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Precision Pharmacotherapy Should Model Genotype as One Layer of a Changing Exposure–Response System

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ABSTRACT

Precision pharmacotherapy is often represented as a progression from genotype to phenotype, exposure, and dose. That sequence is useful but incomplete because the genome is comparatively stable whereas the pharmacological system surrounding it is not. Enzyme and transporter activity can be modified by inhibitors, inflammatory signaling, frailty, organ function, pregnancy, and treatment-mediated physiological change. Drug exposure may consequently diverge from the value anticipated from genotype alone, while pharmacodynamic sensitivity can vary independently of exposure. A clinically useful precision model should therefore distinguish durable genomic information from functional phenotype, changing physiological state, drug interactions, measured or predicted exposure, and response susceptibility. This Systems Perspective develops a proposed exposure–response architecture in which genotype functions as an important prior rather than a contemporaneous assay of whole-patient pharmacology. The framework treats discordance between genomic expectation and observed treatment behavior as information requiring reconciliation rather than as evidence that either genomic or phenotypic data should automatically dominate. It further distinguishes starting-dose prediction from longitudinal dose updating and separates pharmacokinetic uncertainty from pharmacodynamic uncertainty. The proposed model is intended as a conceptual basis for integrating pharmacogenomics with repeated clinical information, model-informed dosing, therapeutic drug monitoring, and decision-support systems. Its value remains conditional on drug-specific evidence, measurement quality, temporal resolution, population transferability, and prospective validation.

Keywords: Pharmacogenomics, Phenoconversion, Precision dosing, Therapeutic drug monitoring, Pharmacokinetics, Pharmacodynamics

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INTRODUCTION

Pharmacogenomics has established that inherited variation can materially influence drug disposition, target response, adverse-event susceptibility, and the probability that a standard regimen will be appropriate for an individual patient [1]. Yet the clinical meaning of genomic information differs substantially among genes, drugs, mechanisms, populations, and endpoints. Genetic effects may operate through pharmacokinetic pathways, pharmacodynamic pathways, or both, and their translation into prescribing decisions depends on the strength and specificity of the underlying evidence [2]. Precision pharmacotherapy therefore cannot be reduced to the

possession of a genomic result. Its more difficult task is deciding how much weight that result should retain when other determinants of exposure and response change.

Implementation studies demonstrate why genomic information should remain central rather than be dismissed. In the PREPARE study, a pre-emptive pharmacogenetic panel linked to prescribing recommendations reduced clinically relevant adverse drug reactions among patients receiving selected actionable drugs [3]. Real-world utilization and whole-genome data likewise indicate that clinically actionable drug–gene combinations occur often enough to make targeted implementation consequential [4]. Nevertheless, the decision to test, when to test, and whether a result is likely to change care remains conditioned by the severity of the possible outcome, the strength of the gene–drug association, treatment alternatives, turnaround time, and the availability of actionable recommendations [5]. These observations support pharmacogenomics as a high-value information layer while simultaneously arguing against a universal genotype-first-and-finish model.

The central problem addressed here is temporal asymmetry. Genotype is generally durable, whereas functional phenotype, physiological capacity, interacting exposure, disease activity, drug concentration, and treatment response can change over hours, days, months, or life stages. A precision system that treats all of these variables as if they possessed the same stability risks converting an informative genomic prior into a false representation of current pharmacology. This Systems Perspective therefore proposes that precision pharmacotherapy should model genotype as one layer within a changing exposure–response system and should update the interpretation of that layer when longitudinal evidence indicates that the functional state has changed.

Genotype within a multilayer pharmacological system

Genotype and contemporaneous pharmacological measurements do not answer the same question. Pharmacogenetic testing estimates a component of expected biological capacity before or during treatment, whereas therapeutic drug monitoring measures a realized concentration after genotype, physiology, adherence, dose, interactions, and other sources of variability have already contributed to exposure. Quantitative comparison of pharmacogenetic testing with therapeutic drug monitoring shows that their relative informational value depends on interindividual variability, interoccasion variability, and measurement error rather than on an intrinsic superiority of either strategy [6]. A concentration measurement can therefore correct an inaccurate exposure expectation without invalidating the genomic mechanism that helped generate the original prior.

Other approaches to functional assessment reinforce this distinction. Pharmacogenomics can characterize inherited metabolic potential, while therapeutic drug monitoring and emerging functional measurements can provide information closer to the patient’s current metabolic state [7]. The relevant question is consequently not whether a dynamic measurement should replace genotype, but which uncertainty each observation reduces. In the proposed framework, genotype occupies the durable-baseline layer; functional measurements occupy time-indexed layers that can increase, decrease, or redirect confidence in the baseline prediction.

The importance of retaining a strong genomic prior is clearest for well-established gene–drug relationships. TPMT and NUDT15 variants can substantially alter thiopurine metabolism and toxicity susceptibility, supporting genotype-conditioned starting-dose recommendations [8]. Such recommendations demonstrate that a stable genomic variable can be highly actionable at treatment initiation. They do not establish that an initial genotype-derived dose remains optimal when disease activity, organ function, co-medication, adherence, or treatment intensity subsequently changes.

