

ClinGen/ClinPGx frameworks for assessing clinical validity and actionability of pharmacogenomic gene–drug pairs

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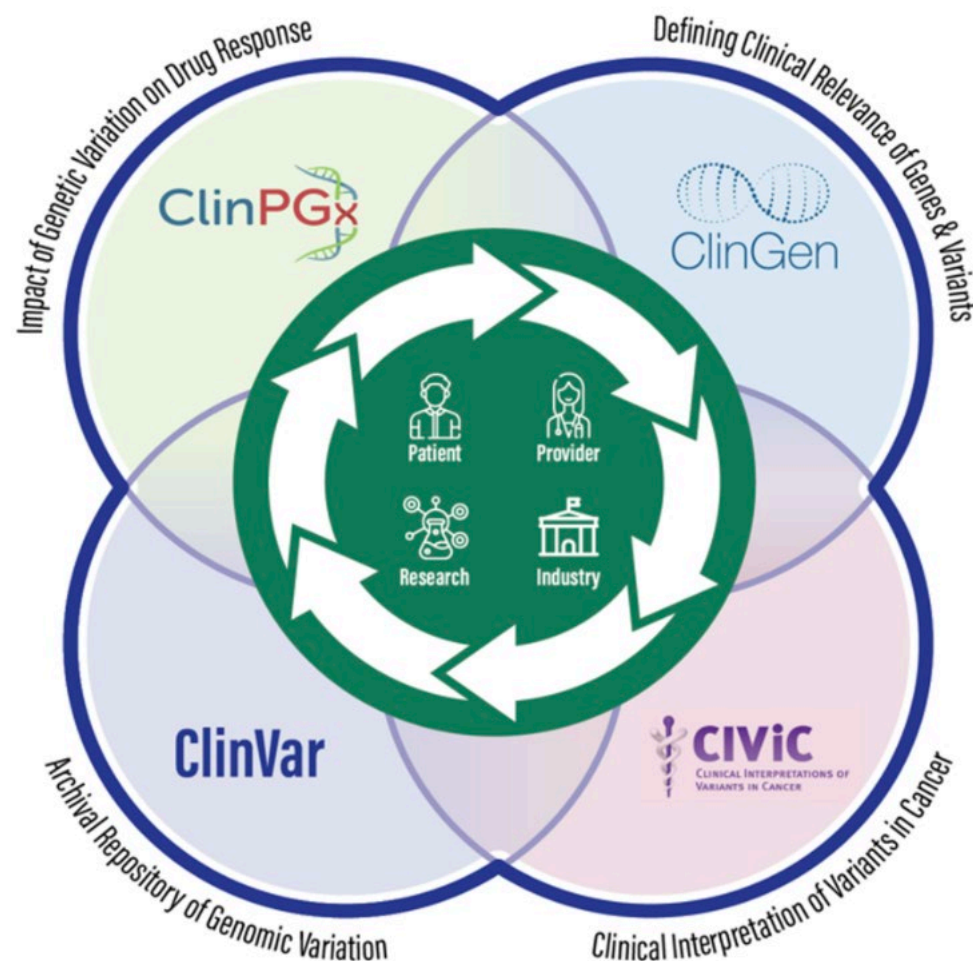
On behalf of the ClinGen PGx Interpretation Committee (PGxIC)

