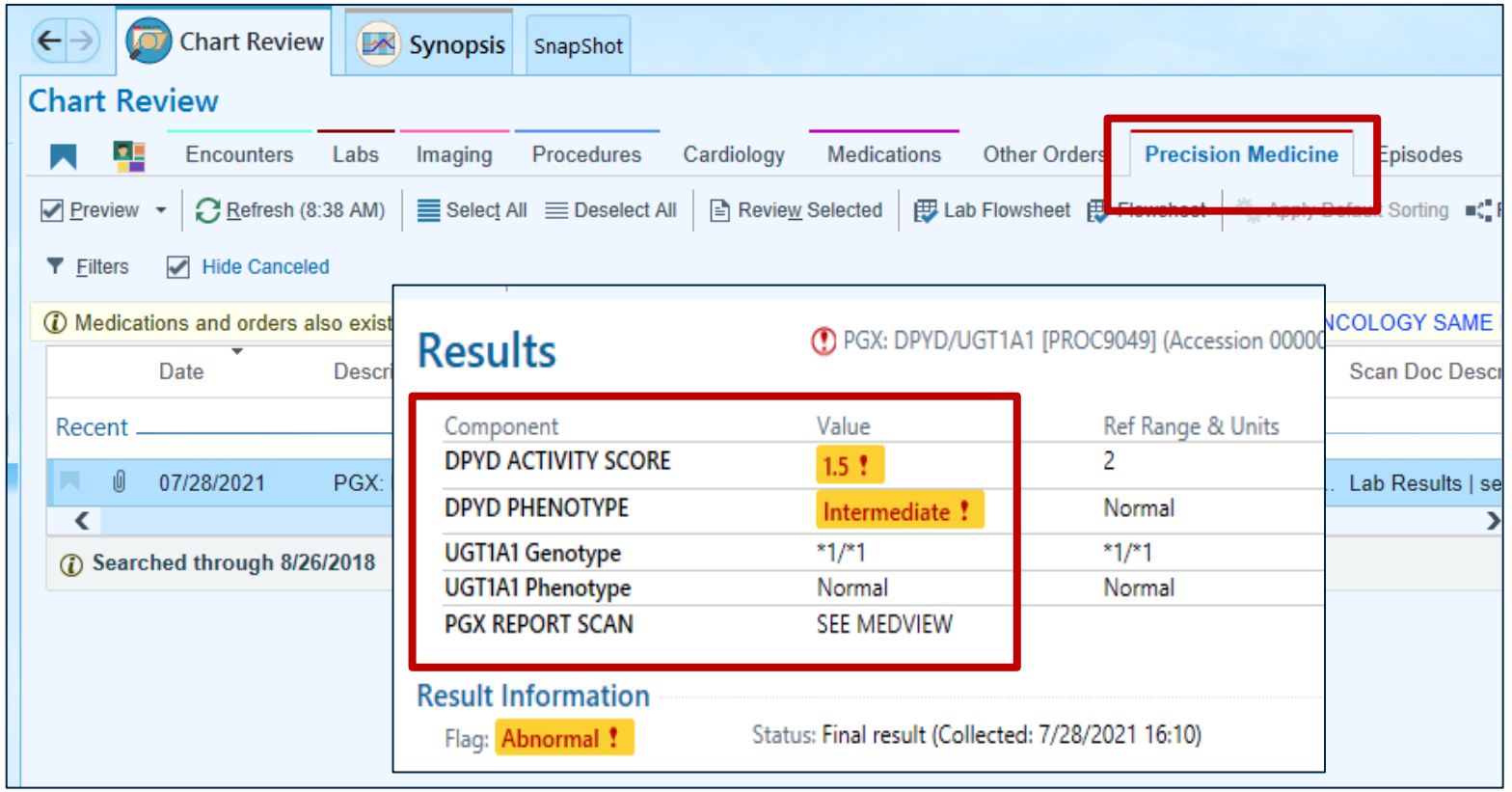
- Prevalence of actionable PGx alleles and diplotypes
- Cost
  - Testing, alternative treatment, reimbursement, new infrastructure, alternative treatment
- Lack of PGx knowledge in the health systems
  - Providers, decision makers

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?

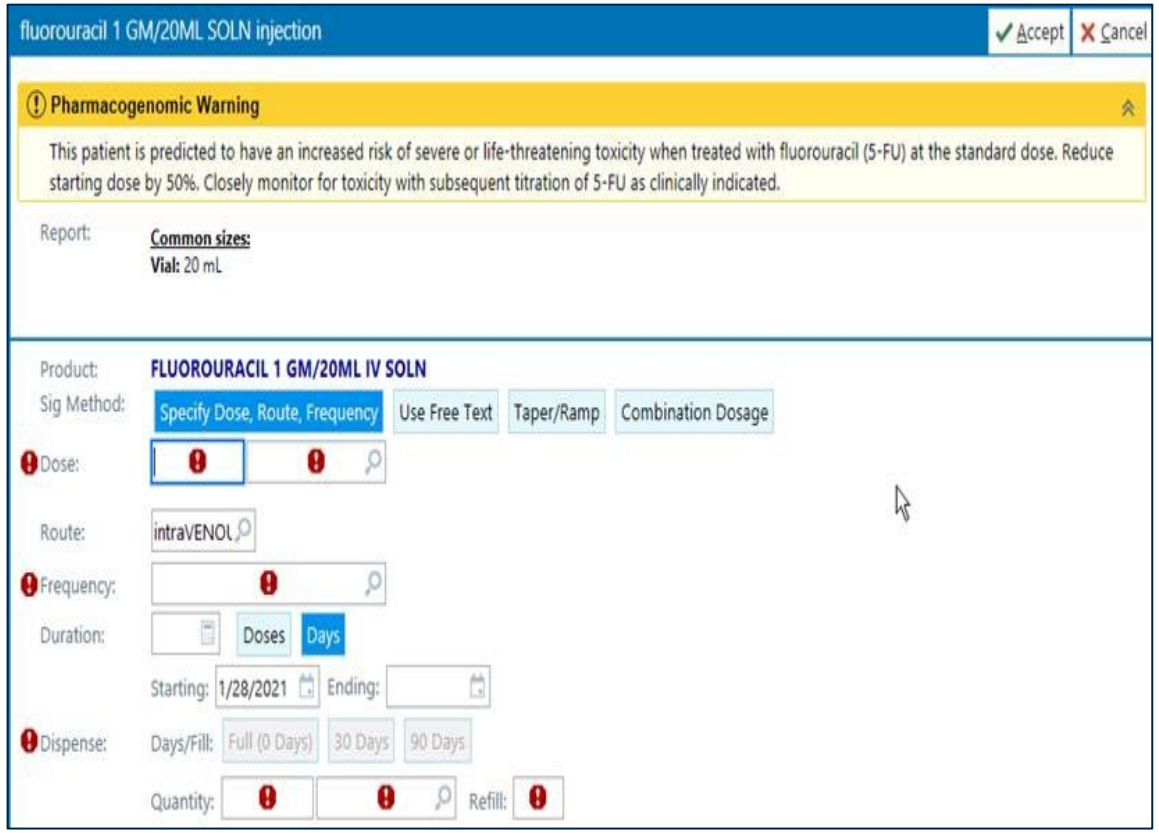
Discrete PGx results in Precision Medicine tab