The converse problem is equally important: not every plausible genomic association deserves the same decision weight. Contemporary beta-blocker guidance illustrates substantial differences in actionability among candidate genes, with more compelling evidence for specific pharmacokinetic relationships than for several proposed pharmacodynamic variants [9]. A multilayer system therefore requires not only multiple data types but also evidence-specific weighting within the genomic layer itself. Genotype should be neither diluted into one generic “risk factor” nor elevated into an unconditional determinant of treatment. Its role depends on what is known for the particular allele, drug, mechanism, population, indication, and clinical decision.

Enzyme and transporter phenotypes

The distinction between genotype and phenotype becomes especially important for drug-metabolizing enzymes. Cytochrome P450 activity reflects more than inherited sequence variation. Enzyme abundance and catalytic activity can also be altered by inhibition, induction, regulatory signaling, age-related biology, disease, and other acquired conditions [10]. Consequently, genotype can inform an expected functional range without directly measuring the enzymatic state operating at the moment a drug is administered.

Phenoconversion provides a direct example. In genotyped healthy volunteers, CYP2C19 inhibitors shifted measured metabolic phenotypes away from genotype-predicted activity, demonstrating that a stable genotype can coexist with a substantially altered functional state [11]. The observed magnitude in that experimental setting should not be generalized to every inhibitor, dose, population, or clinical condition. The more general conclusion is narrower but important: when an acquired modifier is sufficiently strong, genotype-derived phenotype classification can cease to represent current metabolic capacity.

This creates a drug–drug–gene interaction problem rather than a conventional drug–gene problem. Phenotypic models can incorporate genotype-conditioned enzyme activity together with inhibition, allowing genetic and pharmacological influences to be represented jointly rather than as independent annotations [12]. More mechanistic physiologically based pharmacokinetic networks extend this idea by representing combinations of genotype, inhibitor exposure, substrates, and related disposition pathways [13]. Such models can support extrapolation into combinations for which direct clinical data are incomplete, but an extrapolated dose or interaction estimate remains a prediction, not a prospectively validated clinical outcome.

The need for substrate specificity is illustrated by CYP2C19 and clopidogrel. Reduced-function CYP2C19 phenotypes can decrease formation of clopidogrel’s active metabolite and alter antiplatelet response, supporting genotype-conditioned recommendations in defined clinical settings [14]. That relationship cannot simply be generalized to other substrates metabolized by CYP2C19, because the consequence of reduced enzyme activity depends on whether metabolism activates, clears, or otherwise changes the pharmacological species responsible for effect.

The proposed systems interpretation therefore inserts a functional-phenotype layer between genotype and downstream treatment consequences. For some gene–drug pairs, genotype may provide a sufficiently strong approximation of function for an initial decision. For others, interacting drugs or changing biology may materially separate predicted from realized phenotype. The precision task is not to choose permanently between genomic and functional evidence but to recognize when the assumption linking them has become uncertain.

Time-varying physiology

Physiological state adds another source of temporal divergence. Inflammation can downregulate drug-metabolizing enzymes and transporters through cytokine-mediated regulatory pathways, thereby changing clearance independently of germline genotype [15]. Importantly, the size and direction of clinically observed effects are heterogeneous across enzymes, inflammatory disorders, substrates, and experimental designs. Inflammation should therefore be treated as a plausible dynamic modifier rather than converted into a universal dose-adjustment factor.

Treatment can also reverse part of the physiological process that altered pharmacokinetics in the first place. In patients with active rheumatoid arthritis, IL-6 inhibition with olokizumab changed exposure to several CYP probe substrates, whereas the S-warfarin probe did not show a significant change [16]. This substrate-specific pattern is especially informative for a dynamic model: treating the disease may alter the metabolic environment, but the resulting pharmacokinetic change cannot be assumed to be identical across pathways. A genomic result obtained before treatment remains genetically valid while its functional interpretation may require updating.

Biological aging creates another distinction between stable demographic descriptors and changing physiological capacity. In older Chinese patients receiving amlodipine, frailty was associated with altered exposure and modeled CYP3A function, while chronological age itself was not a significant explanatory covariate in the reported model [17]. This does not establish frailty as a universal dosing variable. It demonstrates that a state descriptor reflecting current physiological reserve can, in some settings, provide information that a fixed demographic category does not.

Renal elimination presents the same systems problem at a different level. Renal clearance varies with maturation, body size, filtration, and other physiological processes across the life course [18]. Genomic information relevant to metabolism or transport can therefore remain unchanged while the fraction of total clearance attributable to renal function changes materially. In drugs for which several elimination pathways contribute, the clinical consequence of a pharmacogenomic variant may itself become more or less important as non-genetic clearance pathways change.