September 3, 2026

Outline

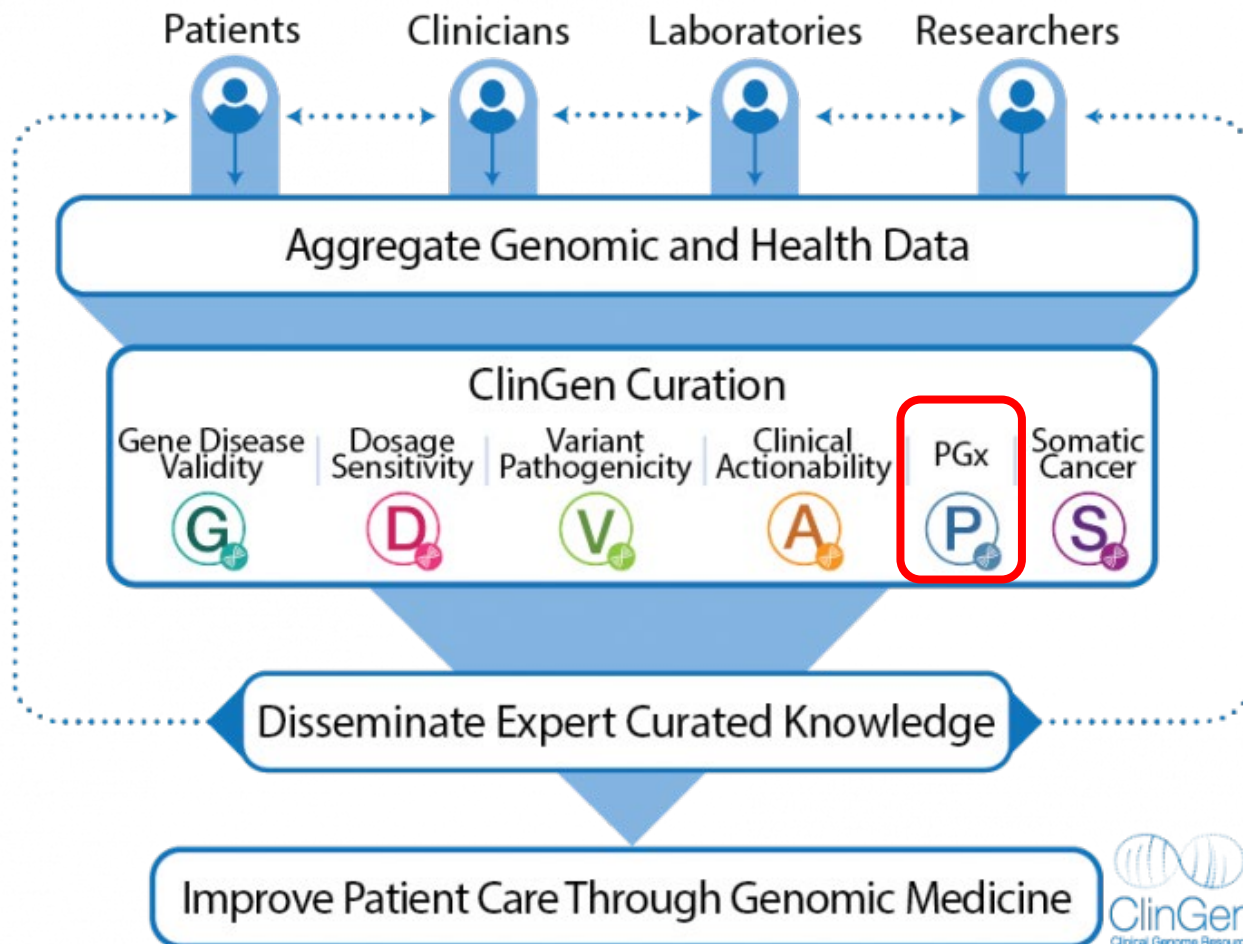
1. ClinGen, ClinPGx and PGxIC
2. Frameworks:
 - Gene-drug validity
 - Gene-drug actionability
3. Pilot validation - 27 gene-drug pairs
4. Next steps and summary

ClinGen (Clinical Genome Resource) and ClinPGx



- ClinGen defines the clinical relevance of genes and variants for use in precision medicine and research
- ClinGen developed frameworks for **gene-disease validity**, **actionability**, **variant pathogenicity** and **dosage sensitivity**
- ClinPGx integrates PharmGKB, CPIC and PharmCAT projects in 2025
- ClinPGx becomes an affiliate grant of ClinGen in 2026
- Benefit both ClinGen users and the PGx community by disseminating PGx information to ClinGen's larger clinical genomics community

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How PGx Differs from Medical Genetics

Pharmacogenomics Interpretation Committee

The Pharmacogenomics Interpretation Committee (PGxIC) is a multi-disciplinary group of researchers and professionals with expertise in pharmacogenomics, clinical pharmacology, medical genetics, and molecular diagnosis.