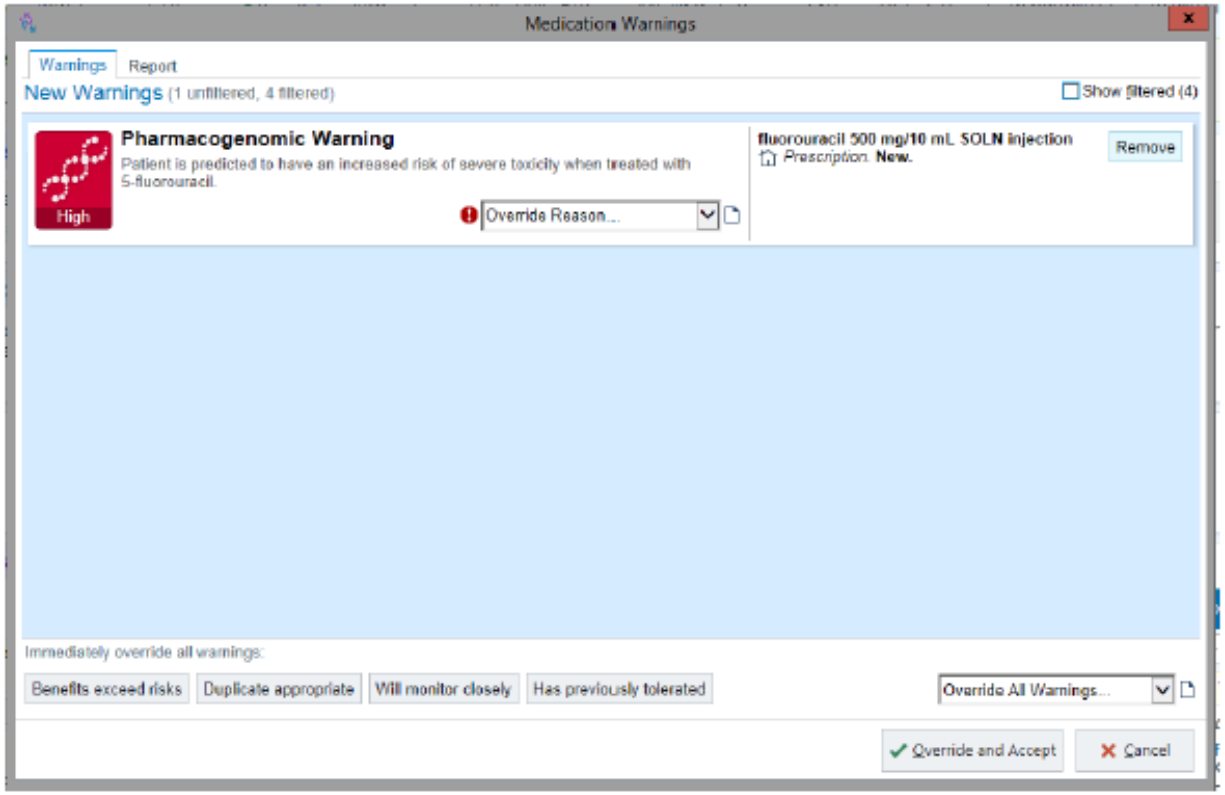
Slide courtesy of Dr. Sony Tuteja

PGx warnings at time of order entry

In-line warnings for patients with actionable results DPYD-High risk medication alert

