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Pharmacogenomic Actionability Is a Clinical State, Not a Genotype Label: Integrating Phenoconversion, Drug–Drug–Gene Interactions, Competing Risks, and Guideline Discordance in Precision Prescribing

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ABSTRACT

Pharmacogenomic results are often represented as durable patient attributes: a genotype is translated into a predicted phenotype, linked to a prescribing recommendation, and stored for future use. This representation captures the persistence of genomic information but can obscure the conditional nature of clinical actionability. Drug exposure, enzyme inhibition, polypharmacy, competing therapeutic priorities, guideline methodology, and the practical capacity to act can change while genotype remains constant. This Perspective argues that pharmacogenomic actionability is therefore better conceptualized as a dynamic clinical state than as a fixed genotype label. The analysis integrates four problems that are frequently handled separately: phenoconversion, drug–drug–gene interactions, competing risks, and non-equivalent pharmacogenomic guidance. It distinguishes stable genomic information from current functional phenotype, regimen-level interaction context, the clinical importance of the gene–drug relationship, competing benefits and harms, and the recommendation source being interpreted. A proposed clinical-state model treats actionability as time-indexed and potentially reversible: the same genomic result may support action, conditional action, or no immediate change as medications, disease state, evidence, and care context evolve. This framing has implications for medication review and clinical decision support because pharmacogenomic information should remain reusable without implying that a previous recommendation remains appropriate indefinitely. The model is conceptual rather than prospectively validated. Its components have heterogeneous evidential strength, phenoconversion does not uniformly predict clinical outcomes, guideline differences may reflect legitimate differences in remit, and implementation capacity varies across health systems. Prospective testing is therefore required before the proposed state model can be treated as a clinical decision rule.

Keywords: Pharmacogenomics, Phenoconversion, Drug-drug-gene interactions, Clinical actionability, Precision prescribing, Pharmacogenomic guidelines

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Introduction

Pharmacogenomics has moved beyond the proposition that genetic variation can influence drug response. For selected gene–drug pairs, genotype can inform clinically meaningful differences in exposure, efficacy, or toxicity, and formal recommendations now translate such evidence into prescribing options. Yet drug response remains jointly determined by genetic and non-genetic factors, including indication, age, organ function, concurrent therapy, adherence, and environmental exposures. A pharmacogenomic result is therefore clinically important without being clinically self-sufficient. The central distinction developed here is between *pharmacogenomic information*, which may remain stable for life, and *pharmacogenomic actionability*, which exists only in relation to a particular drug decision, patient state, regimen, and care setting. Contemporary pharmacogenomics supports

the clinical relevance of selected gene–drug relationships while also recognizing the continuing importance of non-genetic determinants of response [1].

Clinical utility provides an essential starting point but does not eliminate this distinction. In the PREPARE implementation study, pre-emptive panel-guided prescribing reduced clinically relevant adverse drug reactions among participants with actionable drug–gene interactions within a structured multicountry program [2]. That result supports the value of pharmacogenomic prescribing under defined conditions; it does not imply that every detected actionable genotype requires an identical intervention whenever it is encountered. The intervention incorporated drug exposure, a defined panel, guideline translation, and a prescribing workflow. Thus, even strong evidence for pharmacogenomic utility is evidence for a contextually executed clinical intervention rather than for genotype as an autonomous treatment instruction.

The infrastructure for translating genomic information has also matured. The Clinical Pharmacogenetics Implementation Consortium (CPIC) provides systematic evidence appraisal, genotype-to-phenotype translation, drug-specific recommendations, and implementation resources designed for situations in which genotype information is already available [3]. This is indispensable infrastructure, but a recommendation and a patient-level decision are not equivalent objects. The former addresses a defined gene–drug relationship under an evidential framework; the latter must additionally account for the current indication, co-medications, feasible alternatives, competing harms, therapeutic urgency, and patient-specific priorities. The difference becomes particularly important when several legitimate information sources or several simultaneous treatment risks point in different directions.

Practical actionability is further conditioned by whether a health system can retrieve, interpret, and apply pharmacogenomic information at the point of prescribing. Implementation experience in the United States shows substantial progress while continuing to identify informatics, workflow, reimbursement, education, and organizational barriers [4]. These barriers do not make a pharmacologically relevant genotype irrelevant; rather, they distinguish evidence of biological or clinical relevance from the ability to execute an appropriate intervention. This Perspective consequently treats actionability as a clinical state produced by the intersection of persistent genomic information with current phenotype, interacting treatment, competing priorities, guidance interpretation, and ability to act. The purpose is not to replace gene-specific guidelines but to clarify the additional adjudication required when those guidelines enter real clinical contexts.

