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Actionability Before Data Abundance in Precision Dosing: Integrating Kidney Function, Therapeutic Drug Monitoring, Pharmacogenomics, and Exposure–Response Evidence for Patient-Specific Dose Decisions

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ABSTRACT

Precision dosing increasingly combines pharmacokinetic models, organ-function estimates, therapeutic drug monitoring, pharmacogenomic information, and exposure–response evidence. Yet the availability of more patient-specific data does not ensure that a safer or more defensible dose decision can be made. This Current Opinion argues that precision dosing should prioritize actionability before data abundance. Actionability is defined here as the extent to which a dosing signal is sufficiently reliable, temporally relevant, mechanistically interpretable, linked to a clinically meaningful target, and operationally usable to justify a dose action for a particular patient. Kidney function illustrates the problem because filtration estimates are indirect, may disagree across biomarkers, and may become rapidly outdated during changing physiology. Therapeutic drug monitoring is similarly dependent on sampling time, assay interpretation, target validity, and turnaround. Pharmacogenomic information can provide durable prior knowledge, but genotype does not always equal current phenotype when drug interactions or other modifiers are present. Exposure–response evidence supplies the therapeutic objective, yet an accurately predicted exposure is useful only if the target itself is adequately supported. The article therefore develops a proposed precision-dosing actionability architecture in which heterogeneous signals are interpreted according to reliability, temporal validity, target linkage, decision leverage, and uncertainty rather than simply accumulated. The approach is intended as an organizing framework, not a validated dosing algorithm. Its application remains bounded by drug-specific evidence, patient heterogeneity, model performance, assay availability, implementation conditions, and the need for prospective validation against both exposure and patient-important outcomes.

Keywords: Precision dosing, Model-informed precision dosing, Therapeutic drug monitoring, Pharmacogenomics, Kidney function, Exposure-response

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Introduction

Precision dosing has moved beyond adjustment by a single demographic or laboratory variable. Contemporary approaches combine population pharmacokinetic or pharmacodynamic models with patient covariates, measured concentrations, biomarkers, and other individualized information. At the same time, concentration targets derived from populations may not always represent the most informative objective for an individual patient, particularly when more proximal biomarkers of response are available [1, 2]. The central challenge is therefore not simply whether additional data can be acquired, but whether those data can be converted into a defensible decision about dose, interval, route, timing, or the need to defer a change. This article treats that conversion—not data accumulation itself—as the central analytical unit of precision dosing.

Model-informed precision dosing has accordingly been framed as more than prediction. Its requirements include an appropriate model, fit-for-purpose validation, relevant patient information, transparent assumptions, and a clinical process capable of acting on the output [3]. These requirements matter because a precise estimate can still be clinically weak if the model is being extrapolated beyond its validated setting, the patient state has changed since measurement, the exposure target is uncertain, or the predicted difference is too small to justify the risks of intervention. Precision in the statistical sense and actionability in the clinical sense are therefore related but non-equivalent properties.

Digital health infrastructure can make longitudinal data, decision support, and repeated model updating more accessible, but it also shifts part of the precision-dosing problem to workflow, interoperability, governance, and usability [4]. A recommendation that arrives after a dose has been administered, depends on an unavailable assay, or cannot be reconciled with competing clinical priorities is not made actionable merely because the underlying calculation is sophisticated. The clinician, drug regimen, patient trajectory, laboratory process, and health system all contribute to whether a technically credible signal can affect treatment. Actionability is consequently relational: it arises from the fit between evidence, therapeutic objective, timing, and an available clinical response.

Recent precision-dosing scholarship continues to identify unresolved challenges in translation, target definition, implementation, and evaluation [5]. This article develops the position that actionability should precede data abundance as the organizing principle for patient-specific dose decisions. The proposed argument does not establish a universal hierarchy among kidney function, therapeutic drug monitoring (TDM), pharmacogenomics (PGx), and exposure–response evidence. Instead, it asks what each signal can legitimately tell the clinician now, how strongly it is linked to the intended therapeutic objective, what uncertainty accompanies it, and what new information should trigger reassessment.

