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Pharmacogenomic Recommendations Need Explicit Rules for Discordant Genes, Phenoconversion, and Comedication Effects

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ABSTRACT

Pharmacogenomic recommendations are commonly represented as stable mappings from genotype to prescribing action, yet clinical decisions frequently occur in states where genomic prediction is only one determinant of functional drug disposition. Discordance can arise from incomplete variant ascertainment, alternative genotype-to-phenotype translation rules, unequal evidence across genes affecting the same drug, substrate-specific allelic behavior, inhibitory comedications, inflammation, organ dysfunction, and changes in treatment state. These sources of discordance are analytically different and should not be collapsed into a single “conflicting recommendation” category. This Decision Framework Perspective argues that a pharmacogenomic recommendation should be treated as a conditional decision state rather than a permanent property of a genotype. Static genomic evidence should establish a baseline prediction, while current functional modifiers should determine whether that prediction remains applicable at the clinical decision point. The article develops explicit distinctions among baseline genotype-derived phenotype, substrate-specific functional evidence, phenoconversion, comedication effects, disease-mediated metabolic change, and implementation constraints. It further proposes a hierarchical approach in which competing evidence is prioritized by analytical validity, drug specificity, proximity to current functional phenotype, clinical consequence, and uncertainty. The framework is conceptual rather than prospectively validated and is intended to make the assumptions behind genotype-guided recommendations visible, auditable, and revisable.

Keywords: Pharmacogenomics, Phenoconversion, Drug-drug-gene interactions, CYP2D6, Functional phenotype, Precision pharmacotherapy

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INTRODUCTION

Pharmacogenomics has moved from a predominantly explanatory discipline toward an increasingly operational component of precision prescribing. For selected gene-drug pairs, inherited variation provides clinically useful information about drug exposure, efficacy, or toxicity, but genetics remains only one contributor to interindividual pharmacological variation [1]. The practical difficulty is therefore no longer simply whether a genotype can be associated with drug response. It is whether a recommendation derived from that genotype remains valid when the patient, drug, and treatment environment at the decision point differ from the conditions under which the recommendation was established.

Even before patient-specific modifiers are considered, recommendations can disagree. Comparisons of pharmacogenomic guidelines and regulatory labeling have demonstrated substantial variation in whether the same gene–drug relationship is considered actionable and in the actions recommended [2]. Such discordance does not necessarily imply error. Different organizations may use different evidence thresholds, clinical endpoints, translation conventions, or regulatory purposes. The problem emerges when these differences are presented to clinicians as parallel instructions without an explicit rule for deciding which evidence should control the current treatment decision.

The clinical importance of resolving that problem increases as multigene testing becomes routine. In the PREPARE implementation trial, a 12-gene panel linked to guideline-based prescribing reduced clinically relevant adverse drug reactions under the studied implementation conditions [3]. Panel testing therefore creates value partly by making pharmacogenomic information available before a prescription is written, but it also exposes multiple possible gene–drug recommendations simultaneously. Contemporary reviews consequently identify implementation, test selection, infrastructure, interpretation, and cost-effectiveness as continuing barriers despite growing technical feasibility [4].

This Perspective focuses on the interpretive layer between a reported genotype and an actionable recommendation. It proposes that pharmacogenomic decision making should distinguish a baseline genomic prediction from the current functional phenotype relevant to the actual substrate and treatment state. Any hierarchy developed here is explicitly proposed synthesis: the component relationships are evidence supported, but the complete decision architecture has not itself undergone prospective clinical validation.

Sources of discordant pharmacogenomic recommendations

Discordance can begin with the genotype itself. CYP2D6 illustrates why a reported gene call should not automatically be equated with complete molecular characterization. Copy-number changes, deletions, duplications, hybrid arrangements, and other structural variants complicate testing and reporting, and assay platforms differ in the variants they can resolve [5]. A recommendation built on incomplete molecular ascertainment may therefore be internally consistent yet rest on an uncertain upstream state. The appropriate response is not to “correct” the phenotype downstream but to preserve assay uncertainty as part of the recommendation.

A second source lies between genotype and phenotype. CYP2D6 translation historically varied across systems sufficiently to require consensus recommendations harmonizing activity-score and phenotype assignments [6]. Standardization is valuable because it establishes a common baseline language, but that baseline should not be mistaken for an immutable in-vivo phenotype. It represents an inference from inherited variation before current inhibitors, disease activity, organ function, and other dynamic factors are incorporated.

