



Review Article

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Precision Dosing Should Combine Genotype with Dynamic Phenotypes Rather Than Treat DNA as a Complete Prescription

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ABSTRACT

Pharmacogenomics can identify inherited differences in drug metabolism, transport, targets, and toxicity risk, but genotype is a stable biological descriptor rather than a complete representation of the patient's current pharmacological state. A DNA result does not directly observe phenoconversion, inflammatory suppression of drug-metabolizing pathways, organ dysfunction, interacting medicines, medication-taking behavior, or the exposure actually achieved during therapy. This Perspective argues that precision dosing should preserve validated genotype information while repeatedly reconciling it with dynamic phenotype and exposure information. Evidence from pharmacogenomic guidelines, genotype-phenotype concordance studies, phenoconversion research, inflammatory pharmacology, drug-drug-gene interaction modeling, adherence science, and therapeutic drug monitoring supports the component distinctions, but not a universal integrated dosing algorithm. We therefore treat genotype as a durable prior, dynamic phenotype as a state-dependent modifier, and measured exposure as feedback that can confirm or challenge earlier expectations. The resulting approach is intentionally conditional: the value and weighting of each information layer depend on the drug, pathway, therapeutic index, treatment phase, assay, population, and clinical question. Precision dosing is consequently better framed as longitudinal evidence reconciliation than as a one-time translation from DNA to dose.

Keywords: Pharmacogenomics, Phenoconversion, Precision dosing, Therapeutic drug monitoring, Drug-drug-gene interaction, Model-informed precision dosing

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INTRODUCTION

Pharmacogenomics has moved from association discovery toward clinically actionable prescribing for selected gene-drug pairs, yet its success can encourage an overly deterministic interpretation of what DNA provides. Genotype can identify inherited differences that remain relevant throughout life, but the pharmacological phenotype expressed at a particular treatment moment is also shaped by disease, concomitant therapy, organ function, behavior, and time [1]. This distinction does not weaken pharmacogenomics. It clarifies its proper inferential role.

The clinical evidence base itself is heterogeneous. Some gene-drug relationships have sufficiently mature mechanistic, pharmacokinetic, safety, and implementation evidence to support prescribing recommendations,

whereas many genomic associations do not reach the same decision threshold [2]. Even within the genomic layer, routine testing may not capture rare, structural, regulatory, or otherwise incompletely characterized variation that contributes to drug-response diversity [3]. Thus, “genotype” should not be treated as an exhaustive measurement of inherited capacity, still less as a direct measurement of present-day drug handling.

Importantly, prospective implementation evidence shows that pharmacogenetic guidance can improve care when testing is connected to validated recommendations and operational workflows [4]. The problem is therefore not whether genotype matters, but whether an inherited predictor should be treated as the final prescription after treatment begins. Precision-dosing approaches already provide a methodological precedent for combining baseline patient characteristics with pharmacokinetic or pharmacodynamic information as it becomes available [5]. Building on that distinction, this Perspective argues for a longitudinal interpretation in which genotype establishes a durable prior, current phenotype modifies that prior, and exposure evidence tests whether the resulting expectation remains clinically plausible.

Genotype as a stable but incomplete predictor

A useful precision-dosing architecture should begin by preserving what genotype does especially well: it supplies a stable signal that does not fluctuate with infection, short-term comedication, or adherence. For selected antidepressants, for example, CPIC recommendations translate CYP2D6, CYP2C19, and CYP2B6 genotypes into drug-specific prescribing considerations when the evidence is sufficiently mature [6]. In such settings, genotype can legitimately inform an initial dose, drug choice, or monitoring strategy before an individual concentration or treatment response is available.

Stability, however, is not equivalent to sufficiency. The CYP2B6–methadone guideline illustrates a critical boundary: a reproducible pharmacokinetic association does not automatically establish that a genotype-based dose adjustment improves efficacy, safety, or another clinically relevant endpoint [7]. Precision dosing therefore requires separation of three questions that are often compressed into one: does a variant alter biological function, does that alteration change drug exposure or response, and is the effect large and reliable enough to justify a specific clinical action?

Measured metabolic phenotype also demonstrates why genotype should be interpreted probabilistically rather than deterministically. In a multi-enzyme cocktail study, canonical diplotypes discriminated several CYP phenotypes, yet additional genetic factors and sex contributed to residual variation [8]. Real-world genotype–phenotype concordance testing likewise found that predicted and measured CYP activity can diverge, with discrepancies not always explained by known medication effects [9]. Such discordance may arise from unmeasured genetic variation, environmental modulation, disease, assay limitations, or combinations of these factors.