Why genotype alone does not define pharmacogenomic actionability

A genomic result may be persistent, but the clinical question to which it is relevant is episodic. Pre-emptive testing can generate information years before a corresponding medication is considered, whereas reactive testing places the result within an immediate prescribing decision. Neither strategy makes the underlying genotype more or less true; they differ in when genomic information becomes clinically usable and in the infrastructure required to connect it to a relevant encounter. Consequently, a patient can carry a potentially actionable result while having no current pharmacogenomic action to take. Practice-oriented analyses of pharmacogenomic testing similarly emphasize that who is tested and when testing occurs should be matched to expected prescribing context and utility [5].

Even the translation from observed genotype to predicted functional phenotype contains an interpretive layer. Allele-function assignments are produced through evidence appraisal rather than simply read from sequence data, and consensus frameworks are needed to standardize how functional evidence is evaluated and converted into clinical classifications. Such assignments can be refined as new functional data, variant evidence, or curation become available [6]. This is distinct from phenoconversion: revision of an allele-function assignment changes the interpretation of the genomic evidence itself, whereas phenoconversion describes a temporary or contextual divergence between genotype-predicted function and current functional activity. Keeping these layers separate prevents two different forms of uncertainty from being collapsed into a single “genotype result.”

Categorical predicted phenotypes also compress continuous biological variability. Population pharmacokinetic analysis of codeine metabolism has shown that CYP2D6 activity can be estimated quantitatively and that meaningful variability can remain within categories represented by genotype-derived phenotype labels [7]. Such modeling does not mean that every gene–drug pair requires individualized quantitative enzyme estimation. It instead demonstrates a more general limitation of categorical interpretation: a label such as normal, intermediate, or poor metabolizer is an abstraction useful for clinical translation, not a complete measurement of current drug-handling capacity. For exposure-sensitive decisions, the difference between a category and the patient’s present quantitative functional state may matter.

The evidential basis used to assign function is also uneven across populations. An update to CPIC's SLCO1B1 functionality evidence using data derived predominantly from participants of sub-Saharan African ancestry illustrates how broader population representation can refine confidence in allele interpretation [8]. The appropriate inference is not that ancestry deterministically changes the function of an allele. Rather, variant frequency, linkage structure, representation in functional studies, and the populations from which clinical evidence is derived affect the transferability of interpretation. Genotype is therefore stable at the individual level while the evidential meaning attached to some variants can remain revisable at the knowledge-system level. Pharmacogenomic actionability inherits both forms of context.

Phenoconversion and the instability of predicted phenotype

Phenoconversion provides the clearest demonstration that stable genotype need not imply stable functional phenotype. When an interacting drug inhibits the enzyme whose activity has been predicted from genotype, observed metabolism can shift toward lower functional activity without any change in DNA sequence. In genotyped healthy volunteers, inhibitor exposure produced CYP2C19 genotype–phenotype discordance under controlled conditions [9]. The magnitude and clinical importance of such displacement cannot be generalized across all inhibitors, substrates, doses, or baseline phenotypes. Nevertheless, the mechanism establishes a critical temporal distinction: genotype-predicted phenotype describes an expected state in the absence of relevant modifiers, whereas current phenotype can depend on what the patient is taking now.

The potential scale of this problem becomes visible in treated populations. Among youth receiving pharmacotherapy for mental-health conditions, investigators estimated phenoconversion from medication and cannabis exposures in 46% of participants; among those estimated to phenoconvert, 24% had a reclassification that could alter a guideline-relevant recommendation [10]. These figures should not be treated as population prevalence estimates because the study involved a specific clinical population, exposure ascertainment, and rule-based estimation rather than direct enzyme-activity measurement. Their importance is conceptual: a substantial fraction of patients in some medication-dense settings may carry a genotype-derived phenotype that no longer represents the functional state most relevant to the present regimen.