Transferability adds another layer. Pharmacogenetic allele distributions and the depth of available evidence differ among biogeographic populations [7]. High-depth sequencing in sub-Saharan African populations has further demonstrated extensive CYP2D6 diversity, including previously under-characterized alleles and structural complexity [8]. Population information can therefore influence confidence in whether a testing panel or allele catalog adequately represents an individual, but population labels must not be converted into deterministic individual treatment rules. Population evidence defines an uncertainty boundary, not a replacement phenotype.

Discordance may also reflect unequal evidence attached to genes appearing within the same therapeutic domain. The CPIC serotonin-reuptake-inhibitor guideline provides actionable recommendations for several pharmacokinetic gene–drug relationships while finding insufficient evidence to support comparable prescribing use for some pharmacodynamic candidates [9]. Similarly, evaluation of beta-blocker pharmacogenomics identifies stronger actionable evidence for particular CYP2D6–drug relationships than for a broad class-wide genomic rule [10]. A multigene test can therefore return several biologically plausible findings without those findings deserving equal decision weight.

The distinction between association and actionability is especially important. Dutch Pharmacogenetics Working Group guidance for non-SSRI/non-TCA antidepressants identifies specific gene–drug interactions for which therapy adjustment is justified while leaving others without an actionable recommendation [11]. Its antipsychotic guidance likewise supports adjustment for selected combinations rather than treating CYP2D6, CYP3A4, or CYP1A2 status as universally actionable across the class [12]. These examples support a central rule for this article: the presence of a pharmacogenomic association should not itself decide priority when recommendations compete. The relevant unit is the drug-specific, phenotype-specific, clinically consequential evidence state.

Multiple genes affecting one drug

When multiple genes can influence the same therapeutic task, a simple additive interpretation is often inappropriate. Statin guidance illustrates mechanistic separation: SLCO1B1, ABCG2, and CYP2C9 can influence different components of statin disposition or adverse-effect susceptibility, and their relevance differs among individual statins [13]. The number of implicated genes is therefore not a rational proxy for certainty. A gene with strong drug-specific evidence may deserve greater decision weight than several weaker candidate associations combined.

The same asymmetry is visible in opioid pharmacogenomics. CPIC provides clinically actionable CYP2D6 recommendations for selected opioids while concluding that evidence for OPRM1 and COMT does not support comparable prescribing actions [14]. A panel result should consequently not operate as a majority vote among genes. The appropriate question is which gene affects the pharmacological step that is consequential for the specific drug and which relationship has sufficient evidence to alter treatment.

Clopidogrel provides a contrasting case in which one metabolic pathway can dominate the genomic recommendation. Reduced CYP2C19 function impairs formation of clopidogrel's active metabolite and can justify altered antiplatelet therapy in defined clinical settings [15]. By contrast, thiopurine dosing demonstrates why two genes may need to remain analytically parallel: TPMT and NUDT15 variants can independently increase susceptibility to treatment-related myelosuppression and influence starting-dose recommendations [16]. Neither pattern supports a universal multigene rule.

Warfarin makes the broader point explicit. Genotype-guided dosing already integrates genetic information with clinical variables rather than treating genomic data as sufficient in isolation [17]. The proposed principle is therefore not that one gene should always outrank another. It is that evidence should be organized by mechanism, drug specificity, clinical consequence, and current applicability. Multiple genes should be combined only when their relationships are sufficiently characterized to justify integration; otherwise, distinct pathways and uncertainties should remain visible.

Conflicting allelic effects

Discordance can occur even after the correct gene has been identified. Functional categories assigned to CYP2D6 alleles are useful abstractions, but the activity associated with an allele may not be identical for every substrate. Population pharmacokinetic modeling of brexpiprazole, for example, produced allele-specific estimates that did not simply reproduce generalized CYP2D6 activity assumptions [18]. Such results do not justify globally relabeling an allele. They show instead that a generic activity assignment may become less reliable when high-quality evidence exists for the actual substrate being prescribed.

More recent work incorporating substrate-specific CYP2D6 variant behavior and additional haplotype information has shown that finer functional characterization can improve prediction for studied substrates [19]. This creates a hierarchy problem: a standardized star-allele phenotype may conflict with drug-specific functional evidence. The proposed resolution is to preserve both evidence levels and escalate substrate-specific evidence when it is sufficiently direct, validated, and relevant to the current drug. Generic allele categories remain the baseline; they are not granted automatic priority over more proximal functional evidence.

This rule also prevents overcorrection. A conflicting functional result for one substrate should not be exported to unrelated drugs unless transferability has been demonstrated. The decision unit is therefore allele $\times$ substrate $\times$ evidence context, not allele alone.

Phenoconversion

Phenoconversion is the clearest demonstration that genotype-derived phenotype and current functional phenotype are different objects. Models of drug–drug–gene interactions show why genotype and interacting medication exposure must be represented simultaneously when estimating metabolic capacity [20]. Germline genotype does not change when a perpetrator drug is started, yet the effective activity of the encoded metabolic pathway can change substantially. A pharmacogenomic recommendation that ignores this state change may be genomically correct but pharmacologically stale.

