Clinical Pharmacogenomics (ClinPGx)
&
Clinical Genome Resource (ClinGen)

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MPI PharmGKB, CPIC, PharmCAT, ClinGen

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PGx Resources

Over time

2000 — PHARMGKB

2005 — CPIC

2010

2015 — **PharmVar**

Pharmcat

2020 — Partnership between ClinGen + PHARMGKB + CPIC

2021 — Conceptualization of ClinPGx

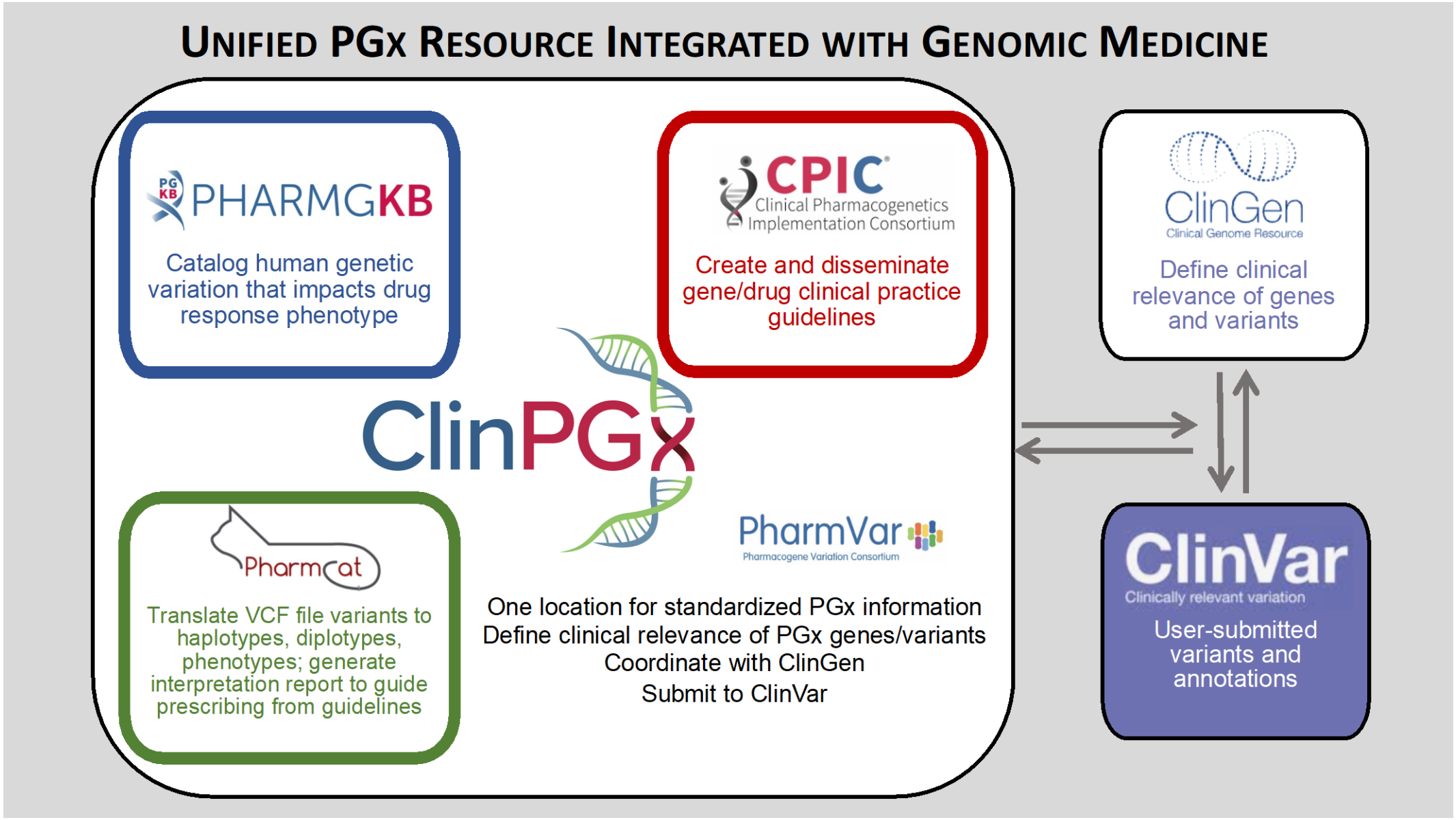
2022 — **PharmGKB** transition to **ClinPGx** grant and establishment of ClinGen **PGx Working Group (PGxWG)**