Pregnancy further demonstrates why “patient characteristics” cannot be treated as static covariates. A systematic evaluation of monoclonal-antibody pharmacokinetics during pregnancy found heterogeneous and often incomplete pharmacokinetic information, with changes differing among products and gestational stages [19]. The evidence does not support a single pregnancy adjustment. Instead, it reinforces a temporal principle: physiological

modifiers have their own trajectories, and the relevance of each trajectory depends on the drug's disposition characteristics.

For precision pharmacotherapy, these observations create recurrent recommendation conflicts. A patient may carry a genotype associated with reduced metabolic capacity while inflammation further suppresses function; the same patient may later improve clinically and partially recover enzyme activity. A previously acceptable regimen may become excessive when renal function declines, or insufficient after an inhibitory medication is removed. The proposed model treats these not as exceptions to pharmacogenomics but as expected consequences of placing a stable genomic layer inside a changing physiological system.

The decision problem is summarized below as a state ledger rather than as a hierarchy of “important” and “unimportant” factors.

Table 1. Clinical decision states created when time-varying physiology changes the meaning of a stable genomic prior

Evidence through time		Transition and reassessment	
Information available	decision state / Unresolved uncertainty	Monitoring requirement / Permissible alternative action	Observation that should trigger reassessment / synthesis consequence
Germline result; current disease activity; prescribed regimen	Manuscript-derived decision state: Genotype predicts reduced metabolic capacity while active inflammation may further suppress the same pathway Unresolved uncertainty: Magnitude of functional suppression beyond the genomic expectation	Monitoring requirement: Clinical response, toxicity indicators, and an exposure or functional measure when validated for the drug Permissible alternative action: Use a conservative genotype-informed regimen while obtaining current-state information	Observation that should trigger reassessment: Major change in inflammatory activity or treatment Proposed synthesis consequence: Retain genotype as baseline but lower confidence that it alone represents current phenotype
Stable genotype; previous dose; changing inflammatory state	Manuscript-derived decision state: Anti-inflammatory treatment is initiated after dosing was selected during active disease Unresolved uncertainty: Degree and timing of metabolic recovery	Monitoring requirement: Reassess response or exposure after meaningful disease-state change Permissible alternative action: Adjust only when clinical or validated pharmacological evidence supports a changed requirement	Observation that should trigger reassessment: Improvement or relapse sufficient to alter functional capacity Proposed synthesis consequence: Treat disease therapy as a pharmacokinetic state transition rather than an unrelated event
Age; genotype; evolving frailty and co-morbidity profile	Manuscript-derived decision state: Chronological age appears stable but frailty or physiological reserve changes Unresolved uncertainty: Whether biological reserve is altering clearance more than chronological age	Monitoring requirement: Periodic physiological and medication review Permissible alternative action: Re-estimate dose need using current functional information rather than age alone	Observation that should trigger reassessment: New frailty, deconditioning, recovery, or major functional change Proposed synthesis consequence: Separate demographic descriptors from dynamic physiological phenotype
Genotype; dose; current renal indices; known elimination pathways	Manuscript-derived decision state: Renal contribution to total clearance changes during treatment Unresolved uncertainty: Relative contribution of renal and non-renal clearance at the new state	Monitoring requirement: Repeat renal assessment and exposure monitoring when clinically appropriate Permissible alternative action: Modify dose or interval according to drug-specific evidence	Observation that should trigger reassessment: Clinically meaningful deterioration or recovery in renal function Proposed synthesis consequence: Reweight the contribution of the genomic pathway when competing clearance routes change
Stable genotype; gestational stage; drug-specific information	Manuscript-derived decision state: Pregnancy progresses across physiologically distinct stages	Monitoring requirement: Stage-appropriate clinical or exposure surveillance where evidence supports it	Observation that should trigger reassessment: Transition in gestational state or postpartum physiology

	Unresolved uncertainty: Product-specific magnitude of gestational PK change	Permissible alternative action: Avoid automatic uniform adjustment; use drug-specific evidence	Proposed synthesis consequence: Treat pregnancy as a trajectory of states rather than one binary covariate
Genotype; historical phenotype assumption; current clinical state	Manuscript-derived decision state: A physiological modifier resolves but the original genotype-based label remains in the record Unresolved uncertainty: Whether the previous functional classification still describes current capacity	Monitoring requirement: Reconcile current state with the persistent genomic record Permissible alternative action: Restore, revise, or retain the regimen according to updated evidence	Observation that should trigger reassessment: Discordance between expected and observed exposure or response Proposed synthesis consequence: Preserve the genomic result while updating the functional interpretation

Note: The final decision-state categories are an original synthesis proposed in this Systems Perspective. They do not constitute validated dosing rules, numerical thresholds, or a ranking of physiological modifiers.

These decision states also expose why a simple gene-to-dose pathway is insufficient. The relevant transition is from durable molecular evidence through a functional interpretation that can become progressively less certain as changing physiology intervenes.