Clinical evidence supports this distinction. In genotyped healthy volunteers, CYP2C19-inhibiting drug exposure produced discordance between genotype-predicted and observed metabolic phenotype [21]. The magnitude of that change cannot be assumed to be identical across inhibitors or genotypes, but the principle is decisive: the medication list is part of phenotype interpretation, not merely a downstream safety check.

Phenoconversion can also arise without a conventional perpetrator drug. In patients receiving voriconazole, inflammatory status altered the relationship between CYP2C19 genotype and measured activity [22]. Such observations complicate any rule that equates genotype with enzyme function throughout treatment. They also require caution: inflammation should not be converted into a universal correction factor, because effects depend on enzyme, disease state, severity, timing, and measurement method.

Clinical implementation work has proposed explicit procedures for integrating CYP2D6 phenoconversion into pharmacogenetic interpretation, including recalculation of phenotype in the presence of relevant inhibitors [23]. This provides a useful operational precedent but not proof that one correction method will be optimal across all drugs or health systems. Moreover, clinical phenotyping studies indicate that CYP2D6 allelic background itself can influence the magnitude of inhibition and phenoconversion [24]. Static and dynamic evidence therefore interact rather than simply replacing one another.

For this Perspective, phenoconversion is defined as a decision-relevant mismatch between the genotype-derived baseline phenotype and the functional metabolic state produced by current non-genetic or treatment-related modifiers. The proposed response is reassessment, not automatic genotype cancellation. When direct functional evidence is unavailable, the recommendation should carry explicit uncertainty about the magnitude and persistence of the modifier.

The central cases are easier to compare when the observed state, inferred explanation, and trigger for reassessment are separated explicitly rather than compressed into a single phenotype label.

Table 1. Phenoconversion Cases That Require Reassessment of a Genotype-Based Recommendation

Manuscript-derived translation case	Genomic evidence retained	Current observed or clinically supported state	Reassessment trigger Evidence	Proposed synthesis consequence
Scientific anchor	Genomic evidence retained	Current observed or clinically supported state	Reassessment trigger Evidence	Proposed synthesis consequence
Baseline genotype predicts normal or high metabolic function but a relevant inhibitor is present	Baseline genotype-derived phenotype remains valid as inherited information	Functional activity may be lower during inhibitor exposure	Reassessment trigger Start, dose change, or discontinuation of the interacting drug Evidence that discriminates competing explanations Current medication exposure, inhibitor relevance, substrate-specific evidence, functional measurement where available	Proposed: do not treat baseline phenotype as the current phenotype without reassessment
Baseline genotype already predicts reduced function and an inhibitor is added	Reduced-function genotype remains informative	Further reduction may occur, but magnitude may not be inferable from genotype alone	Reassessment trigger Addition of a clinically relevant inhibitor Evidence that discriminates competing explanations Residual allele function, inhibitor effect, substrate dependence	Proposed: avoid a fixed additive penalty; assess whether current evidence supports a stronger functional impairment state
Genotype-predicted phenotype conflicts with functional activity during inflammation	Genotype remains unchanged	Disease state may suppress metabolic activity	Reassessment trigger Onset, worsening, or resolution of inflammatory illness Evidence that discriminates competing explanations Temporal relation to inflammatory state, functional or exposure data, competing comedications	Proposed: classify as dynamic genotype-phenotype discordance and reassess when disease state changes
Generic allele assignment conflicts with direct substrate-specific functional evidence	Standardized allele translation remains the baseline reference	Drug-specific behavior may differ from generalized activity assumptions	Reassessment trigger Availability of sufficiently direct substrate-specific evidence Evidence that discriminates competing explanations Assay quality, substrate identity, replication and clinical relevance	Proposed: allow proximal substrate-specific evidence to qualify, not globally replace, the generic allele assignment

Variant ascertainment is incomplete or structural complexity is unresolved	Genomic baseline is uncertain	Functional phenotype cannot be inferred confidently	Reassessment trigger Assay limitation, ambiguous copy number or unresolved allele call Evidence that discriminates competing explanations Confirmatory or broader molecular testing	Proposed: preserve an uncertainty state rather than forcing a deterministic phenotype
A dynamic modifier has been withdrawn or resolved	Germline genotype persists	Functional phenotype may move back toward the baseline state over time	Reassessment trigger Discontinuation of inhibitor or resolution of modifier Evidence that discriminates competing explanations Appropriate temporal reassessment; functional/exposure evidence where clinically justified	Proposed: treat phenotype as time dependent and permit return to baseline only after the modifier is no longer relevant

Phenoconversion becomes clinically interpretable only when static genomic evidence and dynamic modifiers remain visually separate until they converge at the current decision point.