The same caution applies in therapeutically mature areas. Psychiatric pharmacogenomics contains clinically useful examples, but substantial heritable and nongenetic variability in treatment response remains unresolved [10]. A genotype result should therefore be treated as a durable prior about biological capacity, not as a contemporaneous assay of enzyme activity, adherence, systemic exposure, or clinical response. The prior may remain informative throughout treatment even when its observed phenotypic expression changes.

Phenoconversion

Phenoconversion provides the clearest conceptual reason to separate inherited genotype from current functional phenotype. A systematic review identified inhibitors, inducers, smoking, aging, cancer, and inflammation among factors capable of shifting measured CYP activity away from genotype-predicted status [11]. The direction and magnitude of these shifts are not uniform across enzymes, drugs, or patients, and their clinical consequences are not equally established. Phenoconversion should therefore be understood as a state-dependent mismatch requiring explanation, not as a single correction factor.

Experimental work also shows that genotype can condition the consequences of a dynamic modifier without fully determining them. In human liver microsomes, CYP2C19 inhibitors produced broadly comparable relative inhibition across genotype groups, while the resulting phenotypic classifications differed because baseline activity differed [12]. Genotype can thus define metabolic reserve or starting position, whereas the expressed phenotype depends on what acts on that reserve.

Prospective human phenotyping makes the temporal distinction more concrete. In genotyped healthy volunteers, CYP2C19 inhibitor exposure produced frequent shifts in metabolic phenotype even though DNA was unchanged [13]. Those transitions were inhibitor- and genotype-dependent and should not be generalized as population

prevalence estimates. Their importance lies instead in demonstrating that the pharmacological state relevant to dosing can change after a genetic result has been established.

Formal drug–drug–gene interaction models reach a compatible conclusion from another direction. Joint models of genotype and enzyme inhibition show that the two information classes cannot always be treated as independent additive inputs [14]. The exact integration rule remains model- and pathway-specific, but the inferential requirement is clear: when a dynamic modifier is strong enough to alter expressed function, genotype should remain part of the explanation without being mistaken for the current phenotype itself.

Organ function and inflammation

Inflammation is a particularly important source of dynamic phenotype because it can alter drug-metabolizing enzymes and transport systems without changing germline sequence. Clinical and molecular evidence indicates that inflammatory states can suppress several ADME pathways, with especially consistent evidence for CYP3A4 and more variable effects across other enzymes and disease contexts [15]. Cytokine concentration, disease severity, tissue context, and methodological design all influence the observed effect, preventing a universal inflammation-to-dose conversion.

Mechanistic work in three-dimensional human liver spheroids reinforces that inflammatory regulation is pathway-specific rather than a uniform reduction in “metabolism.” IL-1 β , IL-6, and TNF α produced different patterns of ADME-gene regulation, including substantial changes in selected CYP and conjugation pathways [16]. These results support biological plausibility for inflammatory phenoconversion, but they remain mechanistic evidence and cannot by themselves specify an individual clinical dose.

Clinical data show why the distinction matters. Among patients receiving voriconazole, greater inflammatory burden was associated with higher dose-corrected exposure and a weaker correspondence between CYP2C19 genotype and apparent metabolic activity [17]. The study is drug- and context-specific, yet it demonstrates the practical problem: a genotype that was correctly measured can become a poorer description of current drug handling during an altered disease state.

Organ dysfunction introduces a related but broader source of variation. A proof-of-concept study in renal impairment used circulating molecular information to inform individualized PBPK representations of hepatic ADME capacity [18]. The approach is not established for routine dosing, but it illustrates an emerging principle: organ-function effects may involve changing functional pathway expression that is not encoded in germline genotype. Precision dosing should therefore distinguish stable inherited capacity from current physiological capacity and should resist collapsing both into one “patient factor.”

Drug–Drug Interactions

Drug–drug interactions challenge genotype-only interpretation because interacting medicines can change the expression of genetically determined metabolic capacity after the initial prescription. PBPK analysis of simvastatin demonstrated that combinations of transporter and enzyme genotypes with perpetrator drugs can generate exposure patterns that differ across drug–drug–gene scenarios [19]. Such models are not substitutes for prospective clinical validation, but they show why a genotype-based recommendation may require reassessment when the medication environment changes.