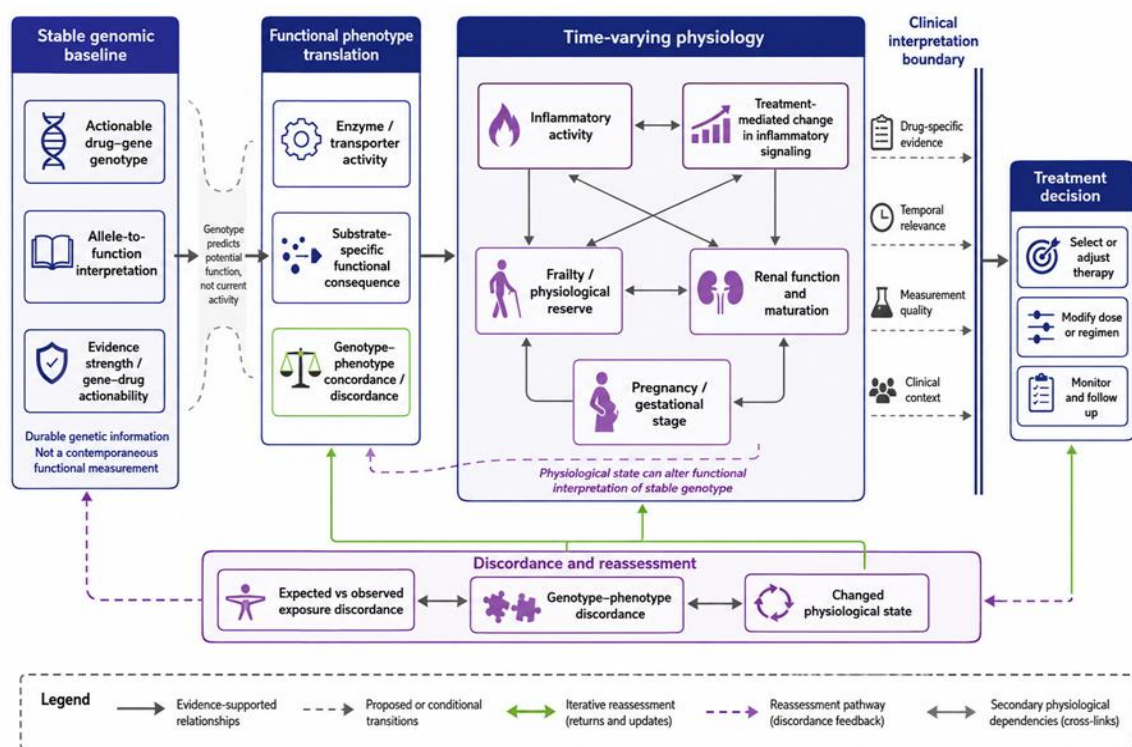


Figure 1. Where a stable genomic expectation loses certainty as physiology changes during treatment

Drug interactions

Drug interactions extend the same principle from physiology to treatment context. Concomitant drugs can change metabolic or transporter activity independently of genotype, while the magnitude of the resulting interaction depends on the pathway involved, the victim drug, inhibitor or inducer potency, organ function, and baseline functional capacity. Renal transporter drug interactions illustrate the difficulty of measuring this process directly. Endogenous biomarkers are being evaluated as tools for detecting inhibition of transport systems such as OCT2, MATE, and OAT pathways, potentially providing functional information beyond static medication lists [20]. Their use remains limited by biomarker qualification, specificity, and transferability across drugs.

Liver disease further complicates interaction interpretation because it can alter enzyme abundance, transporter expression, hepatic blood flow, protein binding, and other determinants of disposition [21]. A drug-drug interaction established in patients with preserved hepatic function may therefore not have the same magnitude in advanced liver disease. Conversely, an apparent interaction may partly reflect disease-mediated reduction in

clearance. The relevant system is thus not simply drug A acting on drug B; it is a genotype-conditioned and disease-conditioned interaction occurring within a changing patient state.

Phenoconversion makes this clinically visible. A patient classified genetically as a normal metabolizer may function as a slower metabolizer during strong inhibition, while withdrawal of the inhibitor may restore activity toward the genotype-predicted range [11]. Models that combine genotype and inhibition can represent such transitions explicitly [12], and mechanistic interaction networks provide a basis for estimating combinations not directly tested in every possible patient configuration [13]. Yet a model-based estimate remains conditional on parameter quality and mechanistic coverage. Disease treatment itself can further change metabolic activity, as illustrated by the pathway-specific changes observed after IL-6 inhibition [16].

The proposed interpretation is therefore interaction-aware rather than merely medication-aware. When predicted and observed treatment behavior diverge, the model should ask whether a perpetrator drug, transporter effect, disease-modified clearance pathway, or changing functional phenotype could explain the difference before attributing the discrepancy to failure of the genomic association. This is a reconciliation process, not a rule that current interaction information automatically overrides genotype.