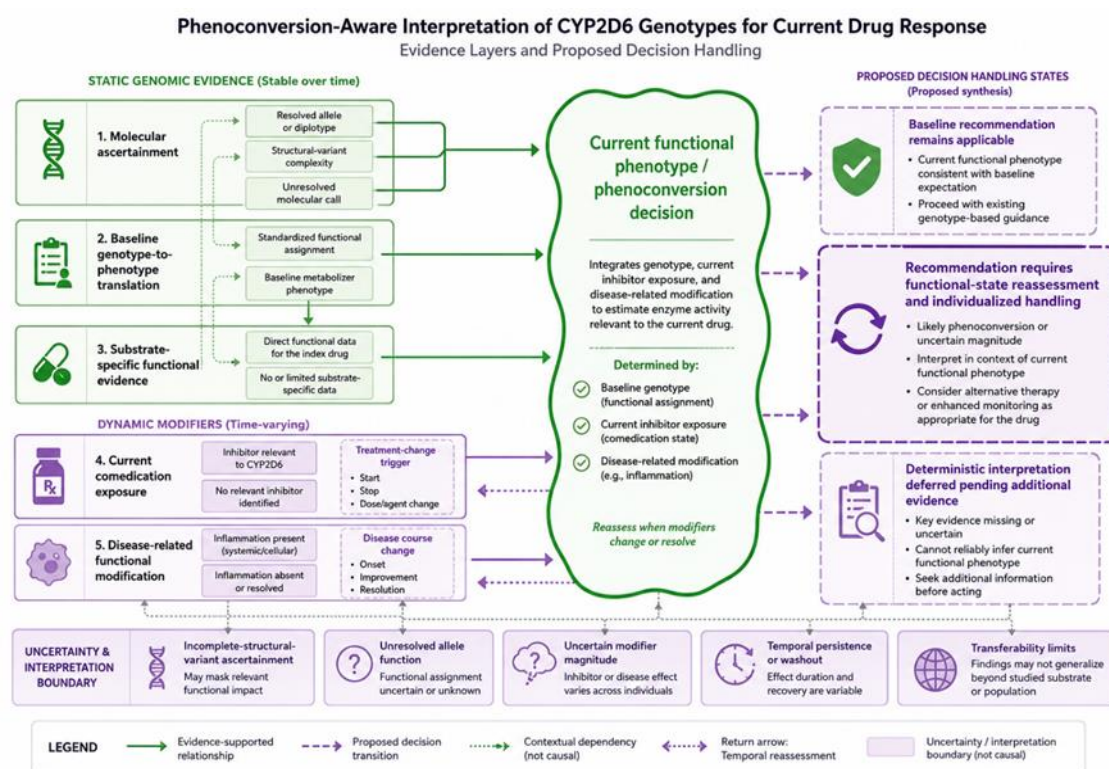


Figure 1. Decision Boundaries Between Genomic Prediction and Current Metabolic Phenotype

Inhibitors and inducers

Comedications complicate pharmacogenomic recommendations because they alter the functional system through which genotype exerts its effect. Mechanistic pharmacokinetic modeling can combine inherited CYP2D6 activity with perpetrator-drug effects and other disposition pathways to represent drug–drug–gene interaction states that cannot be captured by a genotype label alone [25]. Such models are useful because exhaustive clinical testing of every genotype, substrate, perpetrator, and dose combination is unrealistic. Their predictions, however, should remain model-supported hypotheses when the exact scenario has not been clinically tested.

Inhibition is particularly important because it can move functional metabolic capacity in the same direction as a reduced-function genotype. The framework should therefore ask whether a current perpetrator drug modifies the pathway relevant to the substrate, whether the genomic background leaves substantial residual activity to inhibit, and whether the interaction is expected to persist at the decision point. It should not simply subtract an assumed

amount of “activity” from every genotype. The approved evidence supports genotype- and context-dependent inhibition, not a universal phenoconversion constant.

Induction requires a separate logic. It should not be represented as the mathematical inverse of inhibition. The evidence set approved for this Perspective is stronger for inhibitory phenoconversion and inflammation-mediated suppression than for a universal genotype-specific induction correction. Consequently, the proposed framework treats induction as a separately verified dynamic modifier: the affected pathway, perpetrator, onset and offset, substrate dependence, and clinical consequence must be established before it is allowed to change a genotype-based recommendation. No universal induction multiplier is proposed.