Why precision dosing fails when data are not actionable

The limited routine adoption of model-informed precision dosing despite decades of methodological development illustrates that technical capability alone is insufficient. Earlier roadmaps identified scientific, regulatory, operational, and implementation barriers that separate a well-performing model from routine clinical use [6]. That distinction remains useful: a dosing signal can be valid as a measurement or prediction while still failing to alter treatment because its interpretation, timing, or ownership is unclear.

Software adds another layer. Precision-dosing platforms differ in their functions, supported models, interfaces, handling of patient information, and capacity to communicate recommendations [7]. These differences are not merely ergonomic. They determine what evidence reaches the decision maker, how uncertainty is exposed, and whether model outputs can be inspected rather than accepted as opaque numerical prescriptions.

Even before workflow is considered, model selection creates uncertainty. Recent work on model ensembling shows that alternative population pharmacokinetic models can yield different predictive behavior and that model-selection uncertainty can itself become relevant to a priori dosing [8]. A recommendation should therefore not be treated as actionable simply because one model returns a single dose.

Clinical implementation studies reinforce the importance of process design. Development of model-informed vancomycin dosing in practice required attention to how recommendations would be produced, interpreted, and incorporated into existing work [9]. In other words, actionability is partly a property of the decision environment rather than of the data alone.

A broader systematic assessment of implementation barriers and facilitators likewise identifies constraints spanning evidence, technology, professional practice, organization, and infrastructure [10]. The proposed distinction in this article is consequently between data acquisition and decision leverage. Information has decision leverage only when it can plausibly change a patient-specific choice in a timely, interpretable, and evidence-bounded way. More variables can increase descriptive resolution while simultaneously increasing discordance, cognitive burden, or false confidence if the relevance of each signal is not adjudicated.

Kidney function as a dynamic dosing signal

Kidney function is often presented as one of the most familiar inputs to dose adjustment, yet its apparent simplicity can obscure multiple layers of inference. Glomerular filtration rate is not directly observed in routine care; it is estimated from biomarkers and equations whose performance depends on biological and measurement assumptions [11]. For dosing, the relevant question is narrower still: how well does the available estimate

represent the clearance pathway of the particular drug in the patient's current state? An eGFR value can be analytically reasonable without being a complete representation of renal drug elimination.

Temporal validity becomes especially important when kidney function is changing. In acute kidney injury, conventional equations may be applied under conditions that violate their steady-state assumptions, reducing confidence that a current creatinine-derived estimate represents current filtration [12]. The dosing consequence is not that every estimate should be ignored, but that its recency and physiological context should determine how strongly it constrains a dose decision.

Discordance between filtration biomarkers further shows why a single renal number should not automatically be treated as ground truth. In hospitalized patients receiving renally eliminated medications, creatinine- and cystatin-C-based estimates can differ sufficiently to alter renal dosing interpretations [13]. Such disagreement may reflect biomarker-specific non-GFR determinants, changing physiology, or genuine uncertainty. The appropriate response is therefore adjudication rather than automatic averaging or automatic preference for one biomarker.

Kidney replacement therapies create an additional boundary because extracorporeal clearance depends on modality, intensity, treatment schedule, drug properties, and residual endogenous function. Evidence describing medication use during intermittent hemodialysis and continuous kidney replacement therapy underscores that routine kidney-function categories alone may be insufficient for dosing [14]. Within the proposed actionability perspective, kidney function should therefore be treated as a time-indexed dosing signal with three separable attributes: the estimated physiological state, confidence in that estimate, and relevance of that state to the drug's total clearance at the moment of decision.

Therapeutic drug monitoring: measurement, timing, and interpretability

TDM is often described as direct patient-specific evidence because it measures drug concentration rather than inferring exposure only from covariates. However, concentration is not self-interpreting. Antimicrobial TDM guidance and model-informed dosing scholarship both emphasize that the clinical meaning of a measured concentration depends on sampling time, pharmacokinetic context, the exposure metric of interest, the therapeutic target, and patient condition [15, 16]. A laboratory result therefore becomes actionable only after it is translated from "what was measured" into "what this measurement implies for the next dose."