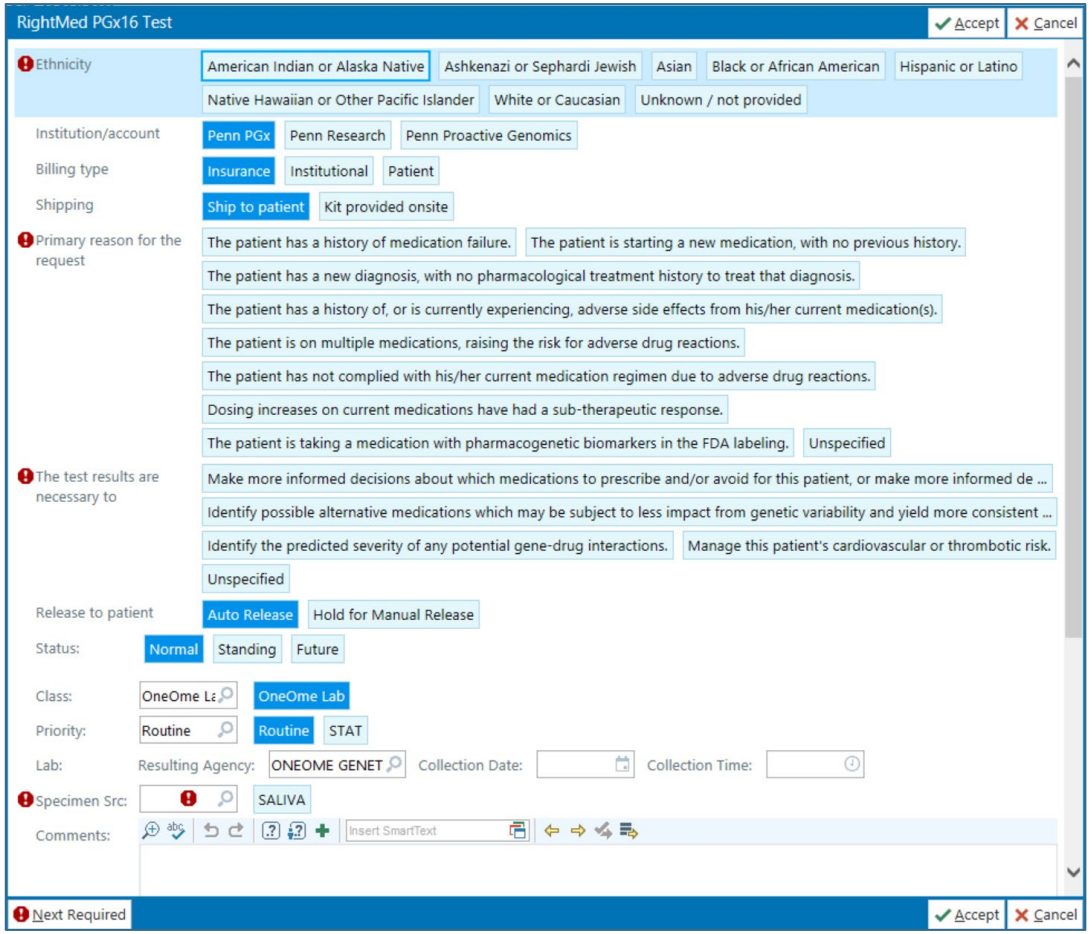


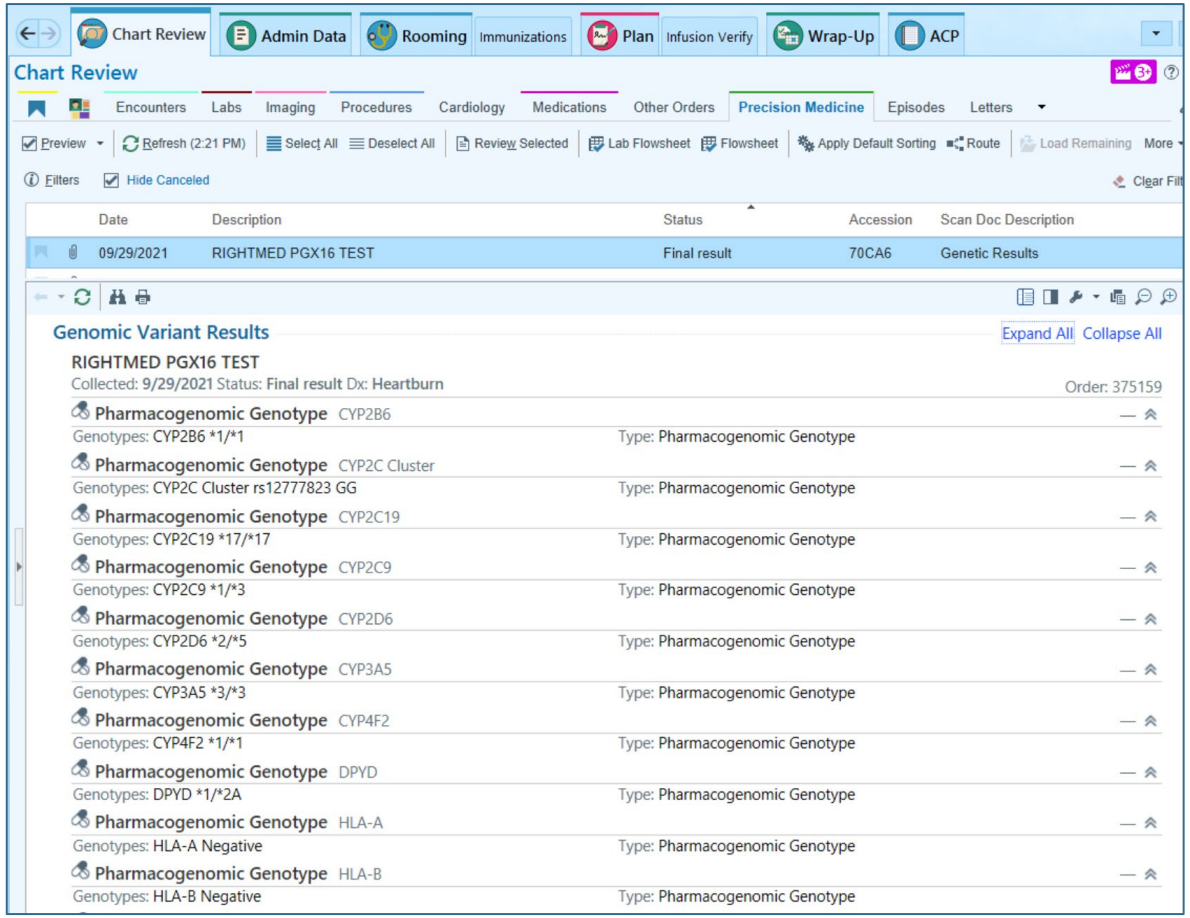
Pop up Med Warning (priority set to high):



Slide courtesy of Dr. Sony Tuteja

Electronic integration with external PGx lab





Slide courtesy of Dr. Sony Tuteja

Perelman School of Medicine, University of Pennsylvania

PennChart Genomics Initiative

Optimizing the EHR for Use in Genomic Medicine

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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.