Documents

Membership



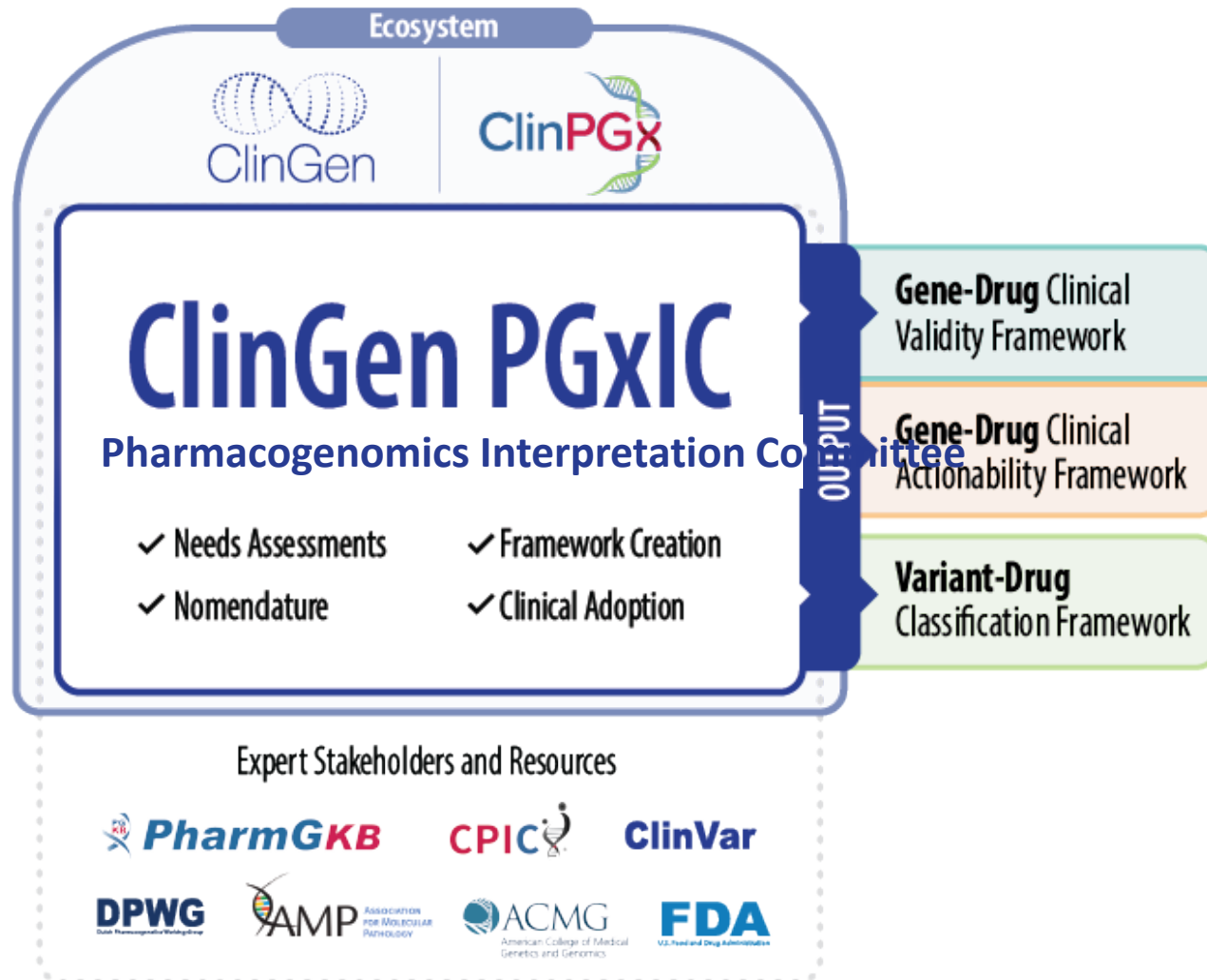
Mission:

- Develop frameworks of evaluating **validity and actionability of gene–drug interactions**, as well as a framework for **classifying germline PGx variants** that influence drug response phenotypes (efficacy, dosing, or adverse event risk)
- Facilitate incorporating PGx knowledge into ClinGen and medical genetics

Members:

42 members (as of 9/2026) from diverse fields specializing in PGx, clinical pharmacology, medical genetics, regulatory affairs, and molecular diagnostics

PGx Interpretation Committee And Frameworks



Frameworks: Transparent, reproducible, scalable assessment of PGx gene–drug relationships

Align with the ClinGen gene-disease clinical validity and actionability frameworks

Leverage well-established PGx resources such as ClinPGx, CPIC, DPWG, and FDA PGx resources (Association Table & drug labels)

Determining Clinical Relevance in PGx: Validity & Actionability Together

Gene-drug validity

Is the gene-drug relationship real?

- Evaluates strength of evidence linking genotype to drug response
- Clinical outcomes, PK/PD, mechanistic evidence
- Focus: association strength, reproducibility and biological plausibility

Gene-drug actionability

Should prescribing change?

- Evaluates whether genetics can guide clinical decisions
- Existing prescribing recommendations from guidelines, labels
- Focus: actional steps in clinical decision making

- Validity and actionability are related, but distinct
- Real association $\neq$ actionable recommendation
- Validity is a prerequisite for actionability
- Separating validity & actionability prevents overinterpretation and clarifies implementation decisions

ClinGen Frameworks and PGx

- PGx frameworks to adopt familiar ClinGen terms so PGx assertions read natively to the genomics community, but use PGx-specific definitions and evidence rules to define levels

Gene-disease clinical validity

Does variation in a gene cause disease?