Phenoconversion should not, however, be promoted from mechanistic plausibility to universal clinical predictor. In patients with psychosis, accounting for CYP2D6 phenoconversion altered metabolic classification but did not consistently improve prediction across the evaluated clinical outcomes [11]. Several explanations are compatible with such findings: the phenotype adjustment may be imperfect, outcome measures may be influenced by multiple pathways, adherence and dose may vary, or pharmacokinetic differences may not dominate the outcome under study. This mixed evidence is important because it defines what the present argument does *not* claim. A more context-sensitive phenotype can be pharmacologically more plausible without necessarily providing superior prediction of every patient-important endpoint.

Operational methods nevertheless make contextual interpretation feasible. A clinical tutorial for CYP2D6 describes structured adjustment of genotype-derived activity in the presence of inhibitors, providing a practical means of incorporating current medication exposure into pharmacogenomic interpretation [12]. Such approaches are useful precisely because they treat phenotype as conditional, but they remain dependent on correct medication reconciliation, reliable classification of inhibitor strength, substrate specificity, and assumptions about how interaction effects modify enzyme activity. They should therefore be viewed as interpretive methods rather than as prospectively validated treatment algorithms. Phenoconversion is best understood as evidence that pharmacogenomic actionability can change while genotype does not—not as proof that every phenotype adjustment should trigger a medication change.

Drug–drug–gene interactions as contextual modifiers

Drug–drug–gene interactions (DDGIs) extend phenoconversion from a single inhibitor adjustment to the broader problem of how genetic and pharmacological determinants jointly shape drug disposition. Phenotypic DDGI models explicitly combine inherited enzyme activity with the effects of interacting medications and show that several plausible mathematical representations can be used to describe their joint influence [13]. This matters clinically because a patient does not experience "the genotype effect" and "the drug interaction effect" as independent labels; both act within the same regimen. The appropriate unit of interpretation is therefore often the current gene–drug–co-medication configuration, with recognition that any model remains an approximation of a more complex biological state.

Mechanistic modeling can make this conditionality quantitatively explicit. A comprehensive CYP2D6 physiologically based pharmacokinetic network evaluated predictions across clinical DDI and DDGI scenarios, illustrating how genotype and interacting drugs can be propagated through a mechanistic exposure model [14]. Such models can explore combinations that would be difficult to study prospectively one by one and can identify contexts in which genetic and interaction effects reinforce, attenuate, or otherwise alter predicted exposure. Their output remains exposure prediction rather than proof of improved clinical outcomes, however. Parameter uncertainty, incomplete pathway representation, adherence, organ function, and untested populations can all separate a modeled scenario from the actual patient decision.

The same distinction is evident in a PBPK network analysis of simvastatin, in which genetic and interacting-drug determinants were represented within a precision-dosing framework [15]. This type of analysis is particularly informative when several metabolic or transporter processes contribute to exposure, because the clinical effect attributed to a pharmacogenomic variant can change as other pathway modifiers enter or leave the regimen. Yet a model-derived dose or exposure estimate remains conditional on the model's structure and validation domain. Mechanistic DDGI modeling is therefore best treated as evidence about how context can alter predicted pharmacokinetics, not as a universal decision engine or a substitute for assessment of treatment indication, toxicity susceptibility, alternatives, and patient priorities.

Clinical services can already bring genomic and conventional interaction information together without claiming that the combined approach has solved the outcome question. In a German academic hospital with outpatient follow-up, integrated pharmacogenomic and drug–drug interaction screening was incorporated into patient assessment and generated clinically interpretable recommendations [16]. The experience demonstrates operational compatibility between PGx interpretation and medication-interaction review, while its single-system implementation, staffing requirements, and nonrandomized design limit claims about comparative effectiveness. In practice, DDGI assessment therefore occupies an intermediate position: it can refine the current functional interpretation of a genotype, but its importance still has to be adjudicated against the actual drug, indication, exposure, available alternatives, and competing risks.

The principal forms of current-context displacement described above are organized in **Table 1** to separate mechanistic change from the prescribing decision that follows it.