Exposure

Exposure is the first layer in the proposed system that directly reflects the combined consequences of dose, absorption, distribution, metabolism, elimination, adherence, physiology, and interactions. For drugs that can be monitored reliably, therapeutic drug monitoring provides information that is temporally closer to the realized pharmacokinetic state than genotype alone. In highly variable antibiotic therapy, the movement from conventional therapeutic drug monitoring toward model-informed precision dosing illustrates how measured concentrations can be incorporated into individualized dose estimation [22]. Such approaches are particularly relevant when baseline covariates fail to explain rapid within-patient changes.

Model-informed precision dosing generalizes this concept by combining prior population knowledge with patient-specific covariates and observed concentrations or effects [23]. In the systems architecture proposed here, genotype can enter that prior when a validated gene–drug relationship exists, but it need not remain the dominant determinant after informative longitudinal measurements become available. The evidentiary weight assigned to each layer should instead depend on what it measures and how directly it represents the present treatment state.

This does not mean that a model-derived exposure estimate is equivalent to an observed biological truth. External evaluation shows that model selection itself can materially affect individualized prediction and that patient-specific model selection or model ensembling may improve performance in some datasets [24]. A precision framework must therefore retain uncertainty about the model used to interpret longitudinal data rather than merely replacing genetic uncertainty with computational certainty.

Validation methodology is equally important. Confidence intervals around predictive-performance criteria can reveal uncertainty that point estimates conceal and can make model evaluation more transparent when models are being considered for clinical dosing applications [25]. The principle extends beyond physiologically based pharmacokinetic modeling: any exposure estimate entering a precision decision should carry information about measurement error, model adequacy, population transferability, and temporal relevance.

Accordingly, the proposed model separates expected exposure from observed or updated exposure. Genotype, phenotype, physiology, and interactions contribute to an expectation. Concentrations or other validated exposure measures can then update that expectation. Discordance is not necessarily evidence that the genomic relationship was incorrect; it may indicate that one or more dynamic determinants changed after the genomic prior was established.

Pharmacodynamic sensitivity

Even a perfectly characterized exposure would not fully determine response. Pharmacodynamic sensitivity can vary because the same concentration may produce different target engagement, downstream signaling, immune activation, toxicity, or therapeutic effects in different patients. Warfarin provides a well-established example in which pharmacokinetic variation related to CYP2C9 coexists with pharmacodynamic variation involving VKORC1 and other determinants incorporated into dosing algorithms [26]. The clinical lesson is not that every therapy requires a combined PK–PD genotype panel, but that exposure and response sensitivity are analytically distinct layers.

Immune-mediated adverse drug reactions provide an even clearer separation. Certain HLA alleles can identify susceptibility to specific drug reactions through mechanisms involving antigen presentation and T-cell activation

[27]. Such an allele may be clinically important even when conventional pharmacokinetic exposure is unremarkable. At the same time, HLA carriage does not imply that an adverse reaction is inevitable. Genetic susceptibility, triggering exposure, immune context, and additional biological factors remain distinct.

Evidence strength within the pharmacodynamic layer is also uneven. Contemporary antidepressant pharmacogenomic guidance supports clinically useful recommendations for several metabolic genes while concluding that available evidence for SLC6A4 and HTR2A is insufficient to support their use in antidepressant prescribing [28]. This difference is central to the proposed systems framework. Biological proximity to a drug target does not automatically create clinical actionability, and a pharmacodynamic association should not be assigned the same decision weight as a validated gene–drug relationship merely because both are genomic.

Response monitoring creates another boundary. Population-level therapeutic concentration ranges can be useful, but an exposure target is not necessarily an individualized response target. Precision dosing increasingly requires biomarkers that represent the patient-specific pharmacodynamic effect rather than concentration alone [29]. Where such biomarkers are unavailable, response uncertainty should remain explicit instead of being hidden within a supposedly precise exposure estimate.

The resulting interpretation contains at least three separate questions: What exposure was expected from the patient’s baseline characteristics? What exposure is currently being achieved? And how sensitive is this patient to that exposure? Genotype may contribute to any of these questions depending on the gene–drug pair, but it should not collapse them into one variable. **Table 2** translates this separation into distinct gene–drug interpretation states without implying automatic movement from genomic evidence to a clinical endpoint.