- **Key dimensions: Human Genetic + experimental evidence**
- **Validity terms: Definitive, strong, moderate, limited, disputed/refuted, No known disease relationship**

Clinical actionability

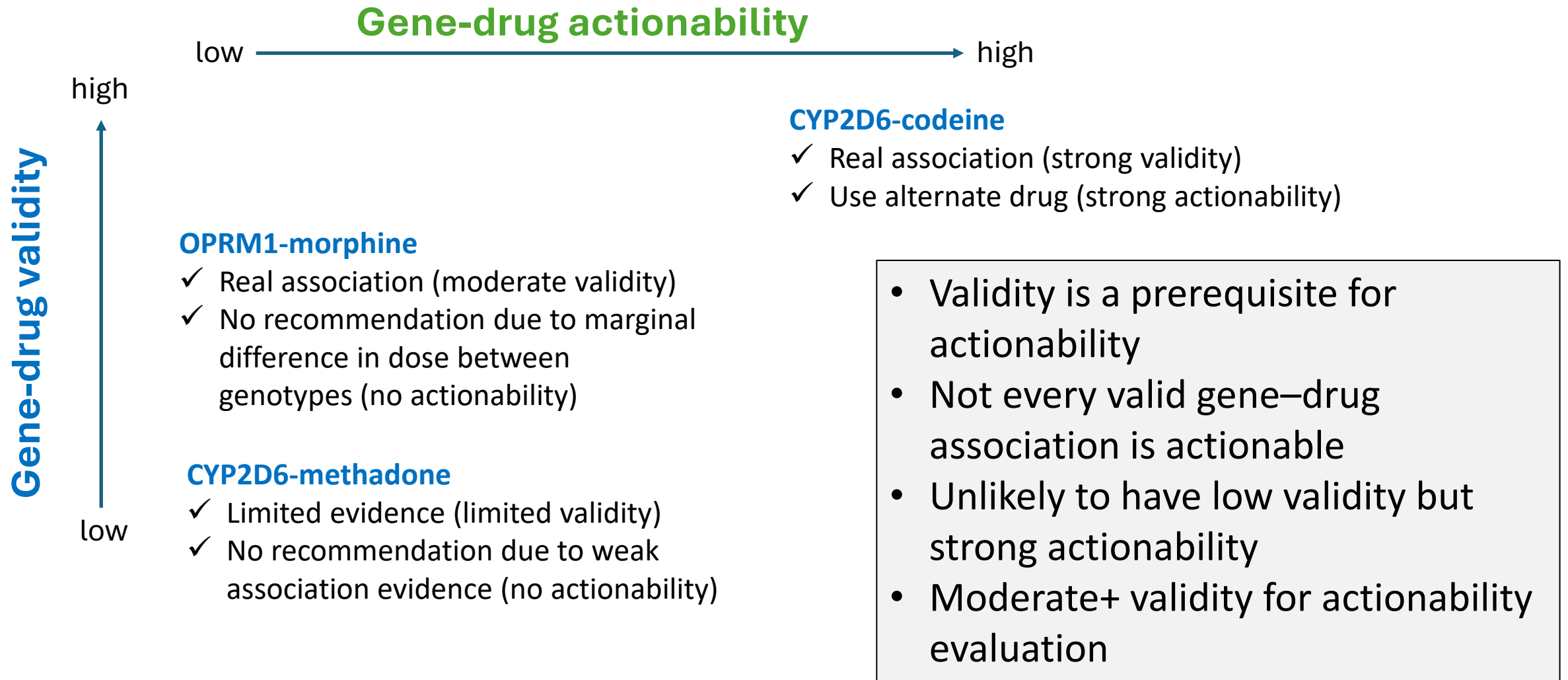
Can disease be prevented or mitigated if the risk were known?