This translation also depends on the integrity of apparently mundane metadata. Administration time, infusion duration, specimen time, dose history, adherence, and turnaround determine whether the measured value corresponds to the pharmacokinetic question being asked. Model-informed TDM can reduce dependence on rigid sampling schedules, but it cannot rescue an observation whose provenance is too uncertain to interpret. The practical distinction is between having a concentration result and having a concentration result whose relationship to recent dosing and the intended exposure target is sufficiently known.

Pharmacometric approaches extend TDM by using measured concentrations to update individual parameter estimates and forecast future exposure. Contemporary antimicrobial precision-dosing work shows why this is useful when variability is high and a single trough or random concentration may incompletely represent the desired exposure metric [17]. Yet model assistance does not remove the need to ask whether the assay is reliable, whether administration and sampling times are documented correctly, whether the model fits the patient, and whether the chosen target is clinically meaningful.

Sampling strategy itself can determine how much information a concentration contributes. Pharmacometric simulation of β-lactam/β-lactamase inhibitor monitoring demonstrates that the interpretability of TDM depends on design assumptions and on whether available observations can distinguish the exposure features relevant to dose adjustment [18]. The proposed implication is that TDM should be treated as a time-sensitive posterior signal rather than as an automatic override of other evidence. A measured concentration close to the decision may deserve substantial weight when its timing and target are sound; a delayed, mistimed, or weakly interpretable concentration may deserve less weight than apparently less "direct" information.

Pharmacogenomics: genotype, phenotype, and clinical relevance

PGx differs from kidney function and TDM because germline genotype is comparatively stable over time. Its actionability depends instead on whether a specific gene–drug relationship has sufficient evidence to support a prescribing recommendation. A large multicentre implementation study of a pre-emptive pharmacogenetic panel demonstrated that clinically actionable gene–drug information can reduce the occurrence of clinically relevant

adverse drug reactions when incorporated into prescribing [19]. The important point for precision dosing is not that genotype should dominate every decision, but that it can provide useful prior information before exposure data have accumulated.

Implementation remains context dependent. Prospective work in psychiatry illustrates how pre-emptive pharmacogenomics can be incorporated into care while still depending on which drugs are used, which actionable variants are present, and whether clinicians can implement the recommended change [20]. Thus, a PGx result can be available yet have little immediate dosing relevance if the current medication has no validated gene–drug recommendation or if the recommended alternative is clinically unsuitable.

Guideline development further reinforces the specificity of translation. The Dutch Pharmacogenetics Working Group provides drug-specific recommendations for defined CYP2D6 and CYP2C19 interactions rather than a generic rule that metabolizer status predicts response across all therapies [21]. Actionability is therefore pair-specific: it depends on the gene, the drug, the phenotype assignment, the therapeutic context, and the available dosing or drug-selection response.

Finally, genotype-predicted phenotype may not equal current metabolic phenotype. Polypharmacy can cause phenoconversion through enzyme inhibition or induction, making an inherited metabolizer category an incomplete description of present drug-handling capacity [22]. A genotype result should therefore remain available as durable prior information while contemporaneous drug exposure, interacting medicines, and other relevant clinical observations update its decision weight. In the proposed actionability framework, PGx is neither a static command nor a disposable background variable: it shapes initial expectations, but its relevance to a particular dose decision must be reconciled with the patient's current pharmacological state.

Exposure–response evidence and target definition

Precision dosing requires an objective against which a dose can be judged. Exposure–response evidence supplies that objective only when the relationship being used has an interpretable clinical meaning. Dose, exposure, and response are linked through mechanisms and study designs that can create associations without establishing that changing dose to achieve a particular exposure will cause the desired outcome. Recent causal-estimand work makes this distinction explicit by showing that dose–exposure–response quantities require identifiable assumptions before they support causal interpretation [23]. A concentration target should therefore not acquire authority merely because it is measurable or statistically associated with response.