Dynamic modifiers can also coexist. PBPK work integrating inflammatory signaling with CYP inhibition demonstrated that disease-related suppression and a perpetrator drug can act on the same metabolic pathway in the same clinical interval [20]. A medication list therefore cannot be interpreted independently of disease state, and an inflammatory marker cannot automatically be interpreted independently of co-medication. The clinically relevant object is the current functional state produced by their combination.

Recent synthesis of drug–gene and drug–drug–gene interactions similarly emphasizes that chemical inhibition or induction and inherited variation must be interpreted jointly, while acknowledging that many combinations lack validated clinical recommendations [21]. The practical implication is not that every interaction requires a new dose, but that the confidence attached to a genotype-conditioned expectation should change when a plausible modifier is introduced, removed, intensified, or resolved.

A useful reconciliation rule is therefore conditional. If genotype, expected functional phenotype, and medication context remain concordant, the genomic prior can retain substantial weight. If a strong inhibitor, inflammatory state, or interacting pathway creates a plausible mismatch, the current phenotype should be reconsidered rather than forcing the observation back into the original genotype category. Controlled phenoconversion and interaction-modeling evidence support the general possibility that a dynamic modifier can change exposure state after genotype is known [13, 19, 20]; the exact dose consequence remains drug-, pathway-, and evidence-specific.

Narrative prose makes these interaction states difficult to compare because the same genotype can have different interpretive meaning under different functional contexts. **Table 1** therefore separates the evidence state, justified inference, reassessment trigger, and unresolved question without converting them into an unsupported numerical score.

Table 1. Reconciling genotype-conditioned expectations with changing interaction states during precision dosing

Current inference state	Interpretation	Boundary	Validation
Scientific anchor	Genomic evidence Current functional interpretation Dynamic modifier Unresolved precision-dosing question	Population or clinical boundary	Reassessment trigger
Proposed concordant baseline	Genomic evidence Actionable genotype is established for the specific gene–drug pair Current functional interpretation Functional state is consistent with the genotype-conditioned expectation Dynamic modifier No major pathway modifier identified Unresolved precision-dosing question How much weight should the stable genotype retain once new functional evidence appears?	Applies only where the gene–drug relationship is clinically validated	Addition or removal of a relevant inhibitor, inducer, or major disease-state modifier
Proposed inhibitor-conditioned discordance	Genomic evidence Genotype remains valid but no longer describes the whole current state Current functional interpretation Expressed activity is plausibly lower or otherwise shifted from baseline Dynamic modifier Mechanistically relevant inhibitor or interacting drug Unresolved precision-dosing question Is the interaction large enough to justify dose change, extra monitoring, or only reinterpretation?	Depends on inhibitor strength, pathway contribution, dose, timing, and alternative clearance routes	Change in interacting-drug dose, discontinuation, or new evidence of functional recovery
Proposed multi-modifier state	Genomic evidence Genomic baseline coexists with more than one dynamic influence Current functional interpretation Current phenotype cannot be attributed confidently to a single modifier Dynamic modifier DDI plus inflammation, organ dysfunction, or another overlapping state Unresolved precision-dosing question Which modifier is decision-dominant, and can their effects be separated reliably?	Evidence is especially context- and model-dependent	Appearance or resolution of one modifier, or discordant clinical/exposure evidence
Proposed unresolved discordance	Genomic evidence Genotype and expected phenotype do not match, but no sufficient explanation is established Current functional interpretation Functional state is uncertain rather than automatically reclassified Dynamic modifier Possible unmeasured DDI, disease effect, assay limitation, or incomplete genomic explanation Unresolved precision-dosing question What additional functional evidence is needed before changing the dose?	Requires pathway-specific investigation	Repeated discordance or clinically consequential change

The same logic is easier to recover visually when genotype, functional phenotype, and dynamic modifiers remain separate rather than being collapsed into one interaction arrow. **Figure 1** therefore places a central reconciliation boundary between what is inherited and what is currently expressed.