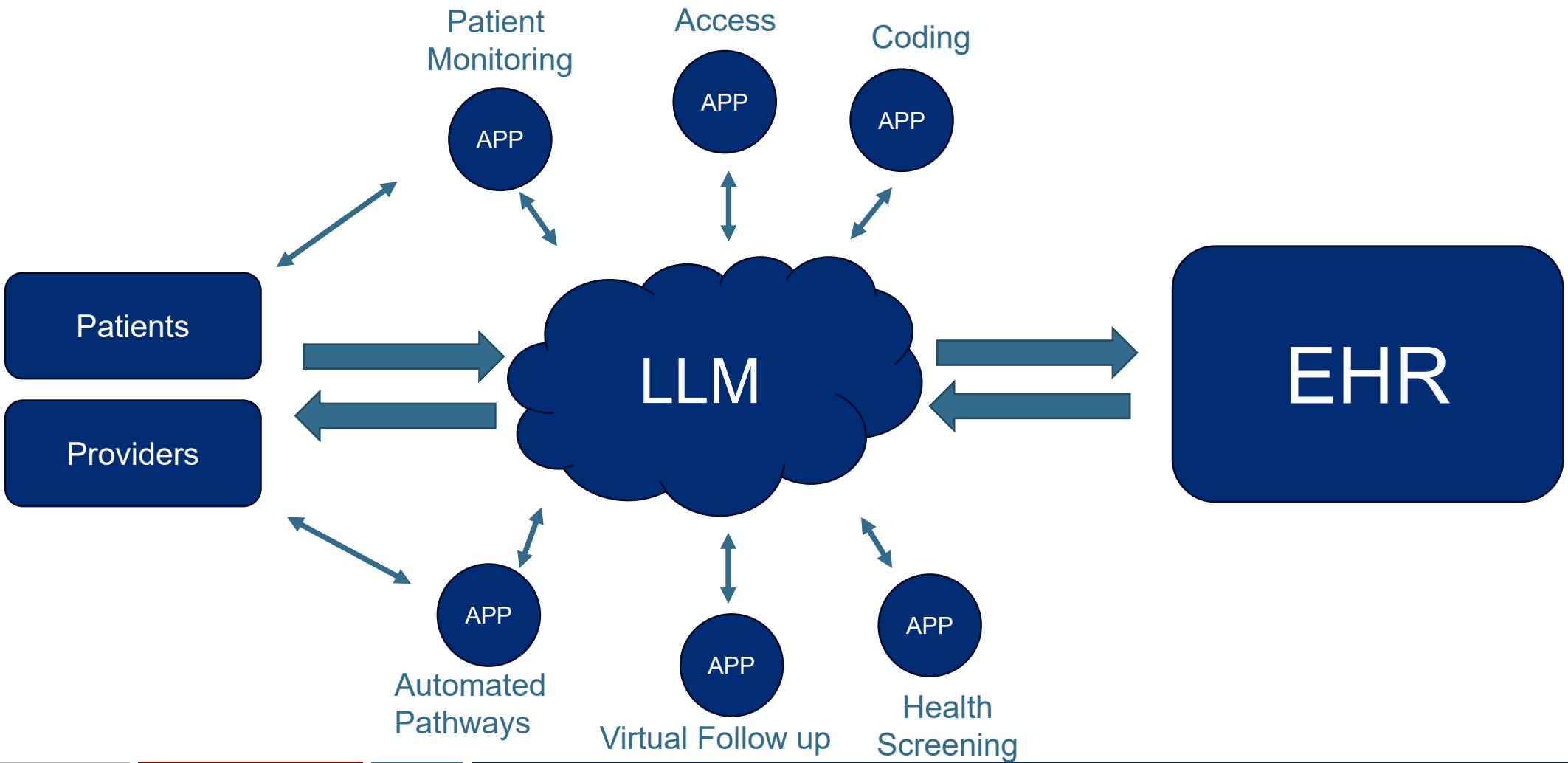
Resources

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

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

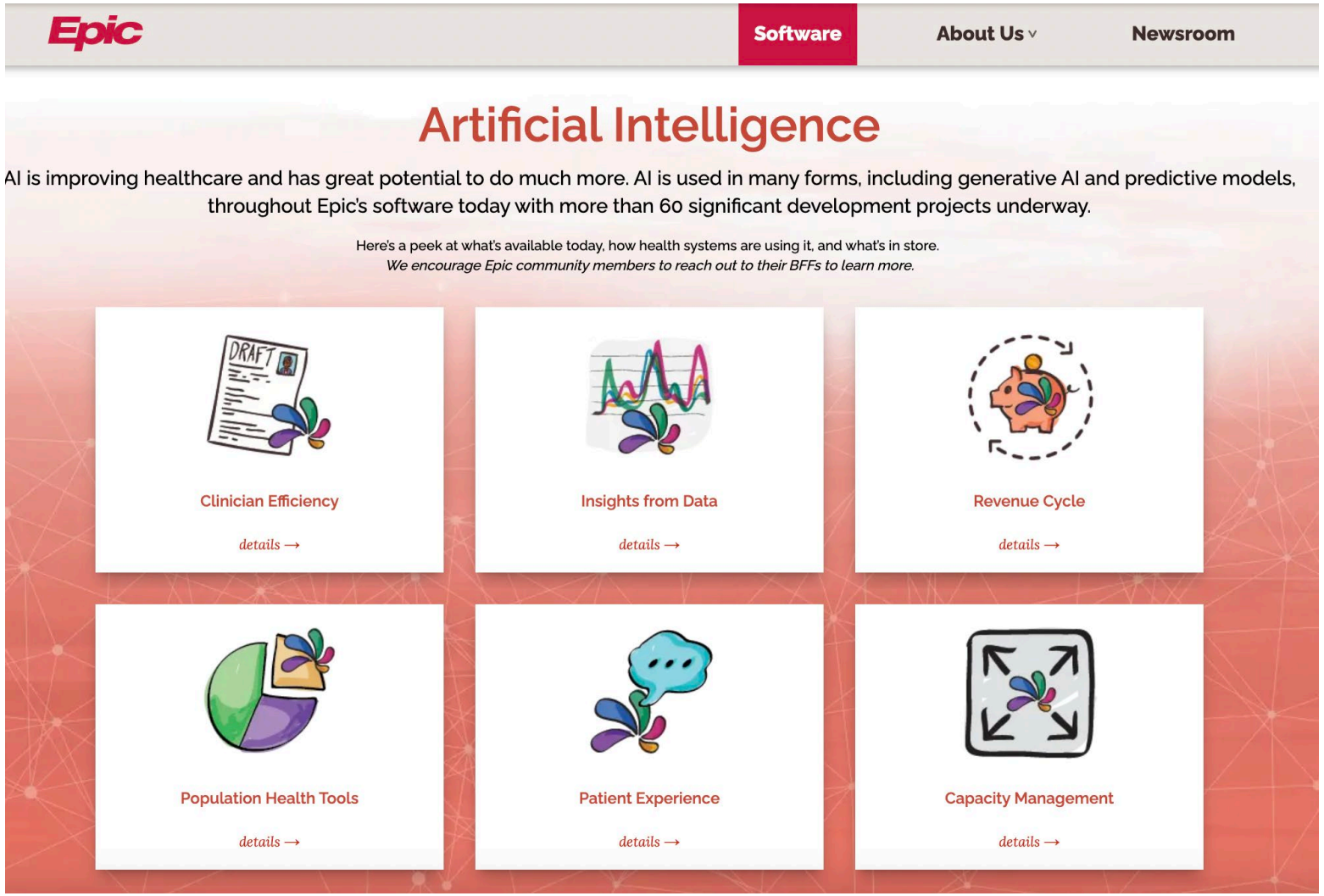
Slide courtesy of Dr. Sony Tuteja

Future state of EHR interfaces?