2023 — **CPIC** & **PharmCAT** transition to single grant

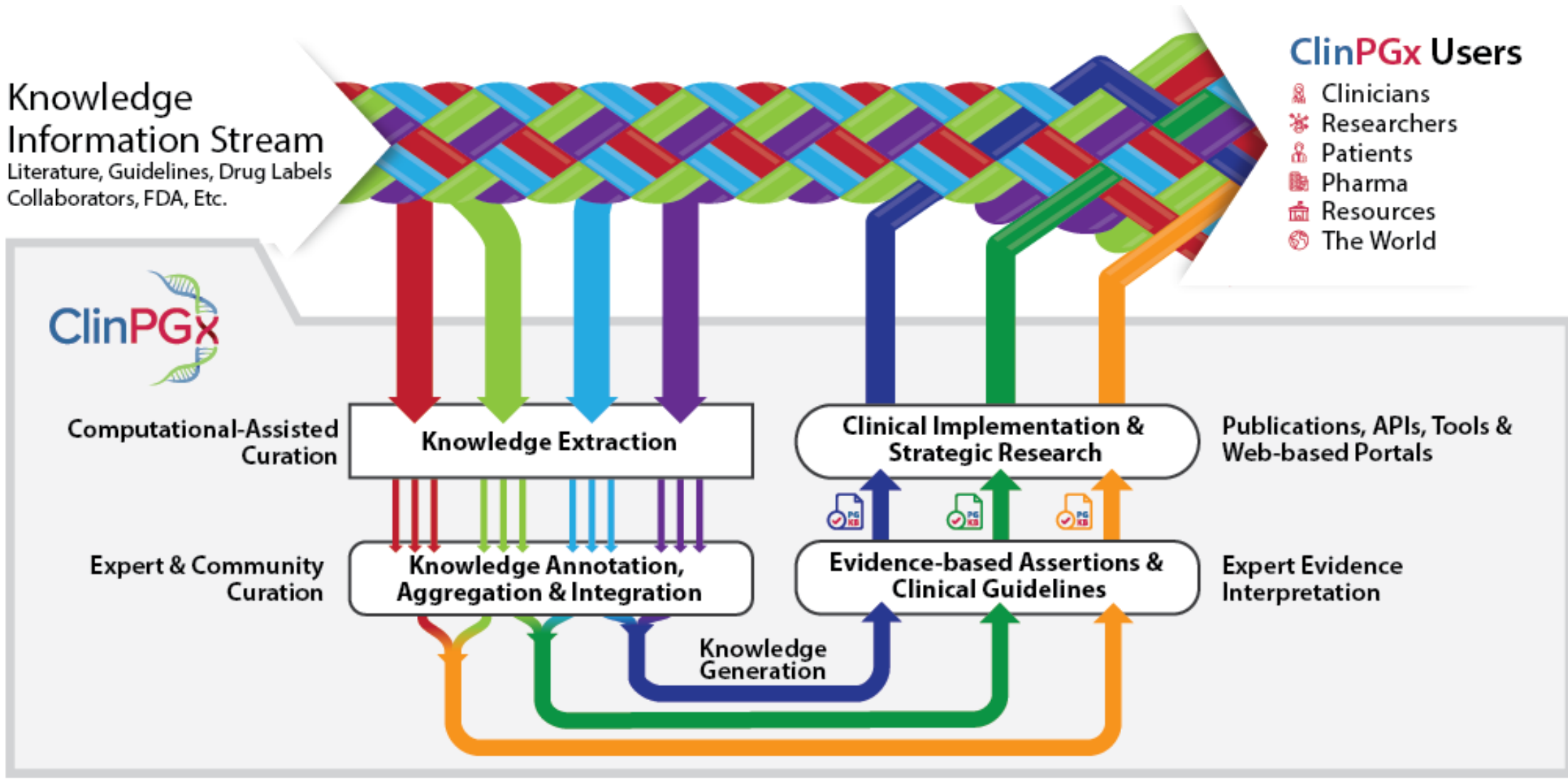
2024 — **DNA-Driven R_x**

2025 — **ClinPGx** with bridge to **ClinGen**

PharmGKB, ClinPGx, PharmCAT, DDR_x with API to **PharmVar**



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.*


Knowledge
Information Stream
Literature, Guidelines, Drug Labels
Collaborators, FDA, Etc.
ClinPGx Users
Clinicians
Researchers
Patients
Pharma
Resources
The World
ClinPGx
Computational-Assisted Curation
Knowledge Extraction
Clinical Implementation & Strategic Research
Publications, APIs, Tools & Web-based Portals
Expert & Community Curation
Knowledge Annotation, Aggregation & Integration
Evidence-based Assertions & Clinical Guidelines
Expert Evidence Interpretation
Knowledge Generation

https://clinpgx.org

ClinPGx (Clinical Pharmacogenomics Resource) integrates the PharmGKB, CPIC and PharmCAT into a single resource. There is confusion in the community at times as to which project (e.g., PharmGKB or CPIC) does what, including specific functionality (i.e., CPIC writes genotype-based prescribing guidelines, PharmGKB implements different ways to access those guidelines including specific diplotype recommendations and compares those recommendations from different resources including CPIC, other guideline groups, FDA PGx and biomarker tables). The multiple websites require significant effort to ensure that the databases/KBs stay in sync not only across these groups, but with outside resources. PharmGKB coordinates this synchronization as well as data deposition from these resources to ClinVar. In addition, multiple resources require more effort by having multiple Scientific Advisory Boards, Steering Committees and work by volunteers, applicant institutions, and the NIH to elucidate the specific job responsibilities (i.e., a curator on PharmGKB vs. PharmCAT vs. CPIC vs. PharmVar). Lastly, as mentioned above, this has created a siloing effect of PGx that cannot and should not be sustained.

Thus, we are excited that in the coming 18 months, we hope to formally launch ClinPGx with all resources below integrated. During this transitionary time, we will begin to introduce ClinPGx wherever appropriate, but will NOT be losing the branding of CPIC and the PharmGKB. For example, the CPIC guidelines will remain the CPIC guidelines and much of the organizational structure for CPIC will remain the same. The big difference will be that you would obtain the CPIC guidelines from the ClinPGx website and the CPIC website will be deprecated.

PHARMGKB

The PharmGKB Blog has transitioned to the ClinPGx Blog

Jun 14, 2024 03:17 pm

We have a brand new blog platform: the ClinPGx Blog.

PharmGKB, CPIC and PharmCAT are transitioning to a unified resource under the ClinPGx umbrella and will subsequently publish news to the ClinPGx Blog. This is the last post made on this blog site; all future posts will be found on https://blog.clinpgx.org. If you subscribe to announcements from the PharmGKB Blog, your subscription will be migrated to the new system automatically. You'll also get the opportunity to sign up for announcements from other ClinPGx projects. More details are available on the ClinPGx Blog.

New blog posts will only appear on the ClinPGx Blog and previous PharmGKB Blog posts are also accessible there, so all posts can be obtained from one place. The PharmGKB Blog will remain online (but not updated) for as long as Blogger will allow. That means existing links to PharmGKB Blog posts will be maintained.

Thank you for your continued interest in PharmGKB, CPIC, PharmCAT and all the other projects we have written about on this blog. We are excited to keep sharing our work with you on the new ClinPGx Blog!

https://blog.clinpgx.org

BY CLINPGX STAFF IN CLINPGX — JUN 14, 2024

Welcome to the ClinPGx Blog!

Photo by Belinda Fewings on Unsplash

This is the brand new home for news about all things ClinPGx, including PharmGKB, CPIC, PharmCAT and PharmVar!

This is the brand new home for news about all things ClinPGx, including PharmGKB, CPIC, PharmCAT and PharmVar!

We are excited to share our transition from the PharmGKB Blog to a brand new platform: the ClinPGx Blog. The new blog refines, simplifies, and improves accessibility to information about ClinPGx and pharmacogenomics. The redesigned blog maintains the core functionalities of the old blog but with a fresh, clean layout. It also integrates email announcements, called newsletters, eliminating the need for external services like MailChimp to manage your subscription. You can use the *Subscribe* button to sign up or the *Account* button to manage your subscriptions after you've registered. We're integrating the management of the PharmGKB, CPIC, and PharmCAT announcement newsletters under a single account to enable convenient subscription maintenance.