Non-drug processes can create inhibition-like states. Experiments in human 3D liver spheroids show that pro-inflammatory cytokines can alter expression and function of multiple ADME genes, with responses differing among genes and inflammatory signals [26]. Clinical phenotyping during acute inflammation similarly demonstrates nonuniform changes across CYP enzymes rather than a common suppression factor [27]. Reviews spanning molecular and clinical evidence reinforce that inflammatory regulation of drug-metabolizing enzymes and transporters is heterogeneous across diseases, pathways, and treatment contexts [28].

The decision consequence is that a low functional phenotype should not automatically be attributed to the strongest visible explanation. A reduced-function genotype, inhibitor, inflammatory state, and combinations of these may produce superficially similar exposure patterns while requiring different reassessment strategies. Classification must therefore precede action.

The distinction between a perpetrator-drug effect and other dynamic metabolic states is summarized below because these states may point in the same exposure direction while differing in evidence, reversibility, and decision consequences.

Table 2. Distinguishing Comedication-Mediated CYP Modulation from Other Dynamic Metabolic States

Manuscript-derived interpretation state	Context	Decision	Decision	Context	Decision
Scientific anchor	Classification basis	Expected exposure implication	Clinical consequence requiring attention	Evidence needed to distinguish the state	Proposed article-specific endpoint
Genotype-derived phenotype with no relevant current modifier identified	Genomic baseline plus current medication review	Exposure expectation follows the supported baseline gene–drug relationship	Standard genotype-guided action may remain applicable	Complete medication list, relevant disease state, adequate variant ascertainment	Proposed: retain baseline recommendation while continuing state surveillance
Relevant inhibitor added to a genetically functional pathway	Direct comedication effect	Reduced metabolic capacity may increase parent-drug exposure or reduce prodrug activation, depending on substrate	Genotype-only recommendation may become stale	Perpetrator relevance, substrate pathway, timing, residual allele function	Proposed: trigger phenoconversion reassessment
Inhibitor superimposed on an already reduced-function genotype	Combined gene–drug state	Additional reduction may occur but cannot be assumed to be linear	Risk of overestimating or underestimating effective metabolic capacity	Genotype, substrate, inhibitor strength/context, direct PK or phenotype evidence where available	Proposed: avoid fixed additive scoring and preserve uncertainty

Suspected inducing comedication	Dynamic induction state requiring independent verification	Potential increase in pathway activity may lower parent-drug exposure or alter active-metabolite formation	Baseline PGx effect may be attenuated, amplified, or become clinically irrelevant depending on substrate	Evidence for perpetrator induction, onset/offset, pathway contribution, drug-specific consequence	Proposed: treat induction separately; do not invert an inhibition rule
Active inflammatory state without a primary perpetrator-drug explanation	Disease-mediated metabolic modification	Functional activity may decrease for susceptible pathways	Genotype–phenotype mismatch may emerge during illness	Temporal disease markers, enzyme/substrate evidence, competing medications	Proposed: classify as non-genetic dynamic modification rather than DDI
Modifier removed or treatment state changes	Transition state	Exposure may move toward the genomic baseline over time	Immediate reversion to the baseline recommendation may be premature	Modifier washout or recovery, timing, clinical or functional reassessment	Proposed: make recommendation state explicitly time dependent

Organ dysfunction and other phenotypic modifiers

Organ dysfunction introduces another reason why genotype should not be interpreted as a complete exposure model. Clinical phenotyping in liver cirrhosis demonstrates that impairment does not change all metabolic pathways to the same extent; the magnitude and direction of pharmacokinetic alteration depend on the enzyme, substrate, and severity of disease [29]. A label such as “hepatic impairment” should therefore not be converted into one pharmacogenomic correction factor. Genotype and organ function describe different causal layers.

The same principle applies more broadly to renal function, age-related physiological change, inflammatory disease, treatment phase, adherence, and measurable drug concentrations when these variables materially affect exposure or response. Not every modifier should supersede genomic guidance. Instead, it should enter the decision hierarchy only when its relevance to the current drug and endpoint is supported.

Model-informed precision dosing offers an existing conceptual precedent for this integration. Such approaches can combine pharmacogenetic information with pharmacokinetic models, concentrations, body size, organ function, and other patient covariates, updating recommendations as clinical information changes [30]. Pharmacogenomics can therefore serve as one prior source of information rather than the final state of the model. The proposed framework uses this distinction to avoid two opposite errors. The first is genomic permanence: continuing to act on a baseline phenotype despite strong evidence that present physiology has changed drug disposition. The second is modifier dominance: discarding validated genomic information whenever a disease or comedication is present. The preferred response is conditional integration. Static genotype establishes what metabolic or pharmacodynamic capacity would be expected in the absence of overriding modifiers; current phenotype, exposure evidence, organ function, and treatment state determine whether that expectation remains applicable now.