Target maturity also varies across therapies. In cytotoxic oncology, opportunities for precision dosing differ by drug because pharmacokinetic variability, exposure–efficacy evidence, toxicity relationships, and feasibility of monitoring are uneven [24]. By contrast, prospective multicentre work with selected oral targeted anticancer therapies demonstrates that TDM-based dose adjustment can be operationalized where drug-specific targets and clinical processes are sufficiently developed [25]. These examples support a bounded conclusion: target-guided dosing can be actionable for selected therapies, but the existence of a measurable exposure is not itself evidence that an individualized target is validated.

The target must also represent competing consequences of exposure. Antimicrobial target scholarship shows why toxicity cannot be treated as an afterthought to efficacy optimization [26]. The proposed actionability view therefore asks three questions before an exposure signal is allowed to drive dosing: Is the exposure estimate credible? Is the target clinically justified for this drug and patient context? Would moving toward that target plausibly improve the benefit–harm balance rather than merely normalize a number?

A further distinction concerns the unit of inference. Population exposure ranges can be useful starting points, but a patient-specific action requires evidence that the observed or predicted deviation is meaningful enough to warrant intervention in that person. This becomes especially important when efficacy and toxicity gradients overlap or when response biomarkers lag behind exposure. Under those conditions, the target functions as a decision aid rather than an absolute boundary, and uncertainty about the target should remain visible in the recommendation.

Table 1 makes explicit the distinctions among the principal evidence signals and the conditions under which each can acquire dose-changing relevance.

Table 1. When patient-specific evidence becomes actionable for precision dosing

Signal	Measurement/ estimate	Actionability prerequisite	Dose implication	Uncertainty source	Reassessment trigger
Kidney function	eGFR plus renal-support context	Current physiology; clearance relevance	Adjust renal dosing component	Biomarker bias; non-steady state	Physiology or support changes
TDM	Timed concentration or modeled exposure	Valid timing, assay, target	Update individual exposure	Sampling error; model mismatch	New dose, level, adherence change
PGx	Gene-specific phenotype assignment	Valid gene–drug action	Inform starting dose or choice	Phenoconversion; interaction	New interacting treatment or discordant exposure
Exposure–response	Efficacy/toxicity target	Credible target–objective linkage	Adjust toward defensible range	Causal and target uncertainty	New response, toxicity, or target evidence

Note: Signal priority is proposed to vary by drug, patient, time point, and decision; entries are not universal dosing rules.

Reconciling discordant dosing signals

The most clinically important precision-dosing problems often arise when signals disagree. A patient may have a genotype suggesting rapid metabolism, a concentration suggesting adequate exposure, and worsening kidney function that predicts reduced clearance. Treating every input as an independent vote invites incoherence. Treating one source as permanently superior is equally problematic because the relative value of kidney estimates, concentrations, genotype, and response evidence changes with timing, measurement quality, and the drug's dominant clearance and toxicity pathways.

Tacrolimus provides a useful exemplar without establishing a universal hierarchy. Prospective evidence has evaluated Bayesian individualized dosing, electronic-file-embedded model-informed dosing, and CYP3A5-informed dosing in kidney transplantation [27-29]. Together, these studies show that model predictions, measured exposure, and pharmacogenetic information can each contribute to patient-specific dosing in the same therapeutic domain. They do not show that one fixed weighting scheme can resolve every disagreement, nor that improved target attainment necessarily translates into harder clinical benefit.

An additional posaconazole evaluation illustrates the importance of confirming that a population pharmacokinetic model is fit for the intended population before using patient concentrations to generate individualized predictions [30]. Discordance can therefore signal model misspecification or weak measurement provenance as readily as true biological complexity.

Signal conflict should also be distinguished from signal redundancy. Two inputs may disagree because they measure different processes rather than because one is wrong. Kidney function may forecast future clearance while a concentration summarizes exposure generated under an earlier physiological state; genotype may explain baseline metabolic capacity while a concomitant inhibitor explains the current phenotype. The proposed adjudication process therefore asks whether disagreement is temporally and mechanistically expected before treating it as evidence failure.

This article proposes adjudicating disagreement according to reliability, temporal proximity, mechanistic relevance, target linkage, and the consequences of acting incorrectly. A reversible dose change with rapid follow-up may tolerate more uncertainty than a large or difficult-to-reverse intervention. **Table 2** translates this reasoning into provisional clinical states rather than a universal scoring rule.