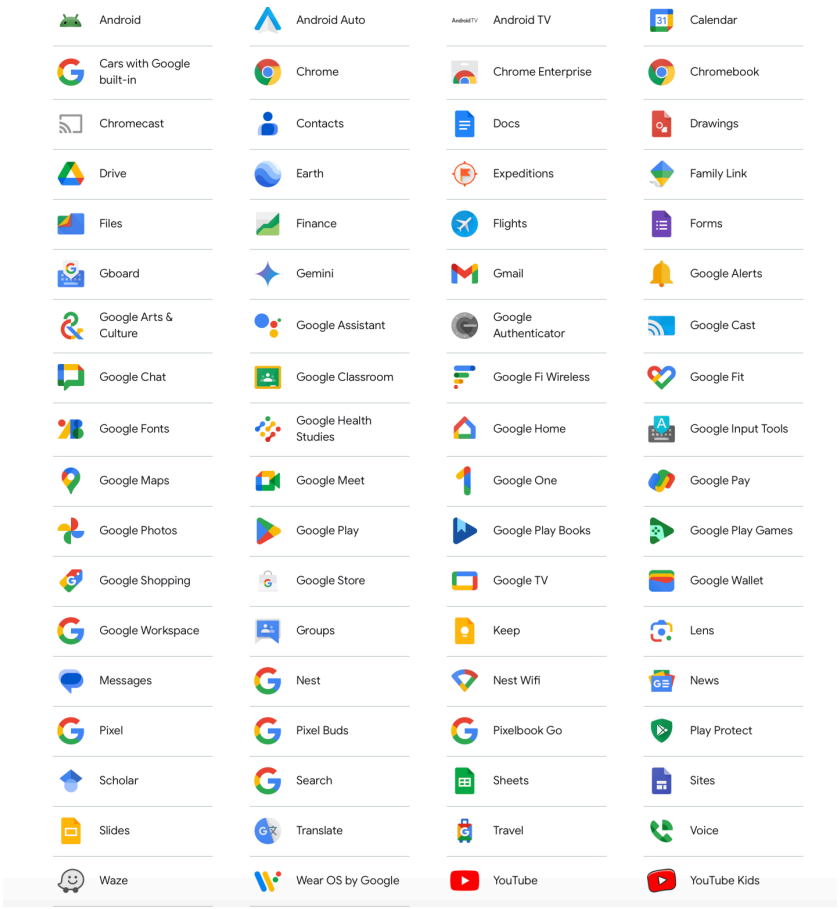
The Newsletters

Subscribing to the "ClinPGx Newsletter" ensures that you will receive all ClinPGx Blog posts, including major announcements about PharmGKB, CPIC, and PharmCAT. We recommend subscribing to this newsletter because it is the best way to stay informed about all ClinPGx projects. **If you were already registered with an existing announcement newsletter (i.e. PharmGKB Blog, CPIC Announcement list, PharmCAT Releases) you will be automatically migrated to the new ClinPGx Newsletter**.

We are also adding three new newsletters for more detailed, technical announcements for PharmGKB, CPIC, and PharmCAT. These newsletters are intended to be of interest to people working with the data and software from those projects but may not be of interest to everyone receiving the ClinPGx Newsletter. It is a great way for us to contact you in case of a problem or breaking change with data or software that may affect you.

How to “think” about ClinPGx?

”Think” Google Suite of Programs (but fewer ☺)