Where these layers disagree and no sufficiently direct evidence resolves the discrepancy, the clinically responsible output is not an invented compromise phenotype. It is an explicitly qualified recommendation that identifies which component is established, which component is dynamic, and which uncertainty requires reassessment.

Prioritizing competing evidence

When pharmacogenomic evidence conflicts, priority should not be determined by the number of genes implicated, the apparent precision of an activity score, or the presence of a published association. A more defensible hierarchy begins with the clinical consequence and the evidentiary proximity of each signal to the current drug decision. This principle is consistent with concerns that pharmacogenomic guidelines are most useful when gene–drug effects are sufficiently large, reproducible, and clinically consequential relative to other sources of pharmacological variability [31].

The proposed hierarchy therefore separates five questions. First, is the underlying molecular result analytically reliable? Second, is the genotype-to-phenotype translation sufficiently established for the relevant allele? Third,

is there drug-specific or substrate-specific evidence that should qualify a generic phenotype assignment? Fourth, are current modifiers such as inhibitors, inflammatory disease, organ dysfunction, or treatment phase likely to alter the functional phenotype? Fifth, does the resulting difference plausibly change a clinically meaningful decision for this drug, dose, endpoint, and patient?

Evidence closest to the present pharmacological state should generally receive greater interpretive weight when it is sufficiently reliable. This does not mean that a transient modifier automatically “overrides” genotype. Genotype remains the inherited baseline. A well-characterized inhibitor, directly measured exposure abnormality, or validated substrate-specific functional observation may nevertheless be more informative about present drug handling than the baseline phenotype alone. Conversely, poorly characterized modifiers should not displace a strong genomic recommendation merely because they are temporally recent.

The framework therefore rejects both genetic determinism and indiscriminate dynamic adjustment. When evidence classes remain irreconcilable, uncertainty should remain explicit. A clinician should be able to see whether uncertainty originates from the molecular call, allele function, substrate transferability, comedication, disease state, clinical endpoint, or implementation context rather than receiving an apparently precise but composite recommendation.

A hierarchical recommendation algorithm

The article consequently proposes a recommendation algorithm that treats pharmacogenomic guidance as a revisable state rather than a permanent genotype label. The hierarchy is conceptual and is not presented as prospectively validated.

The first step is molecular validity. Confirm that the reported genotype adequately captures relevant alleles, copy-number or structural variation, and assay limitations. A recommendation should not proceed as though the genomic state were certain when the molecular result is incomplete or ambiguous.

The second step is baseline translation. Translate the resolved genotype using an established gene-specific convention where one exists. This produces the baseline genomic phenotype, not the final treatment phenotype.

The third step is drug-specific evidence escalation. Determine whether direct evidence for the prescribed substrate materially qualifies a generalized allele assignment. Strong substrate-specific functional evidence may refine interpretation for that drug without redefining the allele globally.

The fourth step is dynamic phenotype assessment. Review inhibitors, relevant inducers, inflammatory or disease states, organ dysfunction, and other current modifiers. A modifier enters the hierarchy only when its relevance to the affected pathway and drug is supported. The phenotype should be reassessed when the modifier begins, intensifies, resolves, or is withdrawn.

The fifth step is exposure and consequence assessment. Ask whether the predicted functional change is expected to alter parent-drug exposure, active-metabolite generation, pharmacodynamic response, toxicity, or another clinically meaningful endpoint. For quantitatively demanding decisions, model-informed precision dosing or measured drug concentrations may provide a more appropriate integration layer than a categorical pharmacogenomic rule.

The sixth step is decision implementation. A recommendation that is analytically correct but unavailable, poorly timed, ignored by workflow, or presented without actionable context is not equivalent to an effective clinical intervention. Real-world studies of pharmacogenomic clinical decision support show variable clinician responses to alerts, demonstrating that implementation is a distinct part of the evidence chain [32].

Finally, the algorithm contains an explicit uncertainty state. If molecular characterization, substrate transferability, modifier magnitude, or clinical relevance cannot be resolved adequately, the system should not manufacture a compromise phenotype. It should preserve the unresolved state, identify what evidence would reduce uncertainty, and determine whether the treatment decision can safely proceed without further clarification.

Because the framework is state dependent, its logic is more faithfully represented as temporal transitions than as a static hierarchy alone.