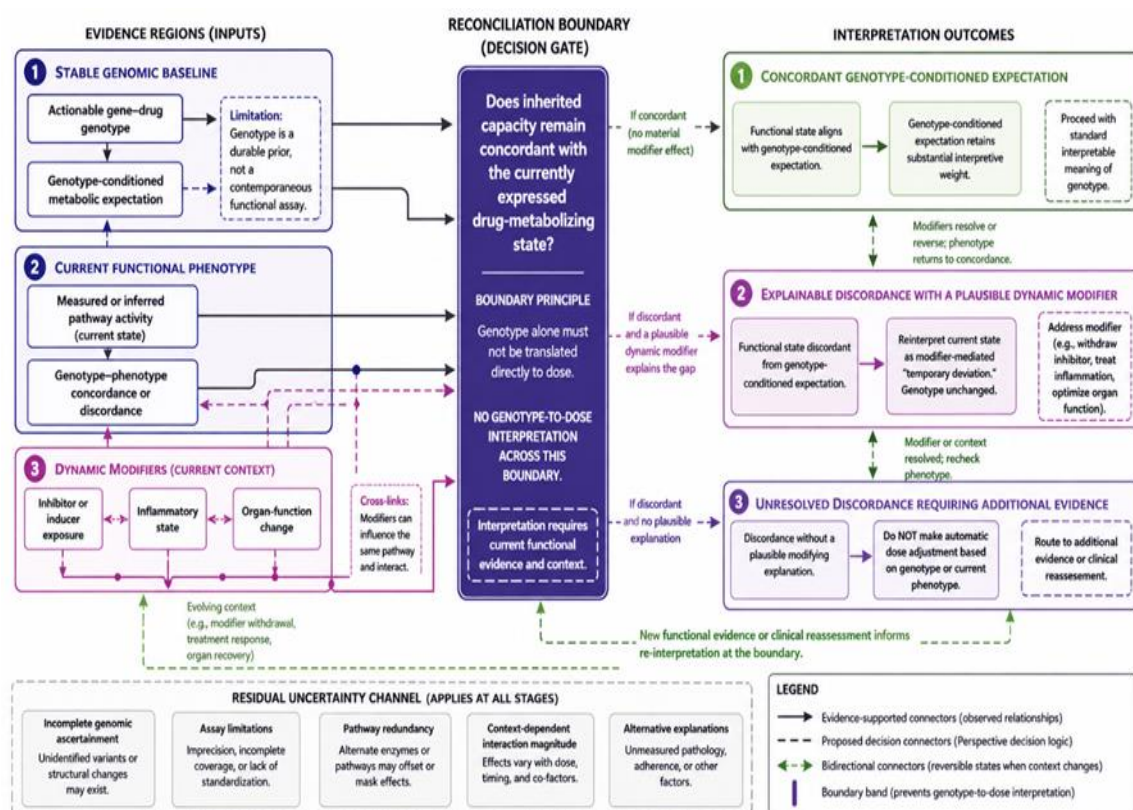


Figure 1. When a valid genotype becomes an incomplete description of current drug-metabolizing state

Adherence and time-varying exposure

Genotype can remain correct while delivered drug exposure changes for a simpler reason: the prescribed regimen is not always the regimen that is taken. Modern adherence methodology distinguishes initiation, implementation, and persistence rather than treating adherence as a binary trait [22]. Each phase creates a different uncertainty. A prescription may never be initiated, doses may be taken inconsistently after initiation, or therapy may be discontinued before the clinician assumes it has ended. None of these states is encoded in DNA.

This matters because unrecognized nonadherence can be misread as unusual pharmacokinetics, poor drug response, or unexplained interindividual variability [23]. Conversely, a clinician should not infer nonadherence merely because an exposure or response appears unexpected. Medication-taking behavior is one competing explanation among pharmacokinetic, pharmacodynamic, disease-related, interaction-related, and measurement explanations. Precision dosing therefore requires an explicit exposure-history question before biological discordance is attributed to genotype or phenotype.

Dynamic information is not automatically useful simply because it changes over time. Pharmacometric work on time-varying covariates warns that causal position and temporal ordering matter: a variable can be a cause of exposure change, a mediator of treatment effect, a consequence of prior dosing, or a correlate that should not be adjusted for in the same way [24]. The proposed framework must therefore distinguish a reassessment trigger from a justified dose modifier.

Table 2 is needed because medication-taking states differ in what is known, what remains uncertain, and what action is defensible before a concentration or response measurement is interpreted.