ClinPGx

powered by PHARMGKB

CPIC™ Clinical Pharmacogenetics Implementation Consortium

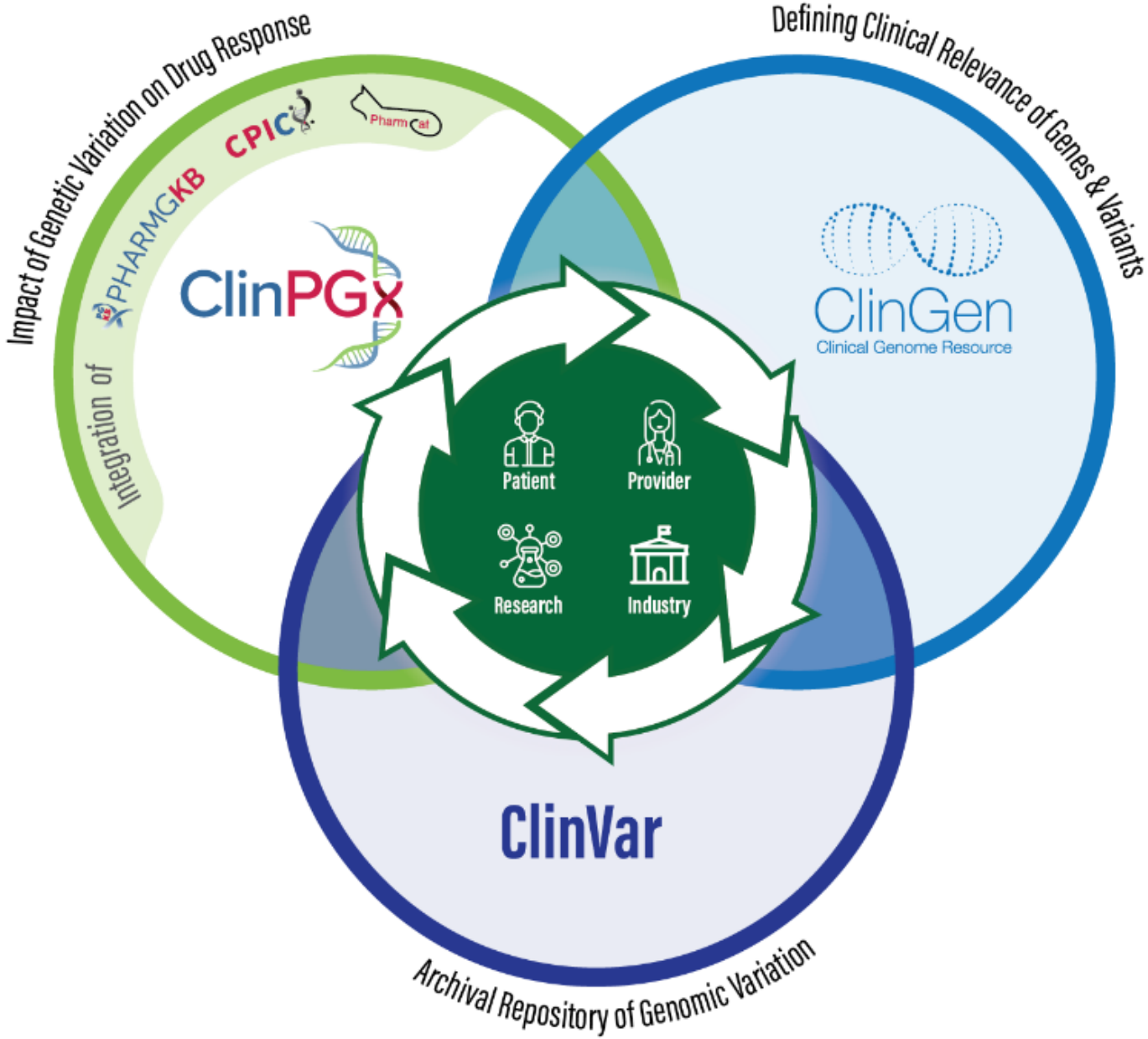
Pharmcat

Rx

Educational Resources

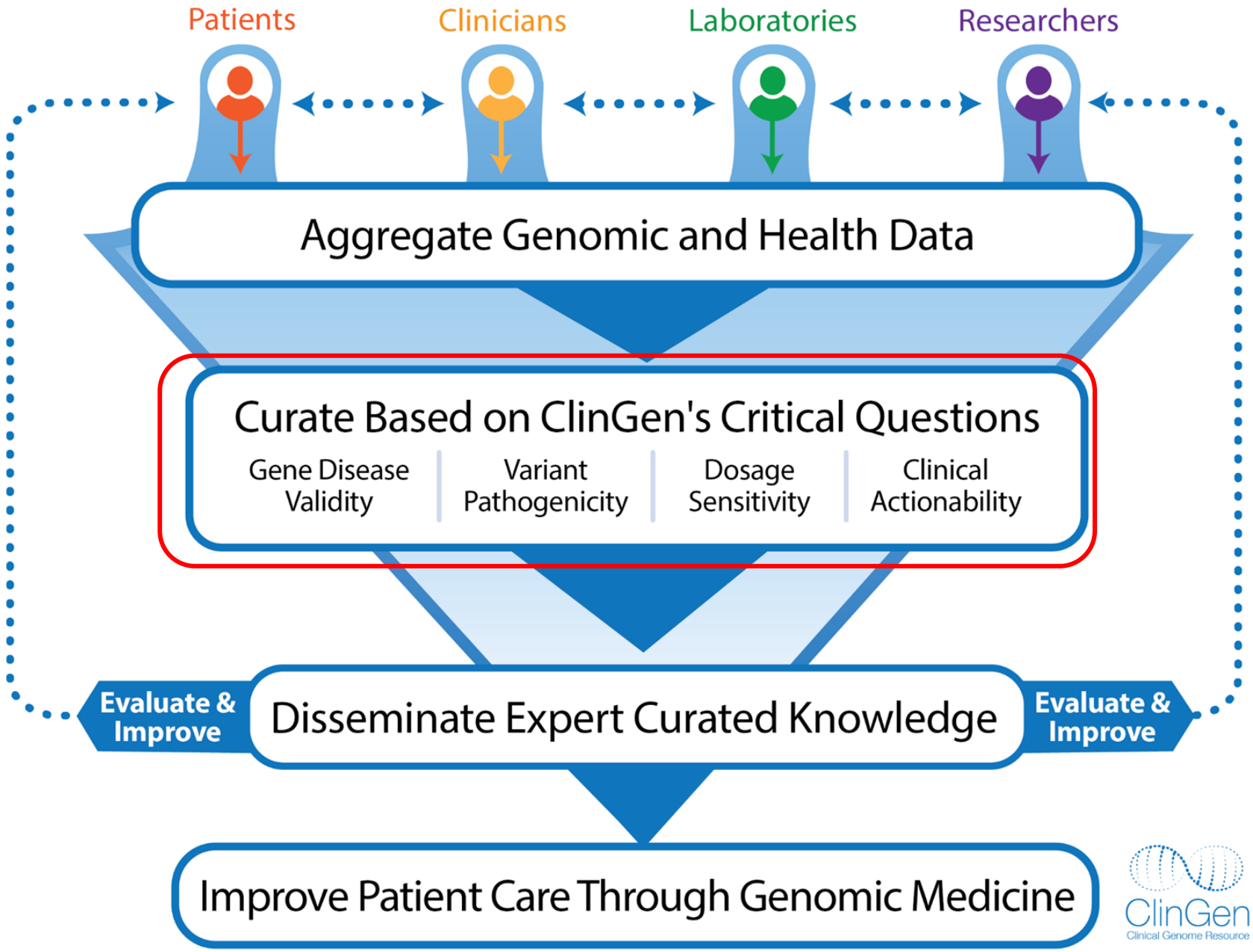
ClinPGx single sign-on (SSO)

Knowledge, Tools, Educational Materials & Videos, AI-generated information for different user groups and whatever the future holds


Impact of Genetic Variation on Drug Response
Integration of
PHARMGKB
CPIC
PharmCat
ClinPGx
Defining Clinical Relevance of Genes & Variants
ClinGen
Clinical Genome Resource
Patient
Provider
Research
Industry
ClinVar
Archival Repository of Genomic Variation

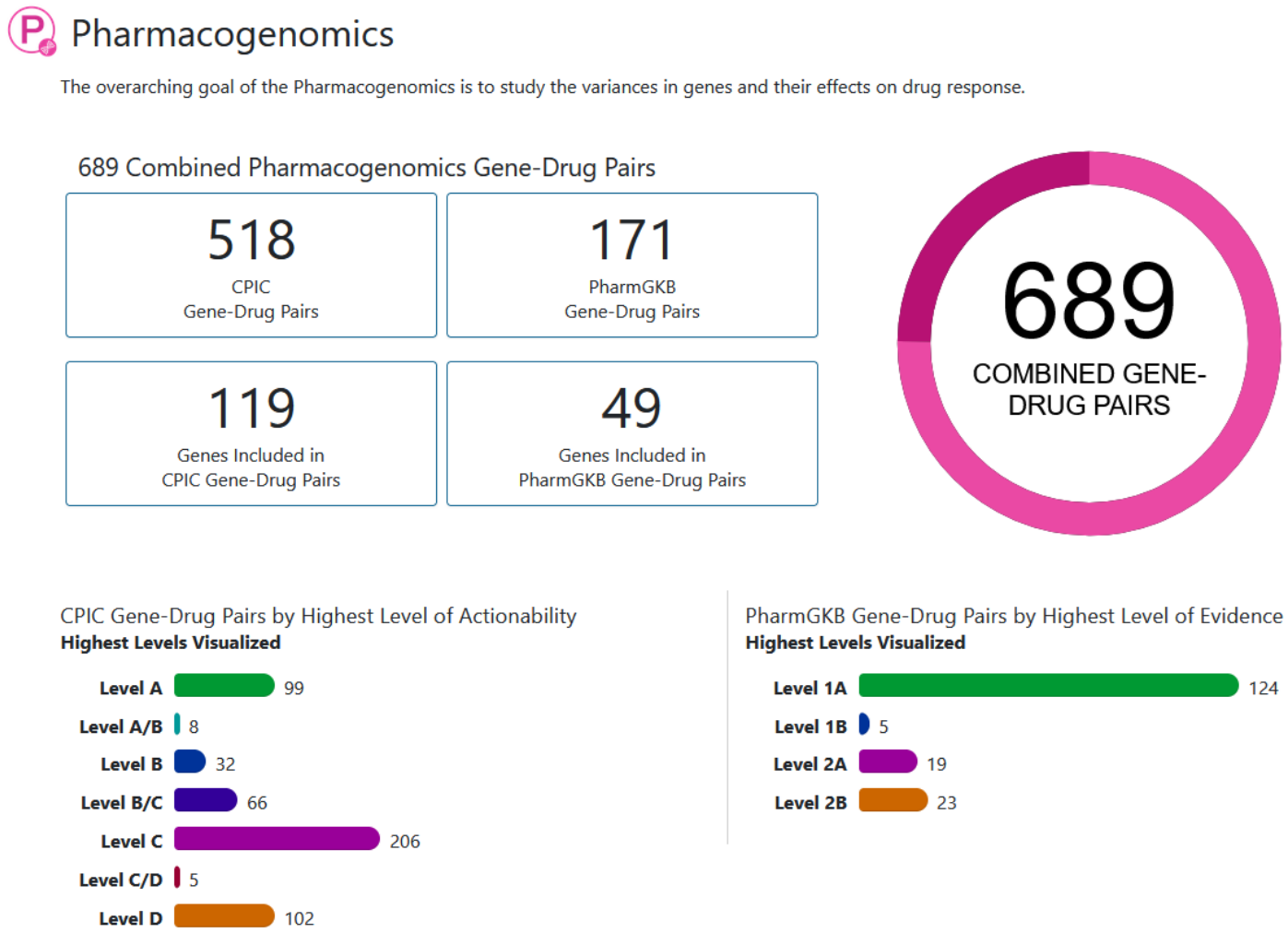
ClinGen
Clinical Genome Resource

Mission: Build and support authoritative central resources that define the clinical relevance of genes and variants for use in precision medicine and research