Table 3. Temporal States Governing Reassessment of a Pharmacogenomic Recommendation

Entry condition Transition	Functional phenotype evidence
	Dynamic modifier
	Drug-exposure implication
	Clinical decision point
	Proposed manuscript-specific consequence

Decision state or window Genomic baseline established	
Entry condition Molecular result adequately resolved and translated Transition or persistence condition Persists only while no material modifier emerges	Functional phenotype evidence Genotype-derived phenotype Dynamic modifier None known to be relevant Drug-exposure implication Expected exposure follows the supported gene–drug relationship Clinical decision point Initial prescribing or preemptive review Proposed manuscript-specific consequence Proposed: use as the starting state, not an immutable final phenotype
Decision state or window Substrate-specific qualification	
Entry condition Direct functional evidence for the prescribed drug materially differs from generalized allele assumptions Transition or persistence condition Persists for the relevant substrate while evidence remains applicable	Functional phenotype evidence Drug-specific functional evidence Dynamic modifier None required Drug-exposure implication Exposure prediction may differ from generic phenotype expectation Clinical decision point Drug selection or dose interpretation Proposed manuscript-specific consequence Proposed: permit drug-specific qualification without global allele reclassification
Decision state or window Active phenoconversion state	
Entry condition Relevant inhibitor, inflammatory process, or other supported modifier is present Transition or persistence condition Persists while modifier remains pharmacologically important	Functional phenotype evidence Current functional phenotype differs from genomic baseline Dynamic modifier Present and clinically relevant Drug-exposure implication Exposure or active-metabolite formation may shift Clinical decision point During active treatment Proposed manuscript-specific consequence Proposed: base interpretation on the current functional state while retaining the genomic baseline
Decision state or window Organ-function-modified state	
Entry condition Clinically relevant hepatic, renal, or other physiological change alters disposition Transition or persistence condition Reassess with change in organ function or treatment phase	Functional phenotype evidence Genomic phenotype plus physiological evidence Dynamic modifier Organ dysfunction or related clinical covariate Drug-exposure implication Pathway contribution may change nonuniformly Clinical decision point Dose selection, toxicity management, therapeutic monitoring Proposed manuscript-specific consequence Proposed: integrate rather than replace genomic evidence
Decision state or window Recovery or washout transition	

Entry condition Dynamic modifier has been removed or disease state is resolving Transition or persistence condition Ends only when the modifier is no longer clinically relevant	Functional phenotype evidence Functional phenotype may move toward baseline Dynamic modifier Declining modifier effect Drug-exposure implication Exposure may normalize with delay Clinical decision point Post-discontinuation or recovery Proposed manuscript-specific consequence Proposed: avoid instantaneous reversion to the baseline recommendation
Decision state or window Unresolved discordance	
Entry condition Competing evidence cannot be reconciled sufficiently Transition or persistence condition Persists until evidence improves or treatment strategy changes	Functional phenotype evidence Functional state uncertain Dynamic modifier One or more uncertain modifiers or evidence gaps Drug-exposure implication Direction or magnitude of exposure change remains uncertain Clinical decision point High-risk or irreversible decision Proposed manuscript-specific consequence Proposed: preserve explicit uncertainty and escalate review rather than invent a composite phenotype

The complete hierarchy requires static genomic evidence, dynamic clinical state, and implementation constraints to remain separable until the final prescribing decision.