- **Key dimensions: severity, likelihood, effectiveness, burden of intervention**
- **Actionability terms: Definitive, strong, moderate, limited**

Example Gene-Drug Pairs

Gene-Drug pair	Validity	Actionability	CPIC Recommendation
CYP2D6-codeine	Strong	Strong	Use alternative drug (strong recommendation)
SLCO1B1-fluvastatin	Moderate	Moderate	Dose change or alternative drug (moderate recommendation)
OPRM1-morphine	Moderate	No	No recommendation due to marginal difference in dose between genotypes
CYP2D6-methadone	Limited	No	No recommendation due to weak association evidence

Example Gene-Drug Pairs



Development of PGx Frameworks

Community input from PGxIC
need assessment surveys

ClinGen gene-disease
validity/actionability frameworks

Collect and review existing
PGx standards (CPIC,
ClinPGx/PharmGKB, DPWG,
FDA, etc.), metrics and PGx
levels definitions



Gene-Drug Validity / Actionability:

- Identify evidence sources
- Define levels and rules
- Set up assertion and scoring matrix
- Test with example gene-drug pairs



Gene-Drug Validity Levels: ClinGen Levels

Score range

Examples

Definitive

Expert Panel

CYP2D6-codeine, CYP2C19-clopidogrel

Strong

12-20
(Expert Panel)

UGT2B17-belzutifen

Moderate

7-11
(Expert Panel)

CYP2D6-oxycodone, SLCO1B1-fluvastatin

Limited

1-6
(Expert Panel)

CYP2D6-methadone

No Known PGx
Relationship

Expert Panel

Conflicting
Evidence

Disputed

Refuted

Expert Panel

Moderate+
considered for
Actionability

Evidence

Gene-Drug Validity Levels: PGx Definitions

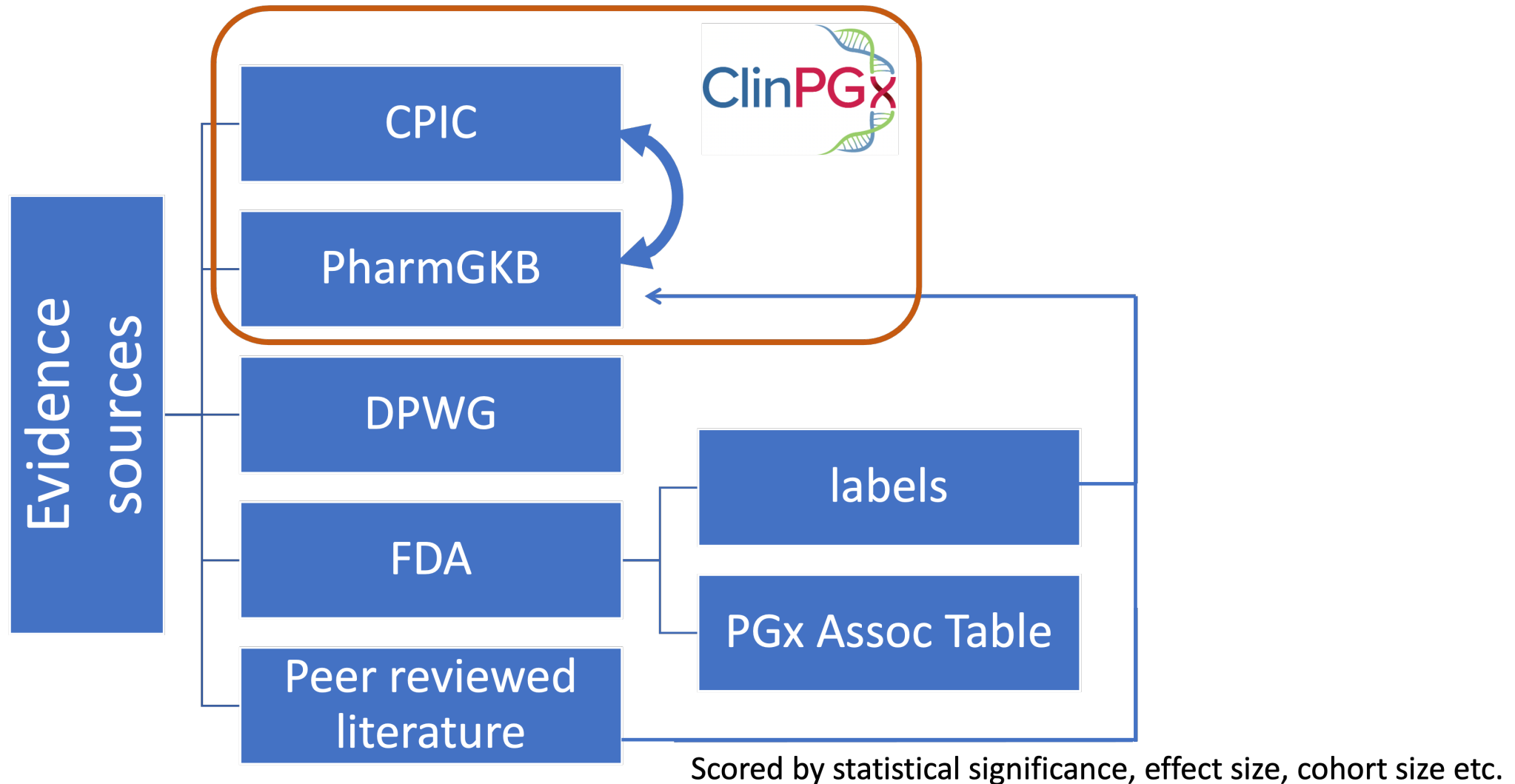
Level		Definition	Score
Definitive		There is strong evidence to support an association between this gene and drug response phenotype, including at least 3 independent, well-designed clinical studies, and other established resources, with no convincing contradictory evidence. This evidence has been upheld over time (in general, at least 3 years).	panel assigned
Strong		There is strong evidence to support an association between this gene and drug response phenotype, including at least 3 independent, well-designed clinical studies, and/or other established resources, with no convincing contradictory evidence.	12-20
Moderate		There is moderate evidence to support an association between this gene and drug response phenotype, typically including at least 2 independent studies and possibly a biologically plausible mechanism explaining how gene variants could influence drug response (e.g., from functional studies), and/or other established resources, with no convincing	7-11
Limited		There is limited evidence to support an association between this gene and drug response phenotype. The association may be based on a single clinical study, preliminary evidence (e.g., a case report or in vitro, molecular, or functional assay evidence), and/or other established resources, or there may be several studies that failed to replicate this	1-6
Conflicting Evidence	Disputed	Although there has been an assertion of association between this gene and drug response phenotype, there is substantial conflicting evidence, leading to active debate in the scientific community about the clinical relevance of the gene-drug interaction. Contradictory evidence may or may not outweigh supporting evidence.	panel assigned
	Refuted	Although there has been an assertion of a gene-drug association, an authoritative pharmacogenomics resource has retracted guidance on this association with a statement that the retraction is due to a lack of validity.	panel assigned