Patients
Clinicians
Laboratories
Researchers
Aggregate Genomic and Health Data
Curate Based on ClinGen's Critical Questions
Gene Disease Validity
Variant Pathogenicity
Dosage Sensitivity
Clinical Actionability
Evaluate & Improve
Disseminate Expert Curated Knowledge
Evaluate & Improve
Improve Patient Care Through Genomic Medicine
ClinGen
Clinical Genome Resource

ClinGen-CPIC-PharmGKB Partnership

- Displays 689 gene-drug pairs
- Active links
- CPIC level and PharmGKB level of evidence



DPYD

View Gene Facts

0	2	0	0	3 / 3	
Gene-Disease Validity Classifications	Dosage Sensitivity Classifications	Clinical Actionability Assertions	Variant Pathogenicity Assertions	CPIC / PharmGKB High Level Records	Follow Gene

Curation Summaries | Status and Future Work (2) | External Genomic Resources | ClinVar Variants

Dosage Sensitivity

Group By Activity | Group By Gene-Disease Pair

Gene	Disease	Working Group	HI Score & TS Score	Report & Date
DPYD	dihydropyrimidine dehydrogenase deficiency MONDO:0010130	Dosage Sensitivity WG	30 (Gene Associated with Autosomal Recessive Phenotype)	01/24/2018
DPYD		Dosage Sensitivity WG	0 (No Evidence for Triplosensitivity)	01/24/2018

Pharmacogenomics - CPIC

Gene	Drug	CPIC Level	Date Accessed	CPIC Clinical Guidelines
DPYD	capecitabine	Level A	04/28/2023	Guideline
	fluorouracil	Level A		
	tegafur	Level C		

Pharmacogenomics - PharmGKB

Gene	Drug	Highest Level of Evidence	Last Curated	Information
DPYD	capecitabine	Level 1A	10/27/2022	View
	fluorouracil	Level 1A	10/27/2022	View
	tegafur	Level 1A	05/24/2021	View

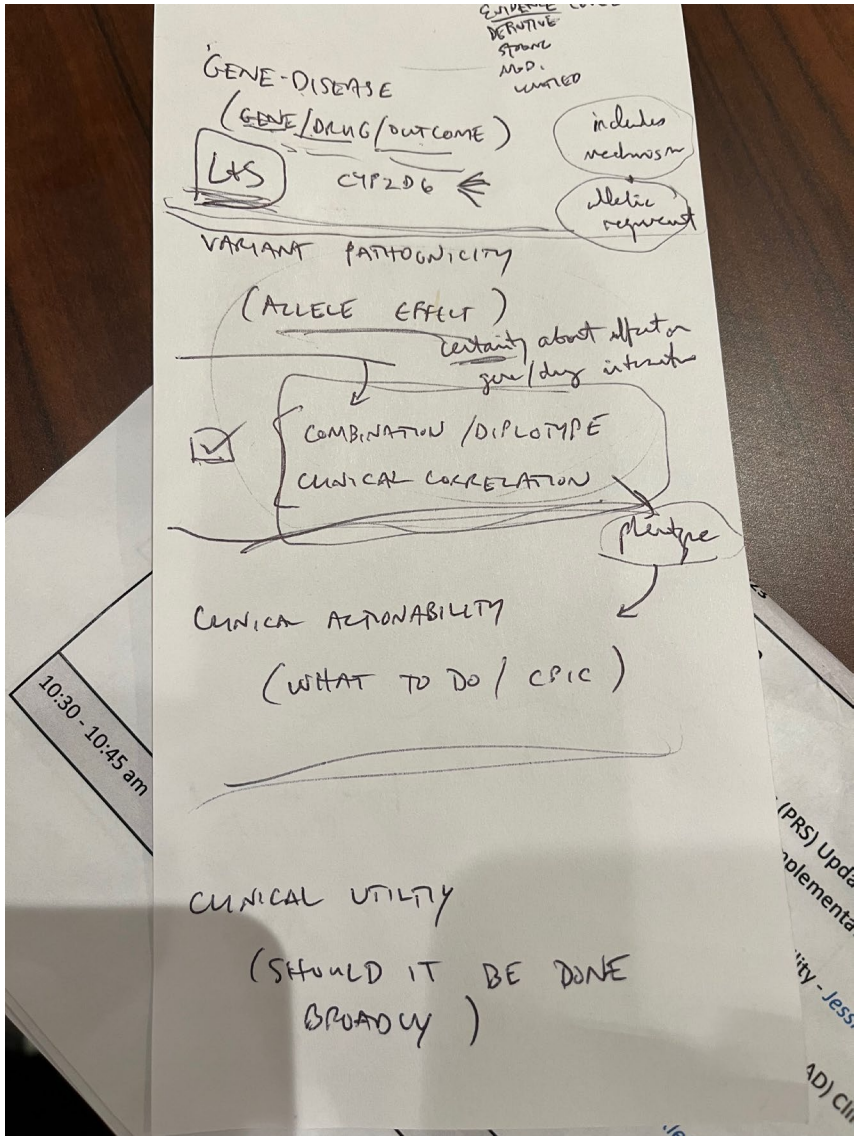
ClinPGx & ClinGen – why are they in the same conversation?

- *Integration between PGx resources & ClinGen*

  Development of ClinPGx
  Re-instituted to PGx Working Group (PGxWG)
    Survey of PGx Community & Clinical Genomics Communities to identify similarities/differences w/ClinGen
      Significant agreement with ClinGen definitions with modification for PGx
  Broad participation across ClinGen in PGxWG including Actionability (Jessica Hunter), Variant Curation (Steve Harrison) and advice on Lumping & Splitting (Courtney Thaxton)

- *Presented to the ClinPGx SAB and ClinGen SC and SC+ESP*

Drawing by Jonathan Berg from ClinGen SC & ESP (May 2023)



Build the PGx frameworks for
Gene-drug validity
Variant classification
Actionability
using the existing PGx resources
PharmGKB and CPIC

Pharmacogenomics is Integral to Genomic Medicine

- Clinical utility of PGx is established
- Integration is critical to achieving the goal of personalized/precision medicine
- PGx differs from disease genomics models
  - Haplotypes and diplotypes rather than individual variants
  - Requires specialized resources
- Time to move away from PGx silos; need for one-stop shopping for PGx

ClinGen PGxWG Members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Sami Amr, PhD


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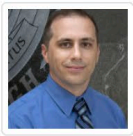
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Joanne McIntyre