Table 1. Phenotype displacement register for current-context pharmacogenomic interpretation (proposed synthesis)

Baseline PGx state	Current modifier	Expected displacement	Prescribing consequence	Evidence boundary	Reassessment need
Genotype-predicted enzyme activity	Clinically relevant enzyme inhibitor	Functional activity may shift downward	Reinterpret exposure-sensitive recommendation in the current regimen	Inhibitor-, substrate-, dose-, and gene-specific	After inhibitor initiation, withdrawal, or material dose change
Genotype-derived phenotype	Multiple interacting co-medications	Combined DDGI may alter predicted exposure beyond the genotype-only estimate	Evaluate the whole perpetrator–victim configuration rather than one label	Model-dependent; incomplete pathways remain possible	With material regimen change
Genotype-associated pathway effect	Metabolic/transporter network modifiers	Net exposure effect may strengthen, attenuate, or change relative importance	Avoid translating an isolated variant effect directly into dose selection	Drug-specific mechanistic validation required	When pathway contributors or organ function change
Stored PGx interpretation	Newly identified interaction during medication review	Previously reasonable phenotype interpretation may become conditionally applicable	Reconcile PGx and conventional interaction information before action	Implementation evidence does not establish outcome benefit	At medication reconciliation and follow-up

Note: "Reassessment" denotes a proposed decision-control step rather than a validated interval or mandatory treatment change. No quantitative displacement threshold is implied.

Competing risks and competing therapeutic priorities

Even an accurately characterized current phenotype does not determine whether acting on it is the most important therapeutic priority. This is especially evident in older adults, in whom pharmacogenomically actionable variants coexist with polypharmacy, medications requiring caution, multimorbidity, and competing reasons to preserve or change treatment. In a large cohort of community-dwelling older adults, actionable pharmacogenetic genotypes

commonly intersected with polypharmacy and cautionary medication use [17]. Co-occurrence identifies decision complexity; it does not rank the competing risks. A pharmacogenomic recommendation may be relevant yet appropriately deferred, modified, or rejected when another clinical concern has greater expected consequence or when the proposed alternative creates a different and more important risk.

Population-scale association data similarly argue against treating actionability as a context-free property of a variant. In a large Chinese cohort, selected pharmacogenetic risk variants were associated with clinically relevant outcomes under corresponding medication exposures, but the observed relationships remained gene-, drug-, exposure-, population-, and outcome-specific [18]. Such evidence can strengthen the case that particular pharmacogenomic signals matter in practice while still leaving unresolved how an individual patient's competing conditions should alter treatment. Prescribing patterns, indication, ancestry-related evidence coverage, health-system context, outcome ascertainment, and residual confounding can all affect transportability. The presence of a supported association therefore contributes to actionability but does not complete the decision.

Complex cardiovascular care illustrates the problem in a more concentrated form. Following non-ST-elevation acute coronary syndrome, multimorbidity and polypharmacy create opportunities for drug–drug, drug–gene, and drug–drug–gene interactions within regimens already balancing ischemic protection, bleeding, hemodynamics, organ function, tolerability, and adherence [19]. Detecting a DDGI in such a setting cannot by itself identify the optimal treatment. The interaction must be placed within the broader therapeutic objective and compared with the consequences of changing the implicated drug. This is the sense in which the present Perspective uses *competing risks*: not as a statistical competing-risk model, but as concurrent clinical hazards and therapeutic priorities capable of changing the relative importance of a PGx-informed action.

Heterogeneity can exist even within a single therapeutic class and guideline. CPIC guidance for beta-blocker pharmacogenetics differentiates evidence and recommendation strength across covered genes and gene–drug relationships rather than treating every pharmacogenetic finding associated with beta-blocker therapy as equally actionable [20]. This illustrates a broader rule for precision prescribing: "PGx-positive" is not a coherent therapeutic category. Actionability depends on the strength and relevance of the specific gene–drug evidence, the treatment indication, the magnitude and reversibility of competing harms, available alternatives, and what is clinically achievable for the patient. The proposed clinical-state approach therefore does not ask only whether a genotype supports an action; it asks whether that action remains justified *now*, relative to the other risks and objectives that define the same prescribing decision.

Guideline discordance and the problem of non-equivalent recommendations

Guideline discordance is not a single phenomenon. A comparison of CPIC and DPWG showed differences in scope, terminology, evidence appraisal, phenotype translation, and recommendation construction [21]. Such differences should not be frozen as a 2026 map of pair-level disagreement because both systems evolve. Their enduring lesson is methodological: two credible pharmacogenomic guidelines can address overlapping evidence without producing interchangeable clinical artifacts.