Table 2. Decision states for medication-taking history before attributing time-varying exposure to biology

	Initiation uncertain Implementation variable Persistence uncertain		
Proposed decision state	Initiation uncertain	Implementation variable	Persistence uncertain
Information currently available	Prescription and intended regimen are known	Treatment has been initiated, but dose-taking is inconsistent or incompletely observed	Earlier treatment use is documented, but continuation is unclear

Main unresolved uncertainty	Whether treatment was actually started	Frequency, timing, and duration of missed or delayed doses	Whether the patient is still exposed to the intended regimen
Permissible interpretation or action	Verify initiation before interpreting lack of effect as pharmacological failure	Reconstruct the dosing history with the best available source; avoid immediate biological reclassification	Establish whether therapy has continued before escalating or changing dose
Reassessment trigger	First credible evidence of medication use or continued absence of use	Change in medication-taking pattern or emergence of clinically important discordance	Confirmed discontinuation, restart, or regimen change
Consequence for genotype-based dosing	Genotype remains relevant but cannot explain exposure to a drug that was not taken	Unexpected response cannot be assigned confidently to genotype or intrinsic phenotype	A stable genotype does not imply stable exposure across treatment interruptions
Medication use appears consistent			
Proposed decision state	Medication use appears consistent		
Information currently available	Available history supports ongoing use at the intended regimen		
Main unresolved uncertainty	Residual measurement error and unobserved deviations		
Permissible interpretation or action	Retain adherence as a lower-priority competing explanation while evaluating biological and interaction factors		
Reassessment trigger	New discrepancy between expected and observed treatment course		
Consequence for genotype-based dosing	Genotype-conditioned expectations become more interpretable, but are still not sufficient alone		

Therapeutic drug monitoring

Therapeutic drug monitoring adds an information class that genotype cannot supply: an observation of exposure achieved under the patient's current dose, physiology, interacting medicines, and medication-taking history. In therapeutic areas with qualified concentration or exposure targets, TDM can be combined with population pharmacokinetic models and patient covariates to estimate individual parameters and update subsequent doses [25]. The methodological advantage is feedback. A baseline prediction can be tested against what actually happened.

The distinction among information layers remains important. Pharmacogenomics, TDM, and emerging functional measurements such as liquid-biopsy-derived ADME signals do not answer the same question [26]. Genotype describes inherited potential; a functional assay may characterize current pathway activity; a concentration describes the exposure realized after dose delivery and disposition. None should automatically replace the others. Their usefulness depends on assay quality, sampling time, pathway contribution, therapeutic index, and whether an exposure–response relationship is sufficiently established to support action.

Prospective oncology experience illustrates the temporal value of repeated measurement. Serial TDM of oral targeted therapies identified underexposure at different treatment points and enabled interventions addressing dose, medication-taking behavior, interacting factors, or administration conditions in a subset of patients [27]. The study does not establish universal clinical benefit for all targeted therapies, but it demonstrates a key principle

for precision dosing: the relevant exposure state can evolve during treatment and can reveal information unavailable at baseline.

TDM also helps adjudicate competing explanations, although it does not resolve them automatically. A low concentration may reflect rapid clearance, an interacting inducer, reduced absorption, missed doses, sampling error, or an inappropriate target. A high concentration may reflect reduced clearance, inhibition, organ dysfunction, inflammatory phenoconversion, or timing. The concentration is therefore evidence about realized exposure, not a diagnosis of why that exposure occurred. Precision dosing should use it to update the prior interpretation and determine what additional evidence is needed.

At this stage, the argument has moved from a static genotype to a sequence of increasingly current observations: inherited capacity, expressed functional state, treatment context, medication-taking history, and measured exposure. The next analytical task is to specify how these information classes should be integrated without treating every new variable as equally reliable or equally causal.

Integrating static and dynamic information

The central precision-dosing problem is not a shortage of patient information but deciding what each information class means at a particular clinical moment. Model-informed precision dosing provides an established methodological family for combining baseline covariates with measured drug concentrations, biomarkers, and other patient characteristics as treatment progresses [28]. Its relevance here is methodological rather than evidentiary proof of the framework proposed in this Perspective. Existing MIPD approaches demonstrate that dosing need not remain fixed after an initial prediction, but the validity of any update depends on the model, target, population, sampling design, and quality of the incoming information.

This distinction becomes especially important when the therapeutic target itself is uncertain. Population concentration ranges are useful summaries but need not identify the optimal exposure for every individual, particularly when pharmacodynamic response, toxicity, disease activity, or other biomarkers differ between patients [29]. A concentration can therefore confirm that a patient achieved an expected exposure without proving that the exposure is optimal. Genotype, phenotype, concentration, and clinical response should be treated as sequentially related but analytically distinct evidence classes.