Table 2. Cross-scale interpretation states separating genomic evidence, functional phenotype, exposure, and pharmacodynamic response

Source state and scale		Transfer conditions	Qualification endpoint
Gene–drug interpretation state / Classification basis / Genomic evidence / Functional phenotype or intermediate mechanism	Dynamic modifier separation / Exposure-level interpretation / Pharmacodynamic sensitivity interpretation	Population or transferability boundary	Reassessment trigger / Permissible clinical interpretation / system endpoint
Gene–drug interpretation state: Strong pharmacokinetic genotype with a defined dosing consequence Classification basis: Validated functional allele and drug-specific evidence Genomic evidence: High-value baseline prior Functional phenotype or intermediate mechanism: Altered metabolism or activation is mechanistically supported	Dynamic modifier requiring separation: Interacting drugs, inflammation, organ function Exposure-level interpretation: Exposure or active-metabolite formation may shift in the expected direction Pharmacodynamic sensitivity interpretation: Response consequence still depends on the drug’s exposure–effect relationship	Allele frequencies and recommendations may differ among populations	Reassessment trigger: Observed exposure or response inconsistent with the genotype-conditioned expectation Permissible clinical interpretation: Use genotype for initial stratification while preserving longitudinal reassessment Proposed system endpoint: Genomic prior retained; current state updated
Gene–drug interpretation state: Genotype predicts metabolic phenotype but current function is discordant Classification basis: Functional allele assignment plus current phenotypic evidence Genomic evidence: Genotype remains valid Functional phenotype or intermediate mechanism: Measured or inferred activity no longer matches baseline classification	Dynamic modifier requiring separation: Inhibition, induction, disease state, treatment-mediated physiological change Exposure-level interpretation: Realized exposure may depart from genotype-only prediction Pharmacodynamic sensitivity interpretation: Response may follow realized exposure rather than the historical phenotype label	Assay and drug specificity constrain transfer	Reassessment trigger: New interacting exposure or measured genotype–phenotype discordance Permissible clinical interpretation: Reconcile competing causes before changing the genetic interpretation Proposed system endpoint: Functional state temporarily reweighted

Gene–drug interpretation state: Pharmacokinetic and pharmacodynamic genomic layers both contribute Classification basis: Separate evidence for disposition and response pathways Genomic evidence: More than one genomic mechanism may matter Functional phenotype or intermediate mechanism: Disposition mechanism affects concentration while response mechanism affects sensitivity	Dynamic modifier requiring separation: Clinical covariates can modify both Exposure-level interpretation: Exposure cannot fully represent response liability Pharmacodynamic sensitivity interpretation: Target or pathway sensitivity modifies consequence at a given exposure	Evidence may be therapy and ancestry specific	Reassessment trigger: Unexpected response despite plausible exposure Permissible clinical interpretation: Preserve PK and PD genetic evidence as analytically separate Proposed system endpoint: Multilayer response estimate
Gene–drug interpretation state: Genomic susceptibility acts mainly at the pharmacodynamic level Classification basis: Drug-specific susceptibility allele Genomic evidence: Genotype informs hazard susceptibility rather than clearance Functional phenotype or intermediate mechanism: No requirement for altered metabolic phenotype	Dynamic modifier requiring separation: Triggering exposure and immune or disease context remain necessary Exposure-level interpretation: Conventional exposure may be within expected range Pharmacodynamic sensitivity interpretation: Response risk can still be markedly different among susceptible and non-susceptible patients	Transfer depends on drug, allele, ancestry, and phenotype definition	Reassessment trigger: Drug exposure in a genetically susceptible patient or new clinical signs Permissible clinical interpretation: Use validated susceptibility information without treating carriage as determinism Proposed system endpoint: Response-risk layer weighted independently of exposure
Gene–drug interpretation state: Biologically plausible pharmacodynamic candidate gene lacks sufficient actionability Classification basis: Candidate association without adequate prescribing evidence Genomic evidence: Genomic result has uncertain decision value Functional phenotype or intermediate mechanism: Functional interpretation may be plausible but incompletely validated	Dynamic modifier requiring separation: Population, phenotype definition, treatment context Exposure-level interpretation: Exposure information does not rescue a weak genomic association Pharmacodynamic sensitivity interpretation: Clinical effect prediction remains uncertain	High sensitivity to study design and population	Reassessment trigger: New high-quality validation or guideline change Permissible clinical interpretation: Do not convert biological plausibility into a prescribing recommendation Proposed system endpoint: Evidence boundary retained
Gene–drug interpretation state: Exposure lies in an accepted range but response is inadequate or excessive Classification basis: Current concentration plus clinical response Genomic evidence: Genotype may explain only part of the state Functional phenotype or intermediate mechanism: Functional phenotype may be concordant or unknown	Dynamic modifier requiring separation: Disease progression, target sensitivity, adherence history, measurement limitations Exposure-level interpretation: Exposure appears plausible Pharmacodynamic sensitivity interpretation: Patient-specific response differs from the population expectation	Target ranges may not represent all individuals	Reassessment trigger: Persistent exposure–response discordance Permissible clinical interpretation: Investigate response sensitivity and alternative causes rather than escalating solely from concentration Proposed system endpoint: Shift uncertainty from exposure layer toward response layer

Note: The interpretation states and system endpoints are proposed syntheses of this Systems Perspective. They are not validated scoring categories, clinical thresholds, or universal prescribing algorithms. The table intentionally keeps genomic evidence, functional phenotype, exposure, and pharmacodynamic sensitivity separate so that evidence at one scale is not assumed to transfer automatically to another.