Table 2. Adjudicating contradictory dosing signals without forcing false agreement

Discordance pattern	Likely explanation	Evidence priority	Safe provisional action	Monitoring requirement	Downgrade/reversal condition
Renal estimate worsens; concentration unchanged	Lagging physiology or mistimed level	Current time course and clearance relevance	Avoid large reflex adjustment	Repeat renal function and exposure	Stable physiology or contradictory new level

PGx predicts high clearance; exposure adequate	Phenoconversion or prior dose compensation	Current interpretable exposure	Preserve regimen if clinically suitable	Review interactions; repeat exposure	Modifier removed or exposure shifts
Concentration outside target; patient stable	Sampling error or weak target	Validate level and target	Confirm before major change	Repeat exposure and clinical assessment	Reproducible deviation with credible target link
Model recommends change; patient outside model support	Extrapolation	Direct measured/clinical evidence	Constrain or defer model-led change	Obtain new data; review model	Applicability restored or model externally supported

Note: "Priority" indicates proposed decision emphasis, not a validated universal hierarchy.

The proposed precision-dosing actionability architecture

The proposed architecture treats dosing as a conditional evidence-to-action problem rather than as the accumulation of predictors. Its first layer is evidence acquisition: kidney function, concentrations, PGx information, exposure–response targets, treatment history, and clinically relevant response data. The second layer asks whether each item is interpretable now. A value may be excluded or downgraded because it is stale, mistimed, poorly validated, mechanistically peripheral to the drug, or disconnected from a usable therapeutic target.

The third layer is decision leverage. Here, evidence is compared not by technological sophistication but by its capacity to distinguish among available actions. Adaptive dosing methods illustrate how repeated dosing can be represented as sequential decision making rather than one-time optimization [31]. Machine-learning work in anticancer dosing similarly shows substantial potential for combining complex predictors while emphasizing heterogeneous validation and generalizability [32]. More broadly, machine-learning approaches can expand dose individualization, but prediction remains conceptually distinct from a defensible recommendation [33].

The fourth layer is dose action with explicit uncertainty and a planned opportunity for reversal or reassessment. Continual-learning approaches further show why model priors may need updating when accumulating clinical data reveal population or practice changes [34]. In the proposed architecture, however, model updating does not authorize unsupervised clinical adaptation; it identifies another point at which evidence quality and validation must be reconsidered.

Figure 1 shows how evidence can be abundant yet lose actionability as it passes through interpretation, target, and decision boundaries.