Tacrolimus provides a practical illustration of how static and dynamic information can coexist within a dosing model. Population pharmacokinetic models frequently incorporate CYP3A5 alongside body size and other clinical covariates, while Bayesian forecasting subsequently uses patient-specific concentration data to update individual parameter estimates [30]. The example should not be generalized mechanically beyond tacrolimus. Its importance is architectural: genotype can enter the model as a durable covariate without being treated as the final estimate of clearance after treatment has begun.

The resulting hierarchy is not simply “newer data override older data.” Genotype may remain highly reliable as an inherited descriptor even when its current phenotypic expression is modified. A functional phenotype may be more temporally current but assay-dependent. A concentration is directly observed but reflects the combined effects of dose delivery, absorption, distribution, metabolism, elimination, sampling time, and adherence. A biomarker may be biologically close to response yet insufficiently validated for dose selection. TDM and MIPD therefore support iterative updating, while individualized response targets emphasize that exposure alone may not complete the decision [25, 28, 29].

The proposed interpretation is consequently evidence-reconciliation rather than evidence replacement. When genomic prediction, current phenotype, dosing history, measured exposure, and clinical response align, confidence in the present dosing hypothesis increases. When they diverge, the first question should be which information class is being contradicted. A low concentration after an actionable genotype does not invalidate the genotype; it challenges the expectation that the genotype, current phenotype, administered dose, adherence, and interacting conditions jointly predicted the observed exposure. Precision dosing becomes more defensible when discordance is localized before a corrective action is chosen.

Narrative description alone obscures the different causes of discordance and the different corrective tests they require. **Table 3** therefore begins with the misleading pattern itself and separates its plausible origin from the evidence needed to resolve it.

Table 3. Exception-first triage of misleading genotype–phenotype–exposure patterns before dose revision

Decision point	Observable signature	Plausible discordance source Competing interpretation Corrective evidence Residual consequence
Proposed discordance state Genotype predicts altered metabolism, but exposure is unremarkable		
Before changing an initially genotype-informed regimen	Concentration or response falls within the expected clinical range	Plausible discordance source Compensating pathways, limited pathway contribution, adherence pattern, dose selection, or current phenotype differing from genotype prediction
		Competing interpretation The pharmacogenetic effect may be biologically real but not decision-dominant in the present state
		Corrective evidence or test Confirm treatment history, interacting drugs, sampling validity, and where justified functional phenotype
		Residual consequence after clarification Retain genotype as a background risk descriptor without forcing an unnecessary dose change
Proposed discordance state Genotype predicts ordinary metabolism, but exposure is unexpectedly high		
When toxicity risk or excessive concentration emerges	Higher-than-expected exposure despite an apparently non-risk genotype	Plausible discordance source Inhibition, inflammation, organ dysfunction, reduced clearance through another pathway, or administration error
		Competing interpretation Hidden genetic variation or assay error
		Corrective evidence or test Review comedications and organ state; repeat exposure measurement; consider pathway-specific functional assessment
		Residual consequence after clarification Dynamic phenotype may temporarily outweigh genotype for current dose interpretation
Proposed discordance state Genotype and measured phenotype disagree		
When functional testing becomes available	Metabolic activity differs from genotype-predicted category	Plausible discordance source Phenoconversion, incomplete genomic ascertainment, assay limitations, disease state, or interacting drug
		Competing interpretation Stable constitutive discordance rather than reversible phenoconversion
		Corrective evidence or test Repeat or orthogonally validate phenotype and assess modifiers
		Residual consequence after clarification Dose interpretation remains conditional until the source of discordance is resolved
Proposed discordance state Exposure is unexpectedly low despite a plausible genotype–phenotype match		
Before escalating dose	Concentration below the expected target or previous patient value	Plausible discordance source Nonadherence, reduced absorption, induction, administration conditions, timing error, or inaccurate target
		Competing interpretation Intrinsically high clearance
		Corrective evidence or test Reconstruct dose history and sampling time; evaluate interacting factors and repeat measurement where justified
		Residual consequence after clarification Dose escalation should follow explanation of delivered exposure rather than genotype alone
Proposed discordance state Exposure appears appropriate but clinical response is inadequate		