Karen Merritt

Integration of PGx with ClinGen*

- ClinGen-CPIC-PharmGKB Partnership
- Dialogue with ClinGen efforts began in summer 2022
  - Data harmonization with Allele Registry, Evidence Repository, GA4GH (*e.g.*, nomenclature, identifiers)
  - Batch submission of PGx variants to ClinVar
- PGx Working Group
  - Needs assessment survey development and analysis
  - Gene-drug clinical validity framework
  - Gene-drug actionability framework
- PGx expert representation on VCEPs (*e.g.*, G6PD, DPYD) and GCEPs (*i.e.*, HLA, DPYD)
- Tool development for curation expansion for both PGx and disease curation (*i.e.*, HLA)

*Integration of PGx into ClinGen became a focus of the Baylor/Stanford grant when Teri Klein became MPI in 2021

Needs Assessment Survey

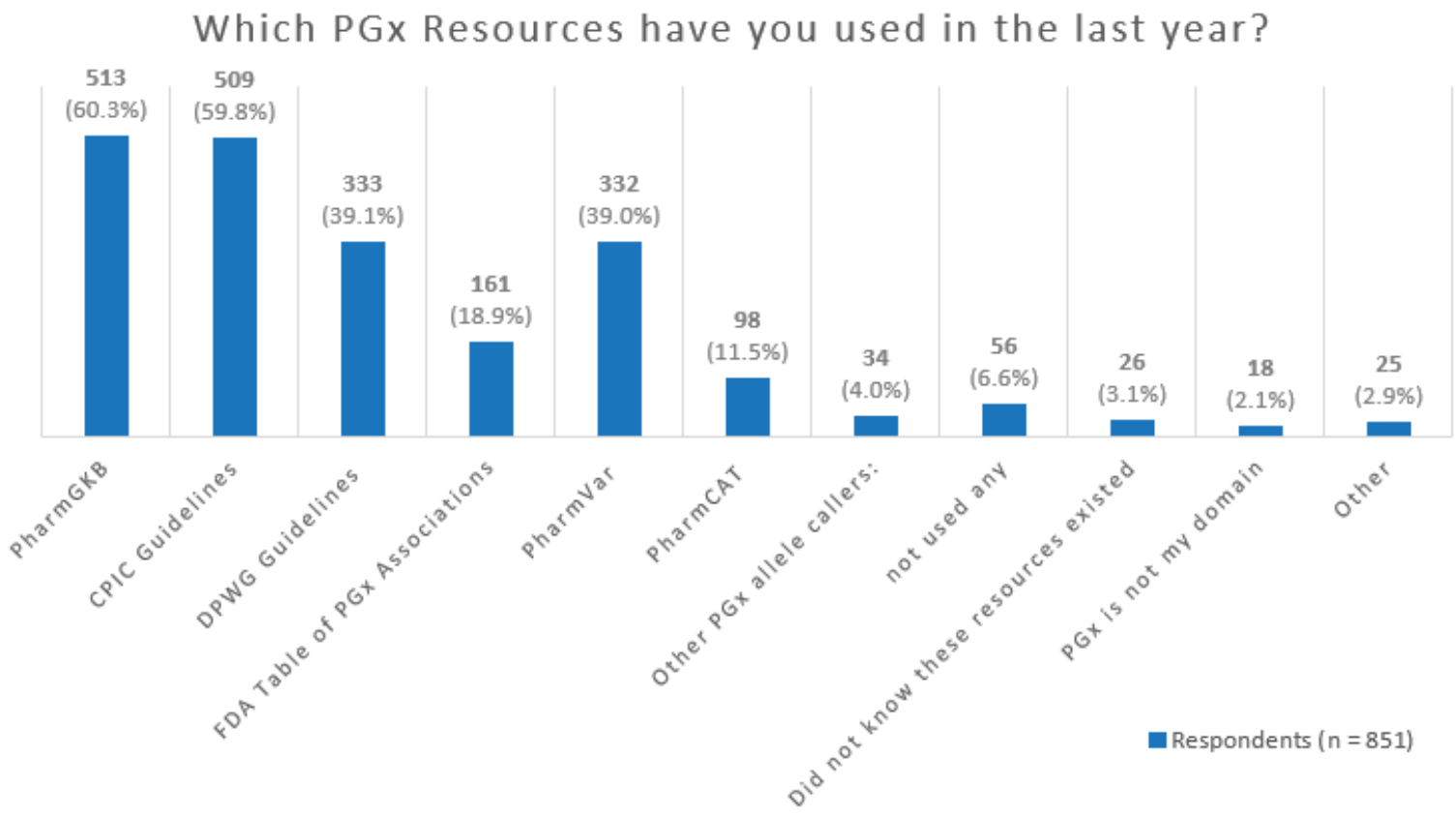
- Survey V1.0 (PGx community, experts):
  - 364 responses (February 2023)

- Survey V2.0 (broader clinical genetics community, stakeholders)
  - 346 responses (June 2023)

- V2.0 includes additional branch for those with limited PGx familiarity

- Broad dissemination, primarily USA respondents but with international representation

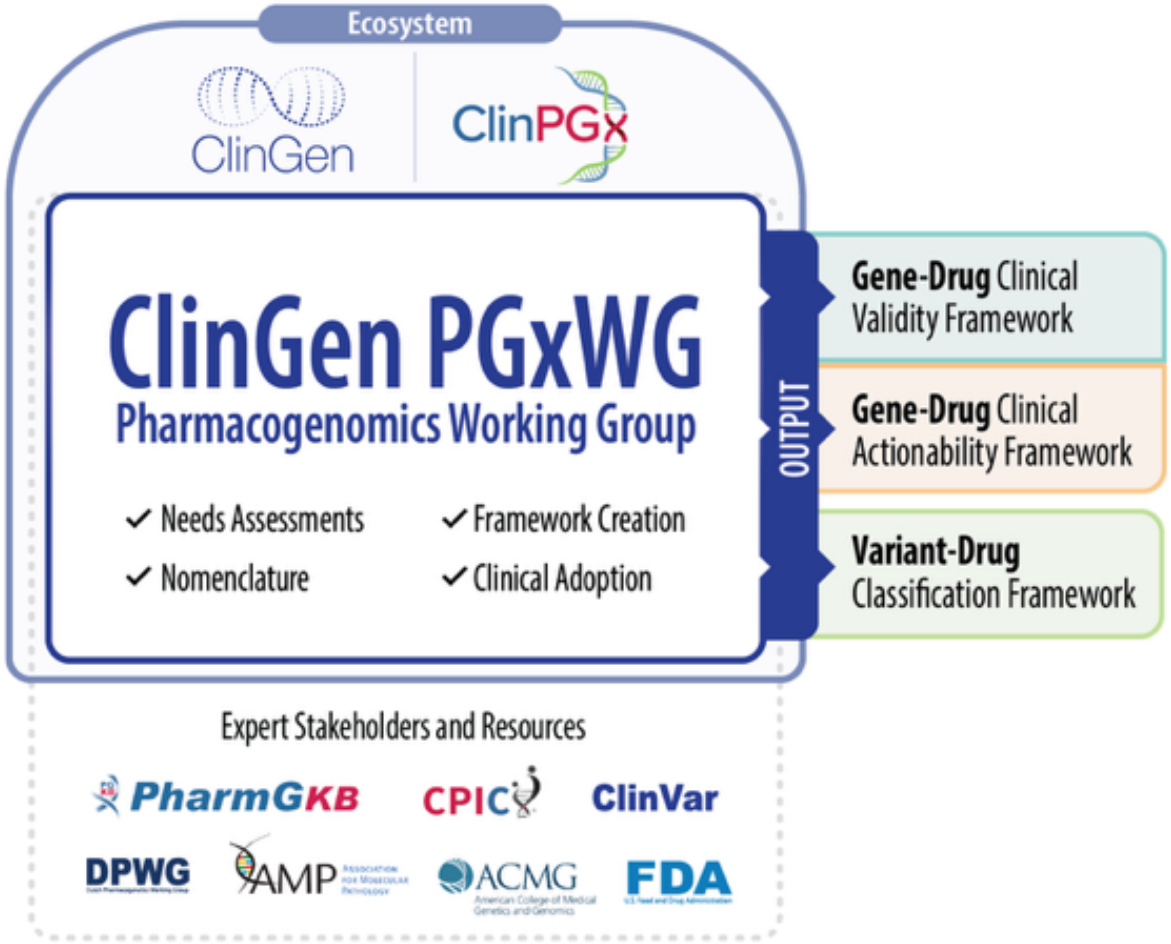
Leading knowledge resources for PGx. Frequently used resources were leveraged for development of the PGx validity and actionability.