Disease-state feedback

Disease can alter the same pharmacological pathways used to interpret genotype. Inflammation can suppress drug-metabolizing enzymes and transporters, changing exposure without changing germline sequence [15]. Treatment can then modify that state: IL-6 inhibition altered several CYP probe exposures in rheumatoid arthritis, although

the effect was pathway-specific rather than uniform [16]. Chronic liver disease similarly changes enzyme, transporter, and other determinants of disposition, making disease severity part of the interaction context [21]. Disease state should therefore be modeled as a feedback variable rather than a static covariate. A dose selected during active inflammation may become inappropriate after remission, while relapse or progressive organ dysfunction may again alter clearance. Unexpected toxicity can also arise from phenoconversion despite an apparently compatible genotype [11]. Conversely, when an exposure measurement is available, therapeutic drug monitoring can help determine whether discordance primarily reflects pharmacokinetics [22]. If exposure is plausible but response remains atypical, uncertainty shifts toward pharmacodynamic sensitivity or the adequacy of the response target [29].

The resulting failure modes require reconciliation rather than automatic rejection of either genomic or longitudinal evidence.

Table 3. Exception states requiring reassessment when disease changes genotype-to-phenotype translation

Observed configuration	Mechanism and competing diagnosis	Corrective discrimination
Corrective observation	Discordant state / Likely origin to investigate / Residual uncertainty	framework action
Reassess interacting drugs, disease activity, organ function, and exposure	Discordant state: Genotype predicts ordinary metabolism but exposure is excessive Likely origin to investigate: Inhibition, inflammation, organ dysfunction Residual uncertainty: Several mechanisms may coexist	Retain genotype; reweight current functional phenotype
Verify dosing history, interacting drugs, and current physiology	Discordant state: Genotype predicts reduced metabolism but exposure is unexpectedly low Likely origin to investigate: Induction, recovery from inflammation, adherence, alternative clearance Residual uncertainty: Genomic effect may persist without dominating total clearance	Increase weight of current-state modifiers
Compare clinically relevant pre- and post-treatment state	Discordant state: Exposure changes after disease improvement Likely origin to investigate: Recovery of metabolic or transporter function Residual uncertainty: Recovery magnitude is pathway specific	Record treatment response as a pharmacological state transition
Reassess response markers and competing clinical explanations	Discordant state: Exposure appears appropriate but toxicity or nonresponse persists Likely origin to investigate: Pharmacodynamic susceptibility, wrong response target, disease progression Residual uncertainty: Exposure alone cannot identify response sensitivity	Shift uncertainty toward the response layer
Confirm measurements and reversible modifiers	Discordant state: Genotype and functional phenotype disagree Likely origin to investigate: Phenoconversion, transient physiology, assay limitations Residual uncertainty: Discordance may remain unresolved	Preserve an explicit discordant state
Recalculate with current medications, physiology, exposure, and response	Discordant state: Historical genotype-based advice persists after major clinical change Likely origin to investigate: Static decision support Residual uncertainty: Original recommendation may still be correct	Update the action without deleting the genomic result

Note: These states are proposed analytical categories, not validated diagnostic algorithms or causal rules.

The cross-scale problem is represented visually below so that disagreement at one level returns to the relevant upstream interpretation rather than collapsing into a single generic “treatment failure” category.