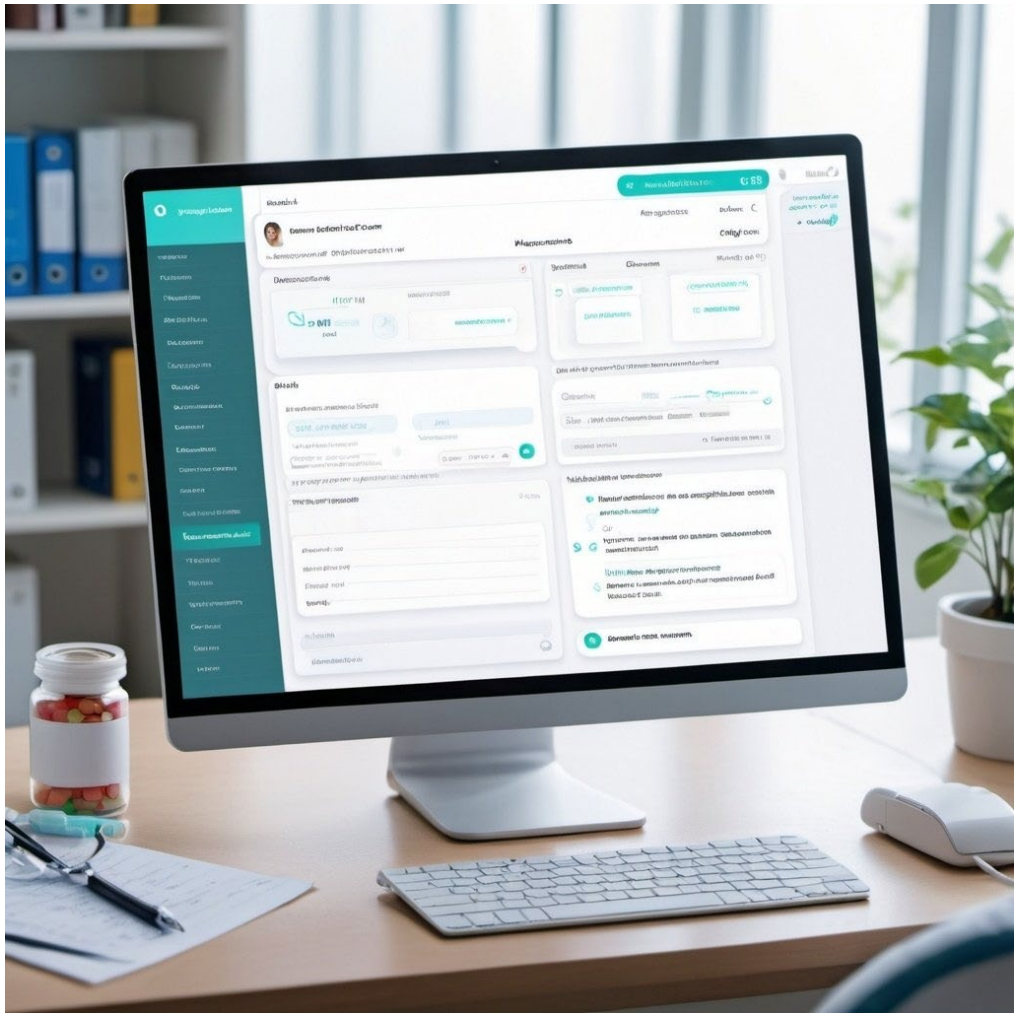
Slide courtesy of Dr. Mitch Schnall

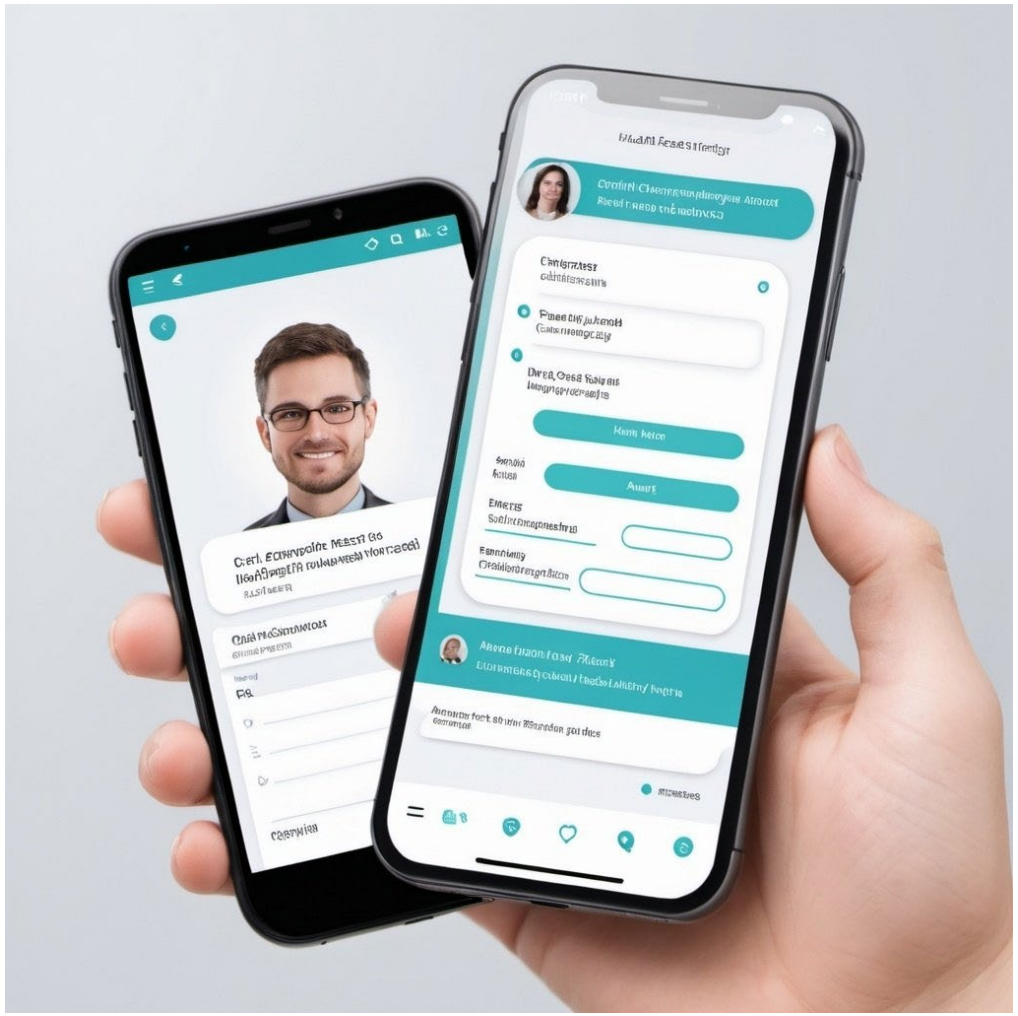
Generative AI and healthcare