How to Integrate Disparate Resources: Purpose of the ClinGen PGxWG

- Build frameworks:
  - gene-drug validity and actionability -> align with ClinGen
  - PGx variant classification -> alternative to ACMG (benign to pathogenic)
- Create a more intuitive terminology for clinical genetics community
  - Reduce PGx testing reporting inconsistencies
  - Aid in determining which PGx genes are worth testing
  - Establish criteria for evaluating PGx relationships (clinical and functional evidence found in literature and databases)
  - Leverage efforts from existing PGx resources

Gene-Drug Validity and Actionability, and Variant/Haplotype Classification

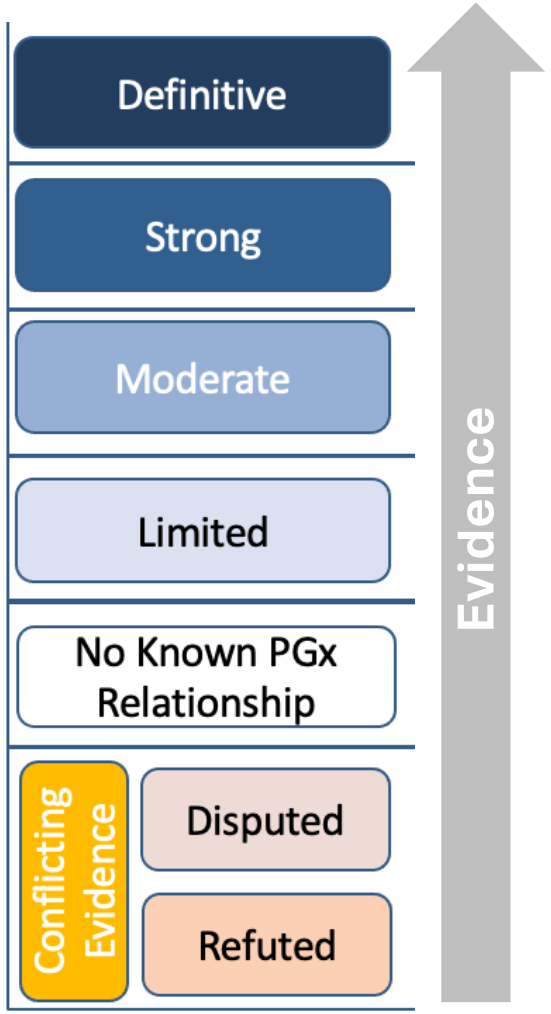


Validity: assess the evidence to determine if a gene is associated with a particular drug response phenotype

Actionability: assess the evidence to determine if gene variation can be used to guide and/or modify drug prescribing

Gene-Drug Clinical Validity

- How strong is the evidence that genetic variations of a gene are associated with clinically relevant PGx outcomes, such as drug response (efficacy), adverse effects, drug dose requirements, PK measurements
- Use parallel ClinGen terms for PGx validity
- Develop definitions for each level of evidence
- Develop a scoring range for each level of evidence
- Test with example gene-drug phenotypes for the scoring matrix



Evidence Category	Evidence Concept	Evidence component	Evidence Concept	Evidence Category
Clinical Outcomes	Efficacy	CPIC 10	0-12 12	0-12 12
		DPWG		
		FDA PGx Table		
		FDA label 6		
		ClinPGx/PharmGKB		
	Toxicity	CPIC 10	0-12 12	
		DPWG 10		
		FDA PGx Table		
		FDA label 6		
		ClinPGx/PharmGKB		
	Dose	CPIC	0-12	
		DPWG		
		FDA PGx Table		
		FDA label		
		ClinPGx/PharmGKB		
Pharmacokinetics	Pharmacokinetics	CPIC 6	0-6 6	0-6 6
		DPWG 6		
		FDA PGx Table		
		FDA label 4		
		ClinPGx/PharmGKB		
Experimental/ Functional evidence/ Pharmacodynamics	Mechanistic evidence/ Functional impact (target/transporter /*in vitro*)	ClinPGx/PharmGKB	0-2 2	0-2 2
Total				0-20 2