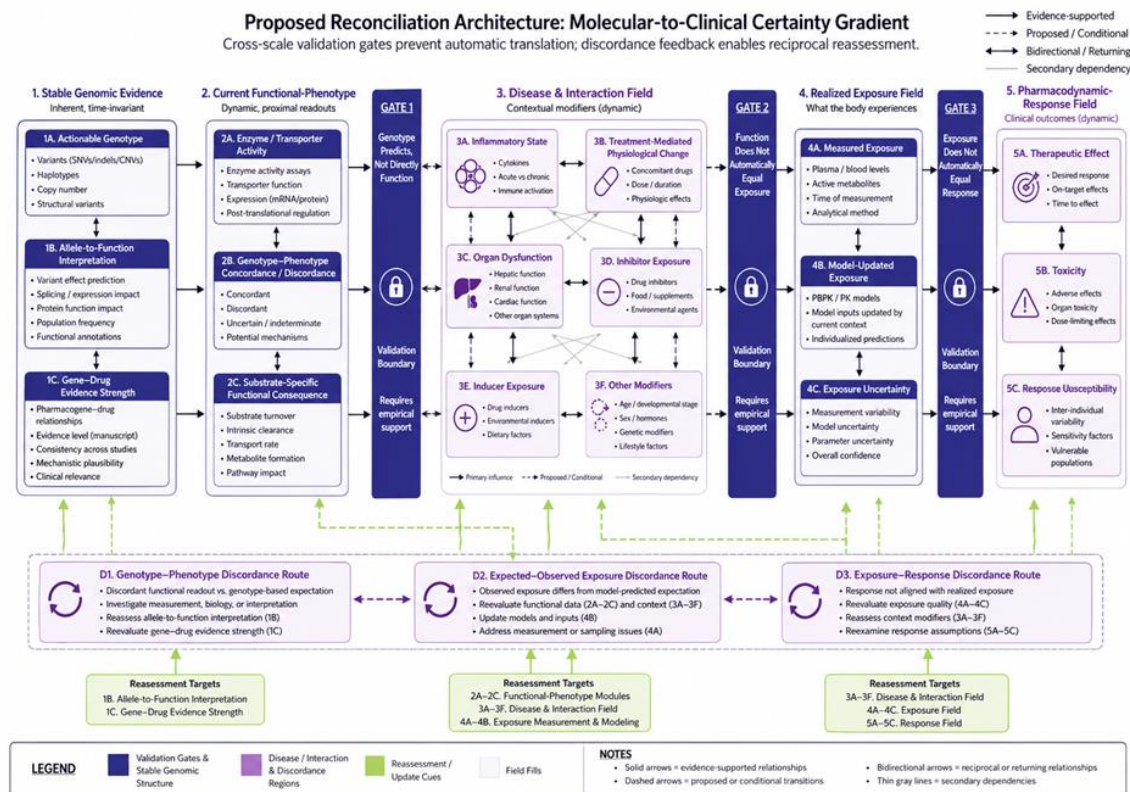


Figure 2. Cross-scale validation gates for resolving disease-modified exposure and response discordance

Integrating genomic and longitudinal information

A dynamic system must distinguish variables by their temporal properties. Genomic information can usually remain persistently available, whereas disease activity, medication exposure, organ function, concentrations, and response require repeated observation. Model-informed precision dosing already provides a basis for combining baseline patient characteristics with new measurements as therapy evolves [30].

Electronic health records can supply longitudinal information, but missingness, coding heterogeneity, irregular measurement, and uncertain phenotype definitions limit naïve reuse of recorded variables [31]. Timing and provenance therefore matter: an old laboratory value or inactive medication cannot represent the present state merely because it remains visible in the record.

Structured pharmacogenomic clinical decision support demonstrates that durable genomic results can be retained and reused across prescribing encounters [32]. The proposed extension is to couple that persistent layer to current physiology, co-medication, exposure, and response rather than repeatedly issuing the same static genomic recommendation.

A dynamic precision-pharmacotherapy model

The proposed model asks five sequential questions: What durable genomic evidence is available? Does current functional phenotype remain concordant with it? Have physiology, disease, or interacting drugs changed? What exposure is currently being achieved? Does observed response agree with that exposure?

This architecture integrates components supported independently by the literature rather than claiming validation of the exact combined model. Pharmacogenetics and therapeutic drug monitoring provide different information under different variability structures [6]. Functional measurements can complement inherited information [7]. Drug-drug-gene models demonstrate that acquired and genetic modifiers can be represented jointly [12]. Model-informed precision dosing permits repeated updating [23], while response-focused dosing emphasizes that concentration does not necessarily equal the individual therapeutic target [29].

Its central proposed rule is reweighting without erasure: new evidence may change the immediate decision weight of genotype without deleting the genomic result or declaring the underlying association false.

Clinical updating and validation

Updating frequency should reflect how rapidly a variable can change. Genotype is generally persistent, whereas interacting drugs, disease activity, organ function, exposure, and response may require reassessment during treatment. The timing of pharmacogenomic testing itself is already recognized as a clinical decision rather than a purely technical one [5].

Validation must extend beyond model fit. Model selection affects individualized prediction [24], while uncertainty around predictive performance should be explicitly quantified rather than concealed by point estimates [25]. A dynamic system must additionally demonstrate that its updates improve decisions across drugs, populations, clinical states, and care settings.

Clinical decision-support infrastructure can retain structured genomic information at prescribing encounters [32]. A dynamic implementation would additionally require reliable triggers for clinically meaningful medication changes, disease transitions, organ dysfunction, new exposure measurements, or response discordance. These triggers require prospective evaluation for data quality, alert burden, interpretability, and clinical consequences. The model should therefore be regarded as a testable systems architecture, not a validated dosing algorithm.

CONCLUSION

Precision pharmacotherapy should preserve genotype as durable and sometimes highly actionable evidence without assuming that it continuously represents the patient's current pharmacological state. Functional phenotype, physiology, interactions, organ function, realized exposure, disease activity, and pharmacodynamic sensitivity can change while genotype remains stable.

The proposed architecture separates these layers and treats discordance as information requiring reassessment. Its governing principle is reweighting without erasure: genomic evidence persists, but its immediate clinical influence can change as higher-temporal-resolution evidence becomes available.

The framework remains conceptual and requires drug-specific, longitudinal, and prospective validation. Its purpose is not to make genotype less important, but to position genomic information correctly within a changing exposure–response system.

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