Broader comparison of DPWG, CPIC, CPNDS, and RNPGx likewise identified heterogeneity in covered gene–drug pairs and recommendation approaches [22]. Apparent conflict may therefore arise from remit, update timing, evidence thresholds, or the action category each organization is willing to specify rather than from incompatible pharmacology alone. Adjudication should first identify the source of non-equivalence before choosing among recommendations.

Regulatory information creates another layer. A historical comparison of the FDA pharmacogenetic associations table with CPIC guidance found substantial non-equivalence in covered relationships and recommended actions [23]. Regulatory association, labeling, and professional implementation guidance serve different purposes and should not be treated as alternative versions of one guideline. Cross-jurisdictional regulatory review further shows that approaches to high-risk pharmacogenomic reactions differ internationally [24].

Accordingly, source discordance should be decomposed before it is called clinical conflict: professional guidelines and regulatory products differ in purpose, evidence frameworks, and recommendation methods [21–23]. **Table 2** operationalizes that distinction without ranking organizations globally.

Table 2. Adjudicating non-equivalent pharmacogenomic recommendations by source of discordance

Drug–gene context	Disagreement type	Likely source of divergence	Clinically material consequence	Adjudication principle	Residual uncertainty

Same relationship in professional guidelines	Action category differs	Evidence threshold, remit, update timing	Different dose, alternative, or monitoring advice	Compare current versions and underlying evidence	Which recommendation best transfers to this patient
Same genotype, different phenotype translation	Translation discordance	Allele-function or phenotype-mapping conventions	Patient may enter a different recommendation stratum	Resolve translation before comparing actions	Functional evidence may continue to evolve
Regulatory versus professional guidance	Product-purpose discordance	Labeling/regulatory remit versus implementation guidance	"Association noted" may not equal a prescribing instruction	Keep regulatory requirement and clinical recommendation distinct	Jurisdiction and product label may change
Across jurisdictions	Policy discordance	National regulation, availability, reimbursement, risk policy	Feasible actions differ despite similar biology	Separate scientific evidence from local executable options	Access and legal context remain system-specific

Note: The discordance categories and adjudication principles are proposed synthesis. They do not imply superiority of one guidance source or that historical differences remain current.

The proposed clinical-state model of pharmacogenomic actionability

Implementation experience from PREPARE indicates that translation depends on how testing, reporting, prescribing workflows, and follow-up are organized [25]. This Perspective therefore proposes a clinical-state model in which genotype is a persistent input, not the final decision variable. Current actionability is adjudicated from genotype-informed function together with current phenotype or DDGI modifiers, the treated condition, competing therapeutic priorities, the recommendation source, and the practical ability to act.

Panel testing illustrates why persistence and actionability should be separated: genomic information can be reusable across future prescriptions, while its clinical value depends on which drugs are encountered and how implementation is organized [26]. The proposed states are actionable now, conditionally actionable, and not currently actionable. These are decision states rather than biological phenotypes and imply no universal score or threshold.

Clinician-facing decision support must also fit workflow and information needs; co-design work in English primary care demonstrates that presentation and usability affect how PGx CDS can be incorporated into practice [27]. The model therefore places clinician/system capacity outside the biological phenotype layer while allowing it to constrain executable action. **Figure 1** shows this proposed adjudication architecture.