https://www.epic.com/software/ai/

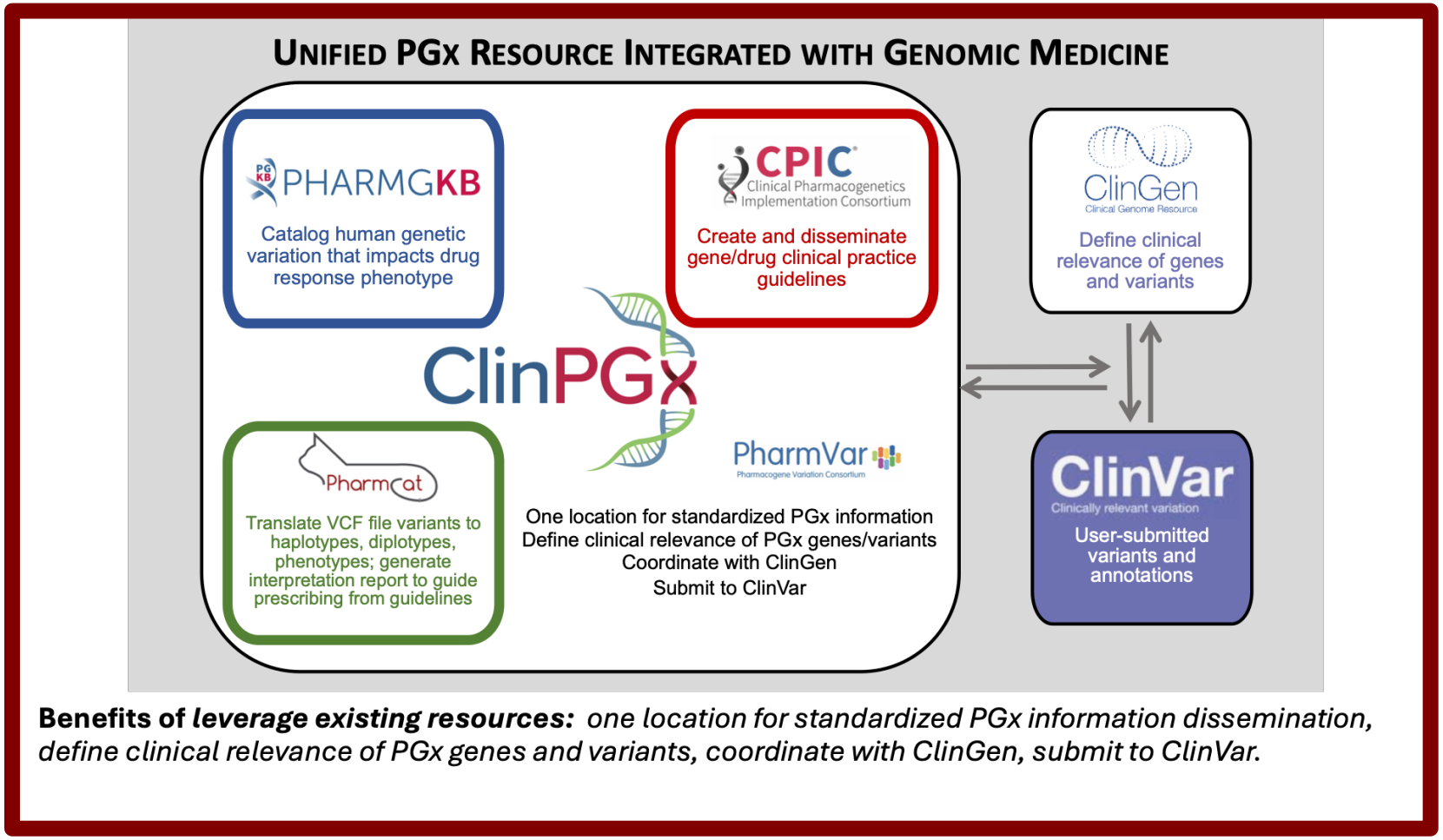
Use LLMs to enable provider & patient education