Gene-Drug Validity Matrix



Semi-quantitative scoring matrix; expert review required, modeled after other ClinGen frameworks

Sources of Evidence



Mapping Resources to Points

Clinical outcome		
Evidence source	Levels	Gene-Drug Validity Score
CPIC guideline	High	10
	Moderate	6
	Weak	2
	No association (or no level)	0
DPWG guideline	4	10
	3	6
	2	2
	1 (or NA)	0
FDA PGx association table	Recommendation	10
	safety/tox	6
	PK	6
ClinPGx-curated FDA-approved drug label	Dose change or alternate drug recommendation	10
	Prescribing information	6
ClinPGx-curated literature	1B	6
	2A/2B	4
	3	2
	4	0

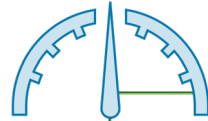
- Score each outcome (efficacy, tox, dose) from available resources, map by evidence strength
- Take the max of the 3 as clinical outcome category score
- No double counting: CPIC and ClinPGx may draw on overlapping literature base. When a pair is already covered by CPIC, ClinPGx evidence is not scored in the same category

Gene-Drug Actionability Levels



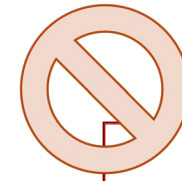
STRONG

- Consistent guidance for using genetics to inform prescribing decisions exists



MODERATE

- Genetics-based prescribing guidance exists, but may be inconsistent across sources, or supporting evidence is limited/unclear