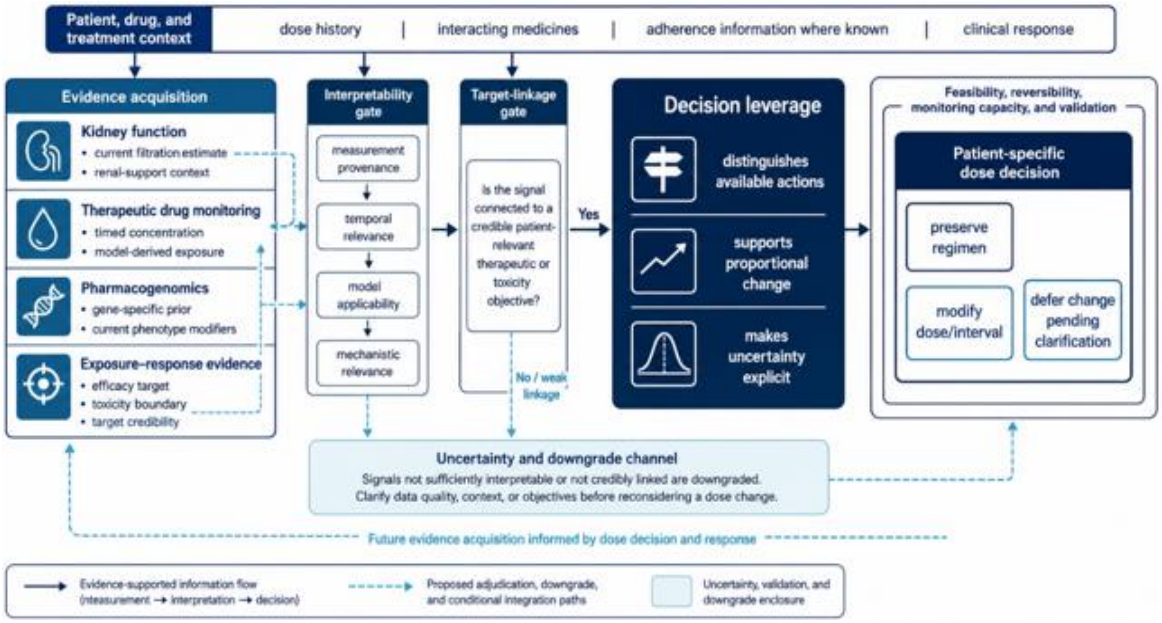

Figure 1. Actionability gates determine whether precision-dosing evidence can justify a dose change

Temporal updating and dose reassessment

Precision dosing is inherently time-indexed because its signals do not age at the same rate. Germline genotype is comparatively persistent, whereas kidney function may change over hours or days and genotype-predicted

phenotype can be modified by new inhibitors or inducers [12]. Phenoconversion makes this distinction clinically important because a stable genetic result may cease to describe the patient's current metabolic capacity [22]. A dosing record should therefore preserve durable priors without allowing their persistence to be mistaken for perpetual decision dominance.

Measured concentrations occupy another temporal position. They can sharply update an individual exposure estimate when sampling and dose history are trustworthy, yet their relevance decays after subsequent doses, changes in clearance, altered adherence, or major physiological transitions. Bayesian individualized dosing demonstrates the value of incorporating new concentration information into later predictions [27]. Sequential adaptive methods similarly formalize the idea that the clinically relevant "state" changes after each observation and action [31].

Model knowledge also has a time dimension. Continued-learning methods suggest that population priors can be revised when accumulating real-world information indicates that the original model no longer represents the treated population adequately [34]. This is distinct from changing an individual dose because one patient changed.

Temporal updating also creates a documentation requirement. A later recommendation is interpretable only if clinicians can reconstruct which dose, concentration, renal estimate, interacting medicines, and response observations were available when the preceding decision was made. Without that provenance, an apparently inconsistent recommendation may reflect a changed patient state rather than model instability. The proposed architecture therefore treats time stamps and decision provenance as part of clinical evidence quality, not as administrative metadata, while avoiding any claim that one documentation format is universally sufficient.

The proposed reassessment rule is consequently event-based rather than tied to a universal interval: reconsider a dose when a signal changes enough to alter interpretation, target proximity, or the expected consequences of the available actions. **Figure 2** depicts these asynchronous update rates and the central need to recalibrate rather than simply append new data.