Before assuming pharmacokinetic failure	Concentration is compatible with the intended range but efficacy is insufficient or toxicity persists	Plausible discordance source
		Pharmacodynamic variability, inappropriate population target, disease progression, or non-PK mechanism
		Competing interpretation
		Exposure target remains valid but response is individually atypical
		Corrective evidence or test
		Evaluate response biomarkers, disease state, endpoint validity, and alternative treatment hypotheses
		Residual consequence after clarification
		Precision dosing may require reconsideration of the therapeutic target, not merely the dose

Figure 2 compresses the same argument into a layered architecture in which genomic evidence remains stable while phenotype, clinical modifiers, delivered exposure, and observed response can change across treatment time.

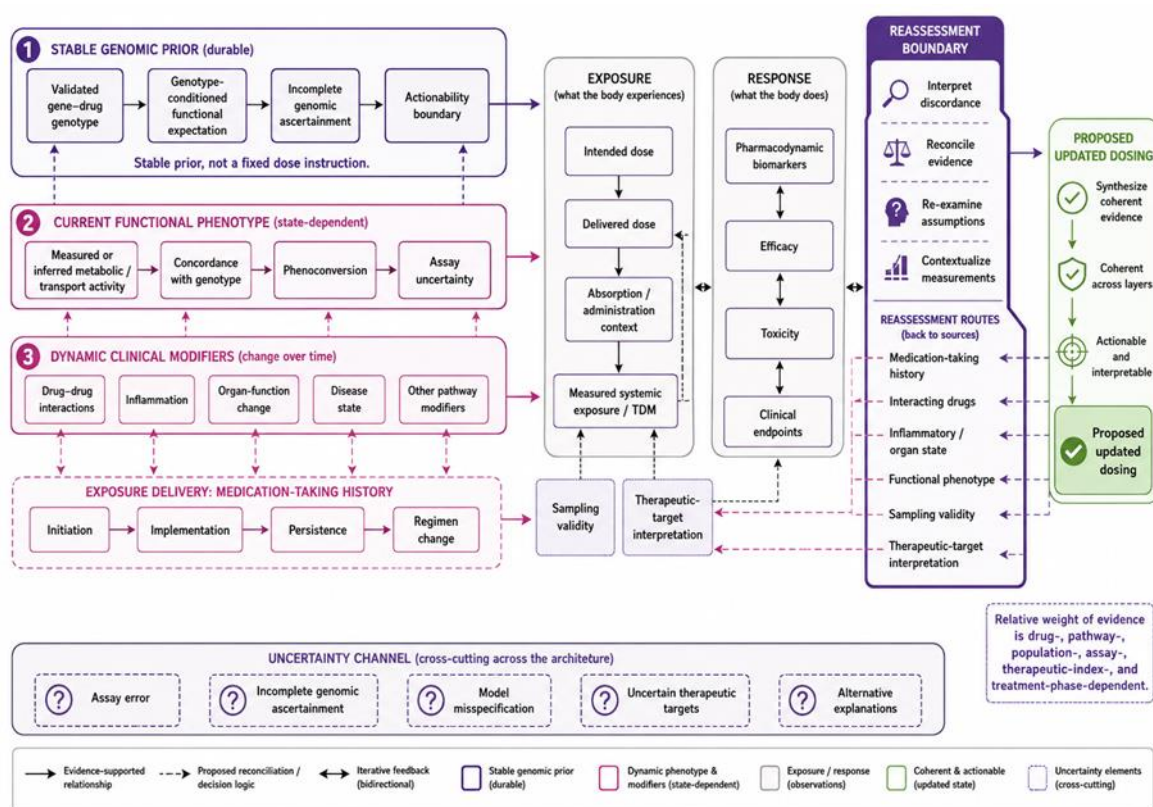


Figure 2. Updating dosing confidence when stable genomic priors encounter changing functional and exposure evidence

A genotype–phenotype–exposure dosing framework

The synthesis developed above supports a proposed genotype–phenotype–exposure dosing framework in which dosing is treated as a sequential state-estimation problem. Adaptive-dosing methodology provides a conceptual precedent for choosing later actions on the basis of an updated patient state rather than repeating an unchanged baseline decision [31]. The framework proposed here does not require reinforcement learning or any particular computational platform; its central requirement is that each dosing decision distinguish durable information from state-dependent information.