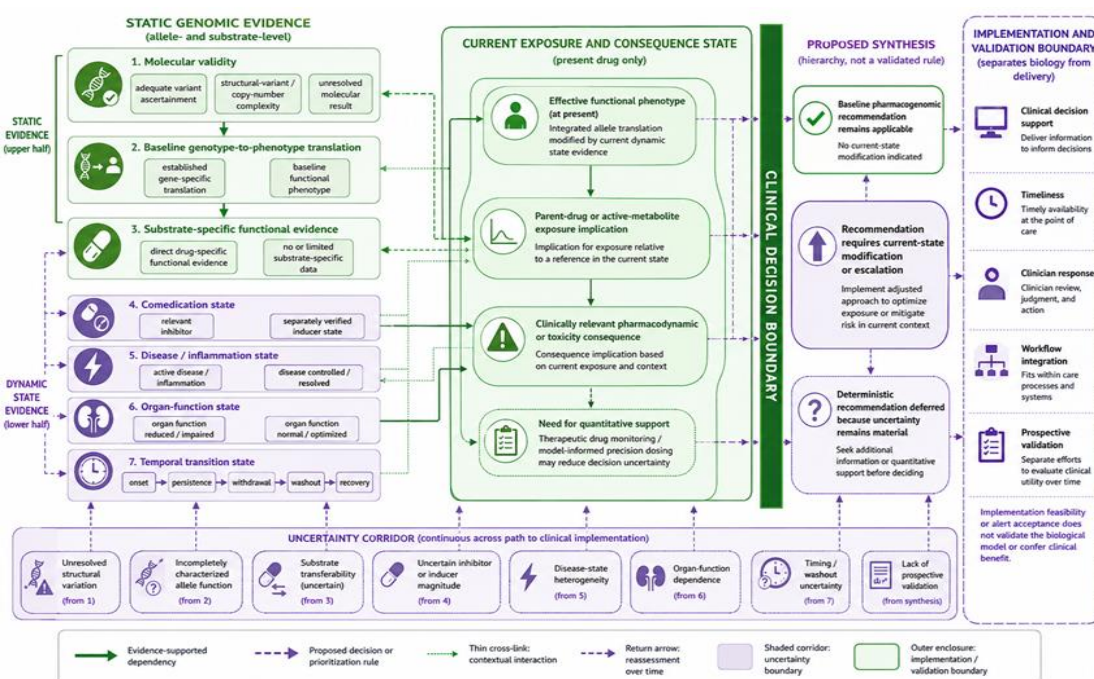


Figure 2. Static Genomic Evidence and Dynamic Treatment State Converge Only at the Clinical Decision Boundary

Clinical edge cases

The value of explicit rules becomes clearest in cases where a technically correct pharmacogenomic interpretation is clinically unusable. Hospital implementation data show that test turnaround can prevent results from becoming available during the admission in which prescribing decisions are being made [33]. A recommendation delivered after the decision window is different from one that is biologically invalid, but both can fail to change care.

Other edge cases include unresolved CYP2D6 structural variation, rare alleles with limited functional characterization, substrate-specific evidence that conflicts with a generalized activity assignment, several simultaneous inhibitors, changing inflammatory disease, or rapidly evolving organ function. In these circumstances, automation should escalate rather than conceal uncertainty.

Therapeutic index also matters. The acceptable residual uncertainty for a low-risk reversible decision may differ from that for a drug with serious concentration-dependent toxicity or an irreversible treatment consequence. The proposed hierarchy therefore does not create universal action thresholds. It requires the clinical consequence of being wrong to be considered explicitly when deciding whether additional phenotyping, concentration measurement, specialist review, or alternative therapy is warranted.

Validation and implementation

A decision framework is clinically useful only if its individual inference steps can be audited and its final recommendation can be delivered at the relevant point of care. Pharmacogenomic clinical decision-support systems remain heterogeneous in architecture, response metrics, and reported effectiveness, and available evidence does not establish one universally superior implementation strategy [34]. Validation of the proposed hierarchy should therefore be modular rather than reduced to a single outcome.

Analytical validation should confirm genotype and structural-variant ascertainment. Interpretive validation should test genotype-to-phenotype translation and substrate-specific qualifications. Dynamic-state validation should assess whether comedications, disease activity, organ function, and temporal changes are captured accurately enough to alter interpretation. Decision validation should determine whether competing evidence is prioritized consistently. Implementation validation should measure timeliness, interpretability, clinician interaction, override reasons, and whether recommendations are available when prescribing occurs.

Large-scale preemptive pharmacogenomic programs demonstrate that genotype information can be integrated into electronic health records and linked to prescribing alerts and testing prompts across multiple genes and medications [35]. Such implementations establish feasibility, not superiority of the present framework. Prospective evaluation would need to compare the proposed hierarchy with existing genotype-only or guideline-specific workflows while preserving drug-specific clinical endpoints.

The most informative future validation studies would record not only the recommendation reached but the state transition that produced it: baseline genotype, relevant substrate evidence, comedications, organ and disease modifiers, uncertainty source, reassessment trigger, final clinical action, and subsequent exposure or outcome where appropriate. Such studies could determine whether explicit discordance rules improve consistency, prevent inappropriate genotype-only decisions, or merely add complexity. Until those data exist, the hierarchy should be understood as an auditable proposal for organizing evidence rather than a validated prescribing algorithm.

CONCLUSION

Pharmacogenomic recommendations should not be treated as permanent properties attached to genotypes. They are conditional interpretations whose clinical relevance depends on molecular validity, allele-to-phenotype translation, the prescribed substrate, current comedications, disease state, organ function, treatment timing, and the consequence of the decision being made.

The proposed framework preserves genotype as the inherited baseline while allowing sufficiently direct evidence about current functional phenotype to qualify its use. It rejects equal weighting of all genes, universal allele effects across substrates, fixed phenoconversion corrections, and automatic dominance of either genomic or dynamic evidence. When discordance cannot be resolved, uncertainty remains an explicit clinical state rather than being hidden inside a composite recommendation.

The practical objective is therefore not to replace established pharmacogenomic guidelines, but to make the assumptions connecting them to individual treatment decisions visible and revisable. Prospective validation is required before the proposed hierarchy can be claimed to improve prescribing consistency, safety, exposure control, or clinical outcomes.

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