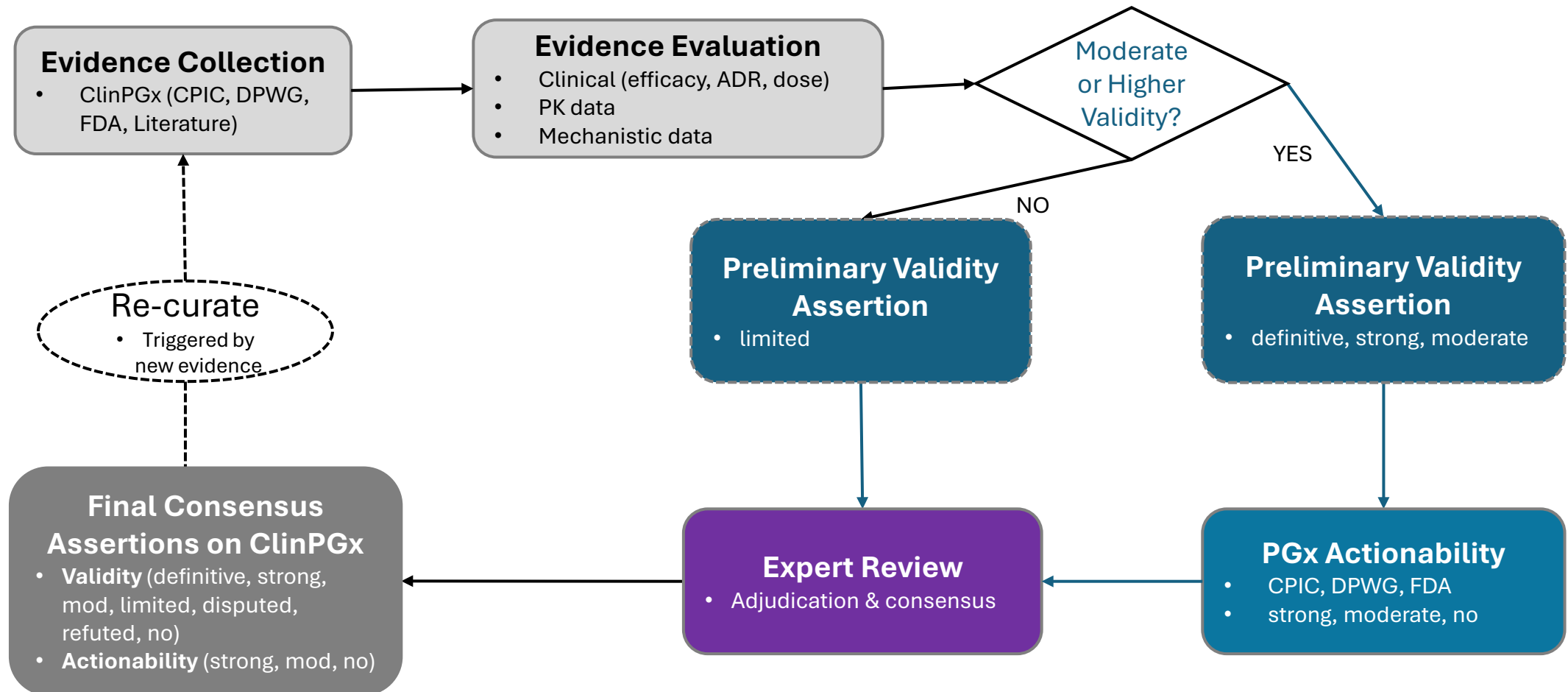


NONE

- Genetics is not expected to be relevant for prescribing decisions

- Actionability: able to modify drug prescribing actions based on PGx data to achieve better clinical outcomes for the patients.
- **Scope limited to pairs with existing guidance (CPIC, DPWG, FDA)**
- Expert review ambiguous language from labels, guidelines; allowed to override

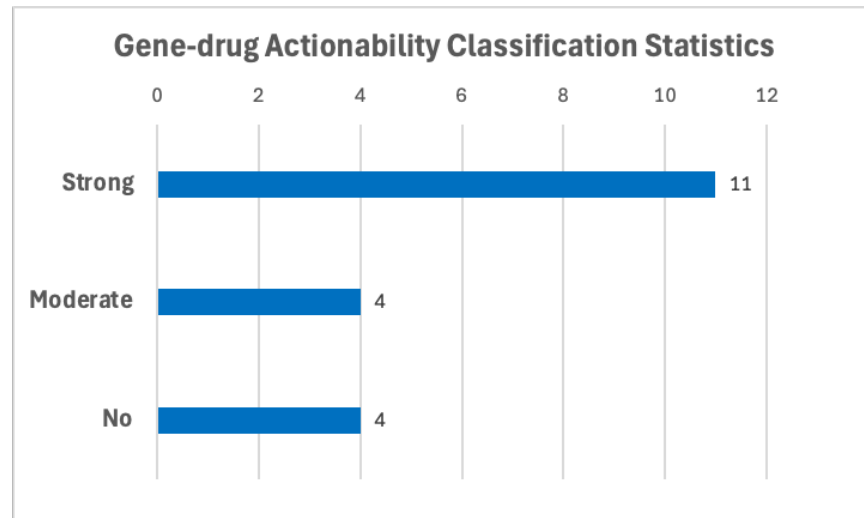
Curation Workflow: Evidence Aggregation to Consensus