The first layer is the genomic prior. A validated genotype may influence initial drug or dose selection when the gene–drug evidence is actionable. Its weight should depend on the quality of the gene–drug relationship, not on the mere availability of a genetic result. Genomic information remains relevant after therapy begins because a phenoconverted patient does not acquire a new germline genotype.

The second layer is the dynamic functional state. Phenoconversion, inflammation, interacting drugs, organ-function changes, and other modifiers may shift the phenotype expressed at the treatment moment. These modifiers should not automatically trigger dose adjustment. They should alter confidence in the baseline expectation and, where justified, prompt functional or exposure reassessment.

The third layer is delivered and observed exposure. Dose history, adherence, administration conditions, and TDM determine whether the predicted pharmacokinetic state is consistent with what the patient actually experiences. Unexpected exposure should trigger diagnostic reconciliation rather than reflexive escalation or reduction.

A fourth, clinically necessary layer is response interpretation. Exposure may be appropriate while efficacy or toxicity remains atypical. In that state, further dose manipulation may be less informative than reassessing the pharmacodynamic target, disease process, endpoint, or treatment choice. The framework therefore stops short of treating concentration normalization as synonymous with therapeutic success.

The proposed decision rule is deliberately qualitative: retain stable evidence that remains valid, update state-dependent evidence when the patient changes, investigate discordance before attributing causality, and revise dose only when the combined information is sufficiently decision-relevant. The relative weighting of these layers must be validated separately for individual drugs and populations. No universal ordering can be justified in which genotype, phenotype, concentration, or response always dominates every other information source.

Clinical workflow

Translation requires more than assembling measurements. Pharmacogenomic clinical decision support already demonstrates that genomic information must be stored, interpreted, delivered at an actionable point, and linked to appropriate recommendations within the clinical workflow [32]. The proposed extension is to make the same workflow capable of recognizing when the assumptions underlying the original genotype-conditioned recommendation may no longer hold.

Operational implementations show that structured pharmacogenomic information can be represented within electronic health records and connected to configurable decision logic [33]. A dynamic precision-dosing workflow would need additional time-stamped inputs rather than a permanently static alert: medication additions and discontinuations, relevant changes in organ function or inflammatory state, adherence information where credible, therapeutic drug concentrations, and response observations. The technical feasibility of storing genomic information does not establish the validity of any particular integration rule.

The clinical workflow should therefore distinguish at least three moments. At initialization, validated genotype and baseline clinical characteristics can influence the first dosing decision. At reassessment, a new interacting drug, major disease-state change, suspected nonadherence, unexpected concentration, toxicity, or inadequate response can trigger review of whether the current phenotype and exposure remain compatible with the original expectation. At **revision**, the dose should change only when the source of discordance is sufficiently understood and the proposed action is supported for that drug and context.

Existing implementation evidence shows that actionable pharmacogenomic information has value only when it is delivered through a usable clinical process [4, 32, 33]. The additional reassessment architecture proposed here remains unvalidated. Its purpose is to prevent a successful pharmacogenomic implementation from becoming static after the first prescribing decision. The future test is therefore not whether a health system can display genotype, phenotype, concentration, and clinical state on the same screen, but whether a specified integration rule improves dosing decisions and patient outcomes compared with existing care.

CONCLUSION

DNA can provide durable and clinically important information about drug handling and response, but durability should not be mistaken for contemporaneous completeness. Genotype does not directly observe phenoconversion, inflammation, organ dysfunction, interacting medicines, medication-taking behavior, achieved exposure, or changing pharmacodynamic response. These processes operate on different biological and temporal levels and should not be collapsed into a single genotype-derived label.

This Perspective proposes that precision dosing treat genotype as a stable prior, dynamic phenotype as a state-dependent interpretation of current functional capacity, and exposure and response measurements as feedback capable of confirming or challenging earlier expectations. Discordance should trigger explanation before dose revision, because the unexpected observation may originate from biology, medication use, interactions, organ state, measurement error, target selection, or model inadequacy.

The proposed framework is not a validated universal dosing algorithm, and no fixed weighting among genotype, phenotype, exposure, and response can presently be justified across drugs and populations. Its value is instead as an evidence-boundary architecture: preserve what genomic information establishes, update what clinical state can change, and require new observations to earn their influence on the dosing decision. Precision pharmacotherapy

is therefore better conceived as longitudinal reconciliation of stable and dynamic evidence than as a complete prescription written once from DNA.

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