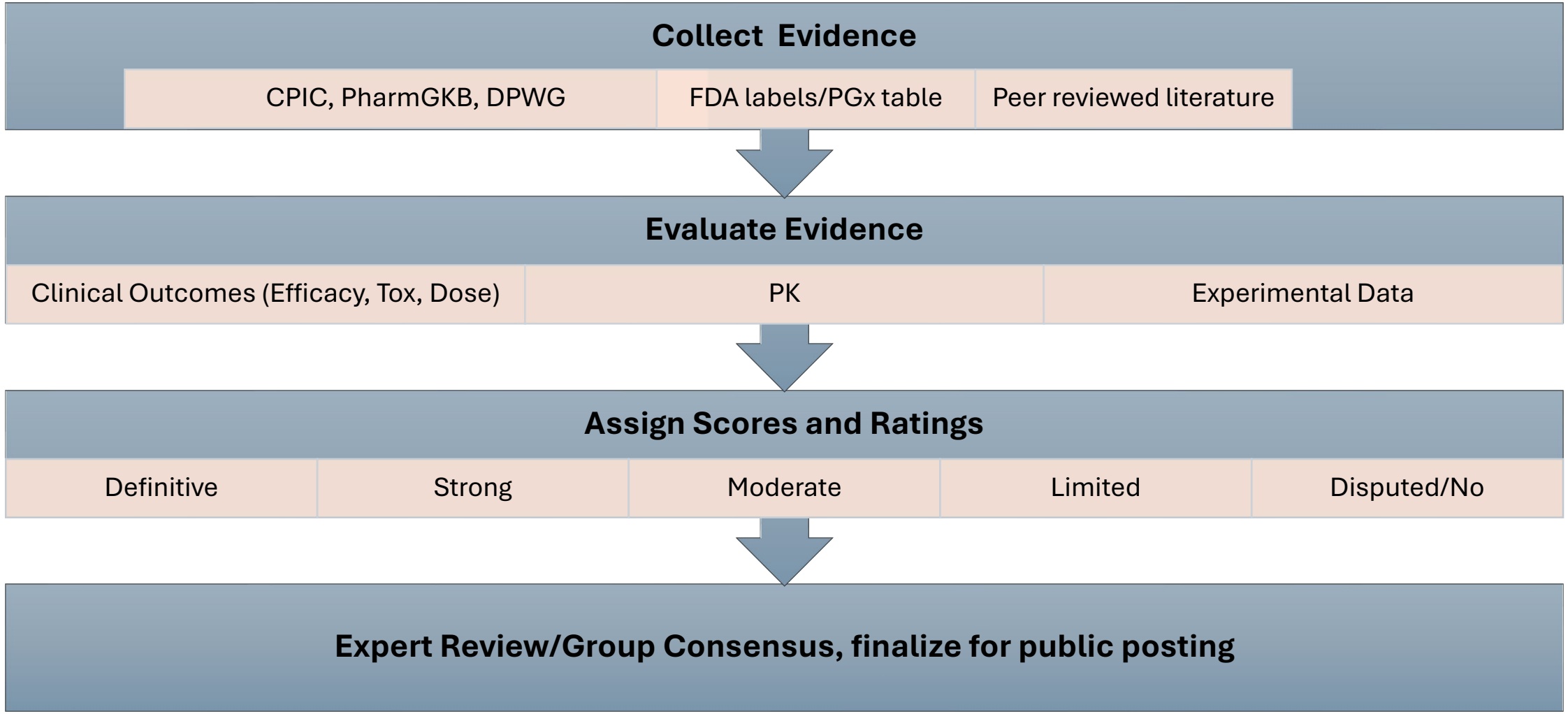
Example: CYP2D6-codeine

Clinical Outcomes	PK	Mechanistic/ function	Total Score	Reolicatoin over time	Classification
12	6	2	20	Yes	Definitive

CYP2D6 plays a prominent role in codeine metabolism

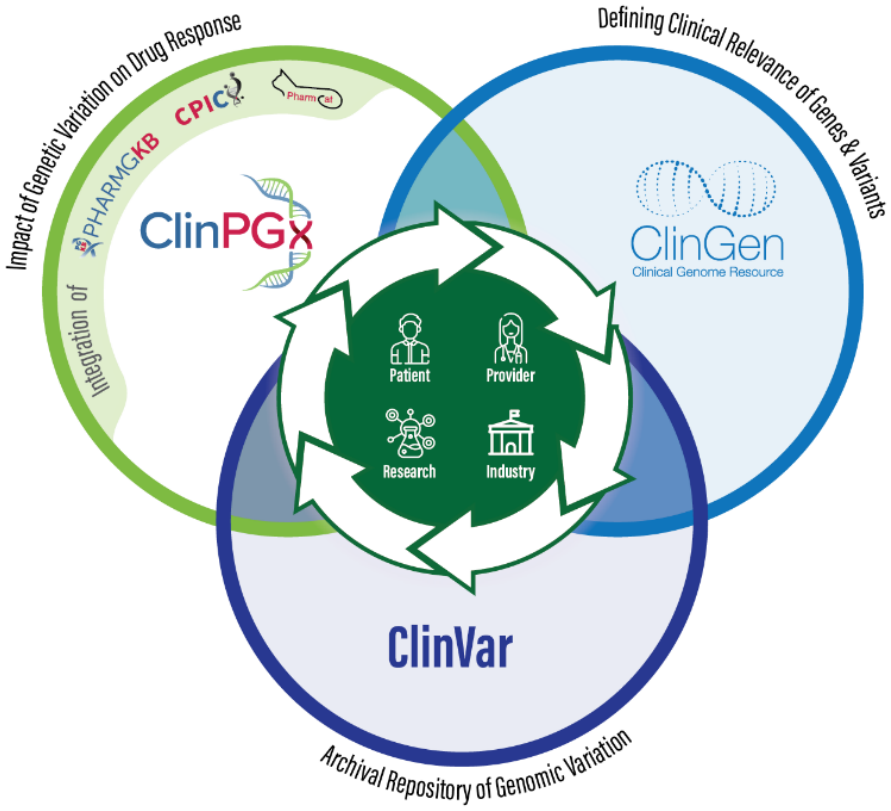
Evidence source	Level	Gene-Drug Validity Score
CPIC Level of evidence	High	10
	Moderate	6
	Weak	2
	No association (no level)	0
DPWG Evidence score	4	10
	3	6
	2	2
	1 (or NA)	0
FDA Table of PGx Associations	Therapeutic recommendation	10
	Safety/toxicity	6
	PK	4
FDA-approved drug label (curation from PharmGKB/ClinPGx)	Dose change or alternate drug recommendation	10
	Prescribing information	6
PharmGKB/ClinPGx Clinical Annotation	1B	6
	2A/2B	4
	3	2
	4	0

Proposed curation workflow – gene-drug validity



Alignment with ClinGen PGxWG Frameworks

- Integrated PGx resource (ClinPGx) will facilitate integration of PGx with ClinGen
- Existing need for standardization:
  - Inconsistency between resources and laboratories
  - Barrier to implementation (*e.g.*, EHR education, insurance coverage, communication between lab and provider)



Long-Term Benefits of ClinPGx Activities

- Reduce duplication of efforts
- Facilitate implementation of PGx (*i.e.*, EHR)
- Increase stakeholder buy-in (clinical, laboratory, insurance) and confidence in science behind testing
- Increase utility of existing resources (*e.g.*, ClinVar, PharmCAT), reduce confusion ***and*** allow for new opportunities
- Expansion of implementation and insurance coverage -> increased access to testing
  - Potentially reducing health disparities

ClinPGx

PharmGKB: A Critical Knowledgebase for Personalized Medicine
(U24 HG010615: Funded March 2023 – Dec 2025; ClinGen's awards end June 2026)
PharmGKB Grant Aims

Clinical Implementation Resources for Pharmacogenomics (CIRP) (aka CPIC & PharmCAT)
(U24 HG013077: Funded September 2023 – June 2026)
CIRP Grant Aims

Clinical Genome Resource (ClinGen)
U24 HG009649; Funded Feb 2021 – June 2026

Others Just as Important:

Kelly Caudle, co-PI CPIC
& her entire team

Marylyn Ritchie, co-PI PharmCAT
& her entire team

Andrea Gaedigk, PharmVar

GECKO Group (aka Klein Lab)
Michelle Whirl-Carrillo (PGx)
Matt Wright (ClinGen)
Gene Curation & Knowledge
Stanford University