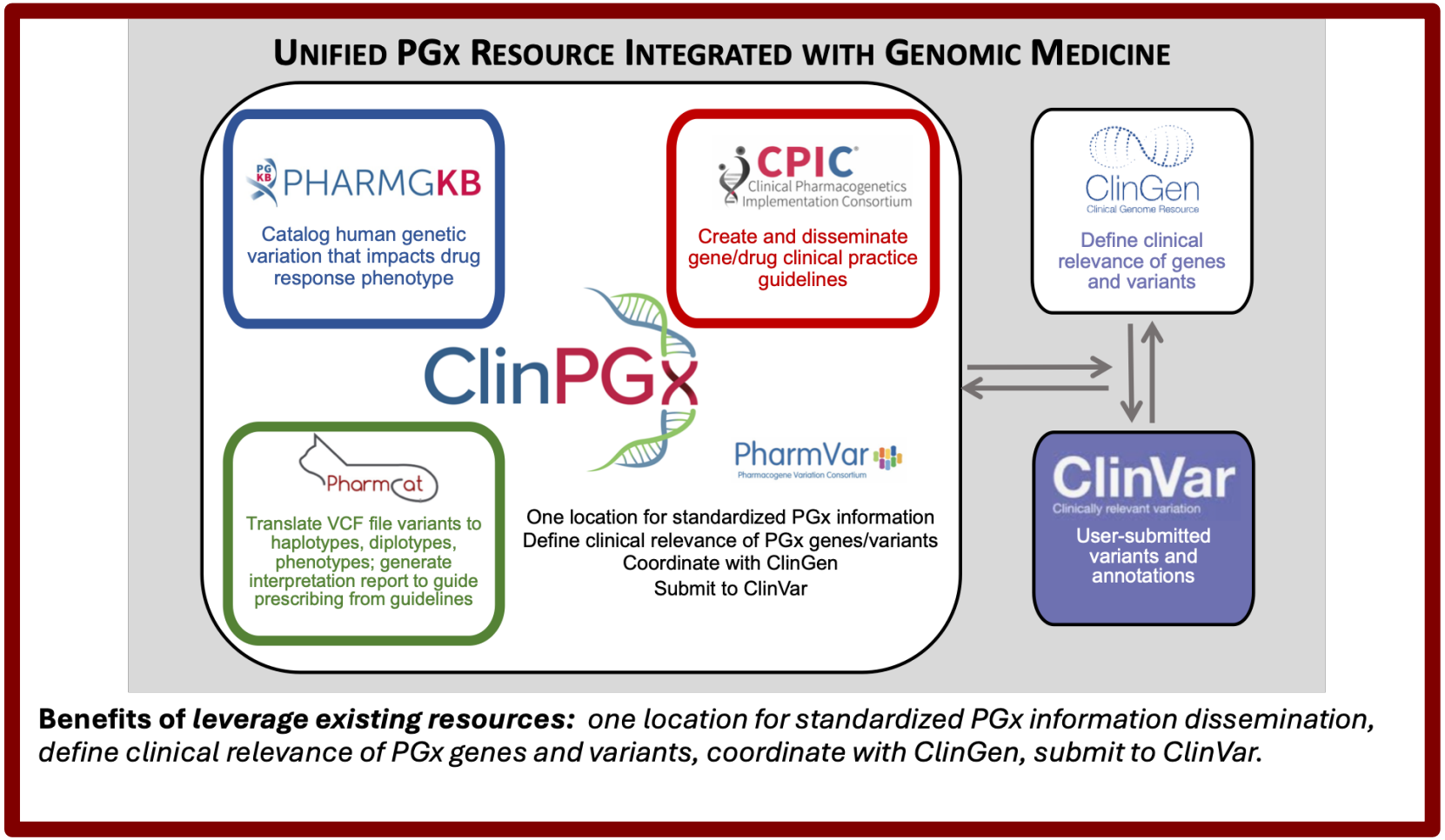
Images generated by OpenArt.ai

Use LLMs to interact with ClinPGx



Benefits of *leverage existing resources:* *one location for standardized PGx information dissemination, define clinical relevance of PGx genes and variants, coordinate with ClinGen, submit to ClinVar.*

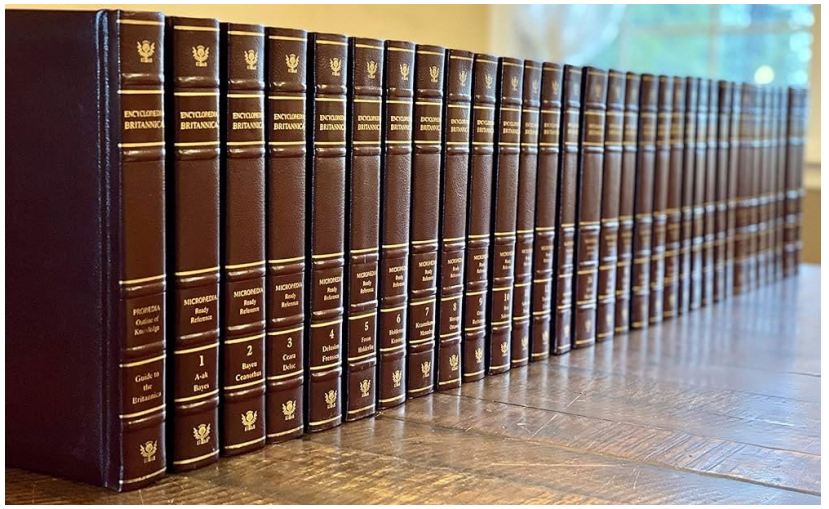
Use LLMs to interact with ClinPGx



Benefits of *leverage existing resources:* *one location for standardized PGx information dissemination, define clinical relevance of PGx genes and variants, coordinate with ClinGen, submit to ClinVar.*