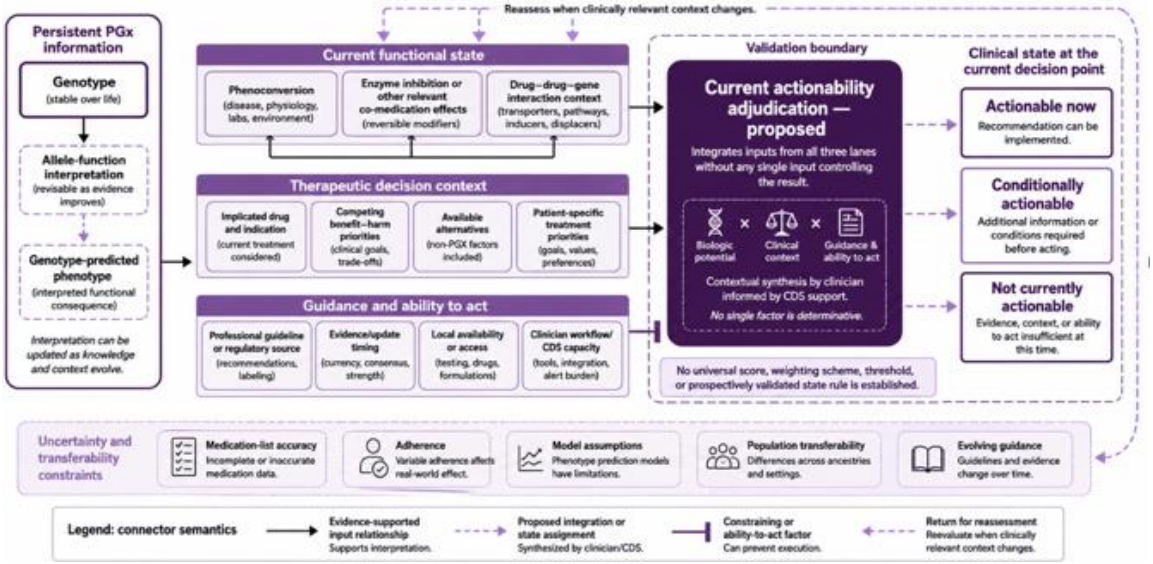

Figure 1. Current pharmacogenomic actionability emerges from stable genotype and changing clinical-state constraints

Reassessment across changing clinical contexts

A clinical state requires temporal indexing. Longitudinal analysis in psychosis showed that predicted CYP2C19 and CYP2D6 phenoconversion risk can vary over time with treatment context [28]. This supports reassessment when relevant exposures change, but not a fixed review interval or an assumption that age or sex independently determines phenoconversion.

Structured EHR storage provides a mechanism for reuse without retesting. Integration of PGx data in the Epic Genomic Module demonstrated that persistent results can later trigger medication-context decision support [29]. Alert generation, however, is an informatics event rather than evidence of clinical benefit; the necessary distinction is between retaining genotype and refreshing its interpretation when a new drug or modifier appears.

Sustainable PGx CDS also requires maintained knowledge, governance, and workflow-sensitive trigger logic [30]. Reassessment should therefore be event-responsive: drug initiation or discontinuation, a relevant inhibitor or inducer change, major treatment-priority change, revised guidance, or a new care context may justify recomputation. **Figure 2** represents these transitions as reversible rather than progressive.

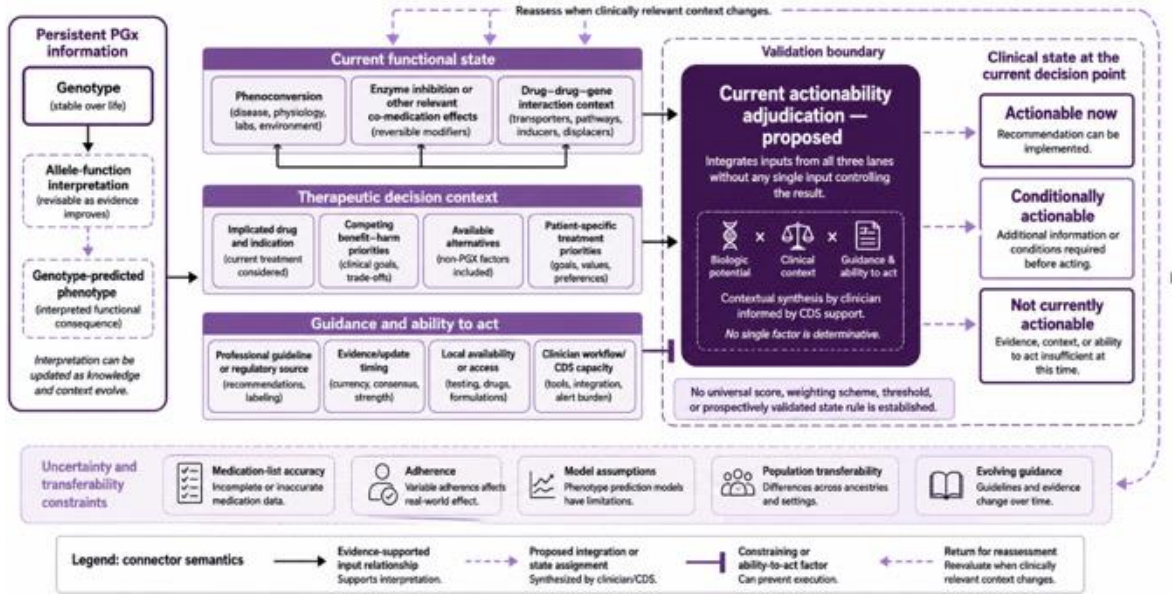

Figure 2. Pharmacogenomic recommendations can strengthen, weaken, or reverse as clinical context changes