Pilot Set and Validation

- 27 gene-drug pairs tested:
 - Span a wide range of validity, actionability levels (from well-established to pairs with emerging, uncertain or conflicting evidence)
 - Multiple therapeutic areas, both PK & PD relationships
 - Both concordant and discordant interpretations across resources
- Curators:
 - Extract/collect evidence using standardized operating procedures
 - Resolve discrepancies and uncertainty through iterative discussion
 - Assign preliminary scores and classifications
 - Pilot: Each pair scored by ≥ 2 curators
- Experts:
 - Review curation, discuss, and confirm or update final classification
 - Pilot: PGxIC expert review, consensus on all (27/27) after discussion

Pilot Set and Validation



Gene	Drug	PK/ PD	Validity Classification	Actionability Classification
CYP2D6	codeine	PK	Definitive	Strong
CYP2C19	clopidogrel	PK	Definitive	Strong
SLCO1B1	simvastatin	PK	Definitive	Strong
UGT1A1	irinotecan	PK	Definitive	Strong
TMPT	azathioprine	PK	Definitive	Strong
NUDT15	azathioprine	PK	Definitive	Strong
CYP2C9	siponimod	PK	Definitive	Strong
Mt-RNR1	amikacin	PD	Definitive	Strong
HLA-B	carbamazepine	PD	Definitive	Strong
G6PD	dapsone	PD	Definitive	Strong
G6PD	methylene blue	PD	Definitive	Strong
CYP2D6	dextromethorphan	PK	Definitive	Moderate
BCHE	mivacurium	PK	Definitive	Moderate
UGT2B17/CYP2C19	belxutifan	PK	Strong	Moderate
SLCO1B1	fluvastatin	PK	Moderate	Moderate
CYP2B6	methadone	PK	Moderate	No
CYP2D6	oxycodone	PK	Moderate	No
OPRM1	codeine	PD	Moderate	No
SLC6A4	escitalopram	PD	Moderate	No
HLA-DQA1	lapatinib	PD	Limited	n/a
CYP2D6	timolol	PK	Limited	n/a
ABCB1	tacrolimus	PK	Limited	n/a
MTHFR	methotrexate	PD	Limited	n/a
CYP2D6	methadone	PK	Limited	n/a
COMT	tramadol	PK	Limited	n/a
DRD2	risperidone	PD	Limited	n/a
CYP2C19	ticagrelor	PK	No	n/a

Four Example Cases

CYP2D6 – codeine

Definitive validity
Strong actionability

Scored 20, consistent functional, pharmacokinetic, and clinical outcome data sustained over time (>3 years).

Strong, genotype-type based prescribing recommendations from CPIC, DPWG, and FDA.

UGT2B17 / CYP2C19 – belzutifan

Strong validity
Moderate actionability

Scored 18, consistent functional, pharmacokinetic, and clinical outcome data (<3 years).

Recommendations from FDA label for monitoring for side effects in PM. No guideline.

The time criterion kept it at strong instead of definitive validity

CYP2D6 – oxycodone

Moderate validity
No actionability

Scored 9, clear mechanism and reproducible PK, inconsistent outcome effect.

Guidelines do not recommend genotype-based dosing.

Validity without actionability

CYP2D6 – methadone

Limited validity
Not considered for actionability

Scored 4, minor contribution to methadone metabolism (PK), weak clinical outcome.

(Guidelines do not recommend genotype-based dosing.)

How Is CPIC Used As Evidence?

- CPIC evidence table is a top-tier resource in every validity domain
 - A CPIC high level evidence maps to the max score in clinical outcome (10), PK (6) and mechanism (2) for validity evaluation
- CPIC and ClinPGx not double counted for validity
 - If CPIC already covered a pair, ClinPGx evidence is not scored again in the same category
- CPIC guidance is key resource for actionability evaluation
 - CPIC actionable (alt drug, dose change etc.) -> strong actionability

How Can Gene-Drug Pairs Be Used?

- Validity and actionability together -> appropriate for clinical testing
- Assertion text can be used in PGx lab reports
- Moderate and higher validity -> appropriate for guideline consideration
- Validity evaluations before guideline can help CPIC avoid including gene-drug pairs in primary literature review that do not have mechanistic support or clear lack of evidence for association

Summary and next steps

- PGxIC: develops parallel frameworks and terminology for PGx
 - Gene-drug validity and actionability
 - Semi-quantitative scoring plus expert review is reproducible
 - Validity and actionability set the foundation for PGx variant classification (ACMG pathogenic -> benign not applicable to PGx)
- Next steps
 - Publication
 - Develop curation tools, interface and training materials
 - Develop DB model and displays for curated information
 - PGx variant classification framework

Acknowledgements



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[Documents](#)

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Curation Workflow: From Evidence Aggregation to Consensus