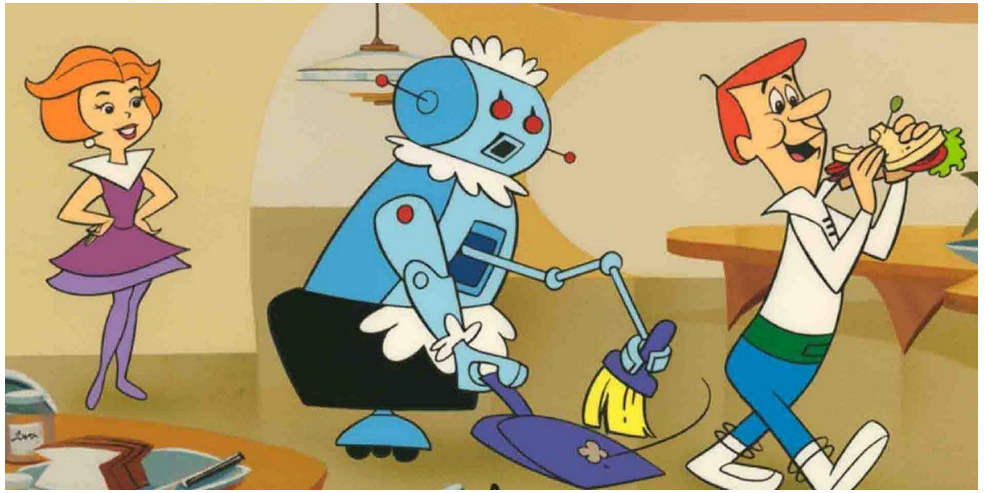
Disruptors

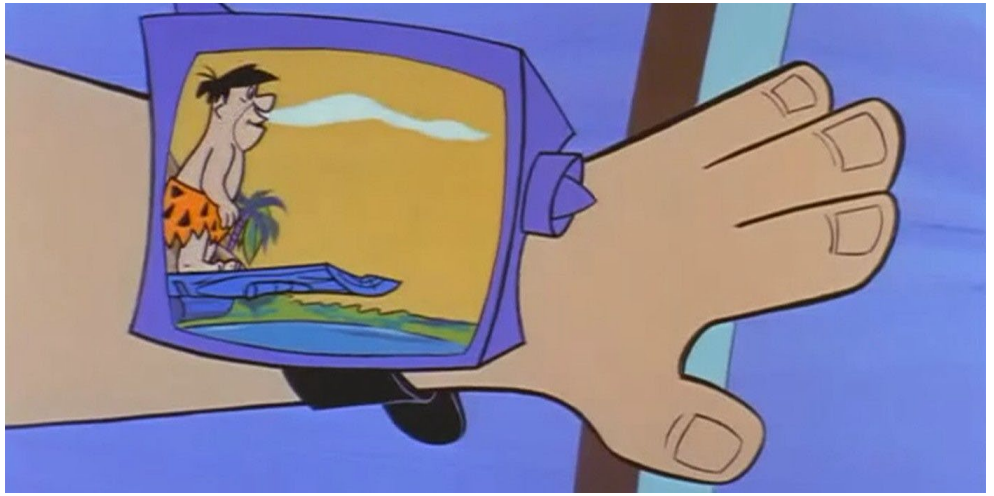
https://www.geeksforgeeks.org/what-is-internet-definition-uses-working-advantages-and-disadvantages/



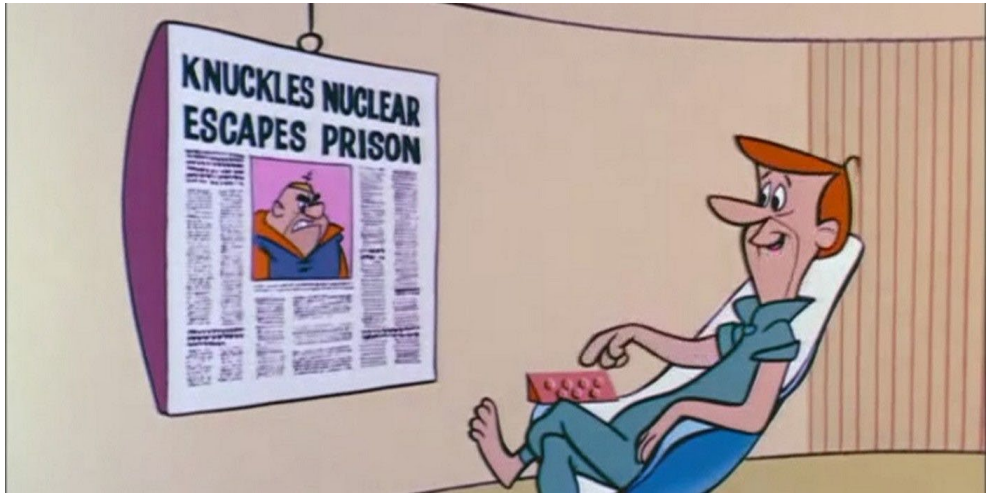
Disruptors

Affymetrix






VACUUM


KNUCKLES NUCLEAR
ESCAPES PRISON

ClinPGx

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

Acknowledgements

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- 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!