Implications for precision prescribing and decision support

The model suggests that precision-prescribing systems should store genotype as durable structured information while calculating or presenting its current relevance close to the medication decision. Implementation reviews, integrated PGx–DDI services, and primary-care CDS co-design converge on the need for workflow integration, actionable interpretation, and sustained infrastructure [4, 16, 27]. Dynamic state recomputation is proposed here as a design principle, not as an effectiveness claim.

Such systems should expose why an action is being suggested: the implicated gene–drug pair, current modifier, competing consideration, guidance source, and uncertainty should remain inspectable. Phenoconversion-aware interpretation particularly depends on accurate co-medication information [12]. Medication lists, adherence, over-the-counter exposure, and external prescribing may be incomplete; therefore, computational sophistication cannot compensate for poor context capture. Persistent PGx data can be reused [29], but the clinical state should remain contestable by prescribers and revisable as knowledge or circumstances change.

The decision-support implication is therefore not “more alerts.” A state-sensitive system should be able to suppress, downgrade, or reframe a recommendation when the implicated drug is absent, when a stronger competing priority dominates, or when an alternative cannot reasonably be implemented. It should also retain a visible route for clinician override and patient preference rather than converting contextual evidence into an automatic order.

Boundary conditions and validation needs

The model is deliberately bounded. Phenoconversion classification has not consistently improved prediction of every clinical outcome in studied psychosis populations [11]. Current phenotype can also be affected by

adherence, dose, endogenous disease effects, organ function, and unmeasured exposures. A state assignment should therefore communicate uncertainty rather than turn a genotype-plus-medication rule into an apparently precise biological measurement.

Mechanistic DDGI models can predict exposure consequences of combined genetic and co-medication effects, but exposure prediction is not equivalent to patient-outcome benefit [14, 15]. Validation should proceed at multiple levels: correct context capture, reproducible state assignment, calibration against measured pharmacokinetics where appropriate, clinician interpretation, treatment decisions, and patient-important outcomes. External evaluation across ancestries, drugs, institutions, and EHR architectures is necessary before any universal state rule is defensible.

Validation should also test whether state transitions are stable enough to be clinically interpretable. A useful system would need to distinguish genuine context change from noisy medication records or transient documentation artifacts, and to show that recalculation does not merely increase alert frequency. Process outcomes, pharmacokinetic concordance where relevant, treatment decisions, patient-reported burden, safety outcomes, and resource consequences should be evaluated separately rather than collapsed into a single "utility" endpoint.

Guideline components also require time stamping. Historical FDA–CPIC comparisons demonstrate non-equivalence of information products, not present-day disagreement for every pair [23]. Prospective pragmatic studies should therefore compare prespecified dynamic-state support with appropriate static PGx support while tracking overrides, competing risks, access, alert burden, and reasons for non-action. The proposed model should be considered useful only insofar as such testing can refine, delimit, or reject it.

Conclusion

Pharmacogenomic actionability should be distinguished from the genomic result that contributes to it. Genotype is durable; the prescribing problem is not. Phenoconversion and DDGIs can alter the functional meaning of a predicted phenotype, competing therapeutic risks can change the priority of a PGx-informed action, and guidelines or regulatory sources can generate non-equivalent recommendations for legitimate methodological or jurisdictional reasons. The central contribution of this Perspective is therefore a proposed time-indexed clinical-state concept in which persistent genomic information is adjudicated with current regimen, patient priorities, recommendation source, and practical ability to act.

This formulation does not diminish gene-specific evidence or replace pharmacogenomic guidelines. It specifies where additional clinical reasoning enters after genotype interpretation. It also implies that a stored result can remain useful while a previous action becomes inappropriate, and that reassessment should be triggered by meaningful contextual change rather than by genomic retesting. The proposed states and transitions are not validated clinical rules. Their value depends on prospective testing, accurate medication context, population transferability, maintained knowledge, transparent decision support, and health-system capacity. Precision prescribing becomes more defensible when pharmacogenomics is treated as persistent information whose actionability must be repeatedly earned by the current clinical state.

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