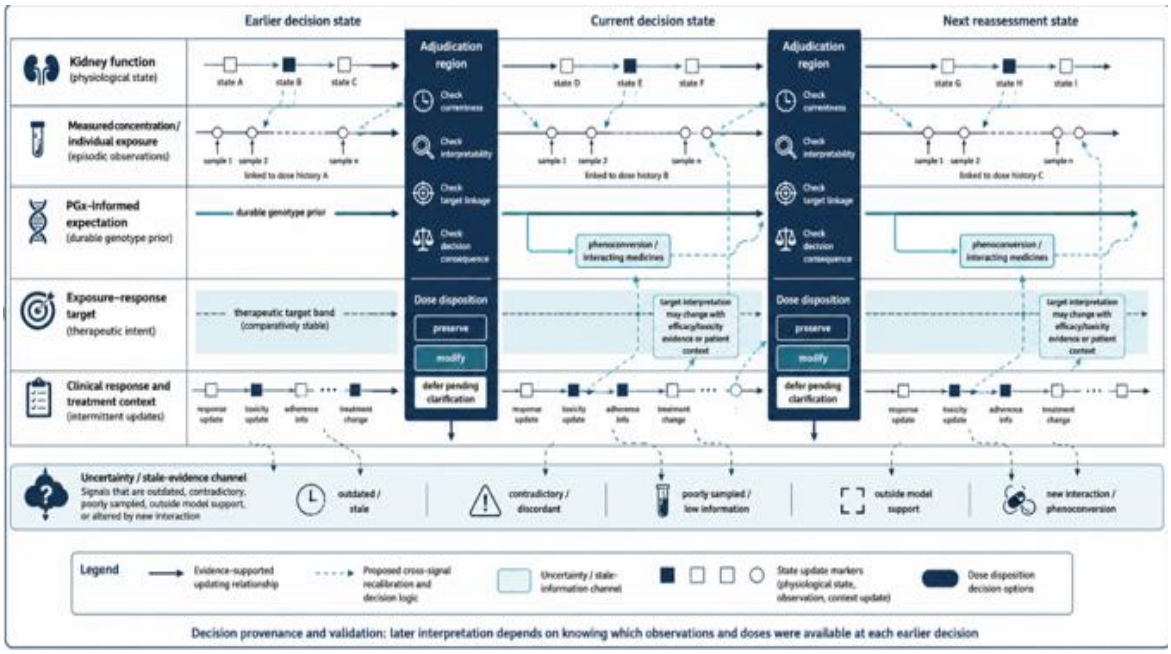

Figure 2. Asynchronous dosing signals require repeated recalibration of the patient-specific dose decision

Boundary conditions, uncertainty, and validation needs

The proposed architecture has several boundaries. First, predictive uncertainty and target uncertainty are different problems. A model may estimate exposure accurately while the therapeutic target remains weakly linked to patient benefit; individual-target scholarship supports keeping those questions separate [2]. Similarly, an observed exposure–response relation should not be treated as causal without the design and assumptions needed for that interpretation [23].

Second, physiological measurements can disagree for reasons that are not resolved by choosing the newest datum. Creatinine and cystatin C have different non-GFR determinants, and disagreement may become particularly

consequential when physiology is changing [13]. PGx adds another form of uncertainty because a validated genotype can coexist with a different current phenotype under interacting treatment [22]. The architecture therefore requires an explicit "uncertain or non-comparable" state rather than forcing every signal into a common scale.

Third, technical actionability does not guarantee operational actionability. Implementation evidence shows that model-informed dosing depends on workflow, staffing, infrastructure, professional acceptance, and the ability to act within the treatment window [10]. Access to testing and decision-support resources may therefore create health-system variation even when the underlying pharmacology is similar.

Validation should proceed at distinct levels. Model calibration, external predictive performance, recommendation concordance, exposure-target attainment, safety, and patient-important outcomes should not be collapsed into one endpoint. Embedded tacrolimus MIPD can improve exposure-target performance without thereby establishing broader clinical benefit [28].

A further validation challenge is intervention dependence: once clinicians change a dose in response to a signal, subsequent concentrations and outcomes reflect both the underlying patient state and the previous decision. Prospective evaluation should therefore document decision timing, accepted and overridden recommendations, reasons for non-action, and whether later evidence confirmed or contradicted the initial interpretation. Otherwise, apparent model performance may obscure how the decision process itself altered the data subsequently observed. Future testing of the proposed architecture should compare it with usual care and simpler rules, examine clinician overrides and failure modes, test external transportability across drugs and systems, and evaluate whether explicit uncertainty management improves decisions rather than merely adding complexity.

Conclusion

Precision dosing becomes clinically meaningful only when patient-specific evidence can support a defensible action. Kidney function, TDM, PGx, and exposure–response evidence differ in what they measure, how quickly their relevance changes, how directly they inform a therapeutic objective, and what uncertainty accompanies their interpretation. Treating them as interchangeable inputs risks converting data abundance into false precision.

This Current Opinion proposes actionability as the organizing principle connecting these domains. The proposed architecture separates evidence acquisition from interpretability, target linkage, decision leverage, dose action, and reassessment. It also gives discordance a legitimate place in the decision process: conflicting signals need not be averaged or forced into agreement when they refer to different time points, biological processes, or evidential levels. In some circumstances, the most defensible action may be a cautious adjustment with close monitoring; in others, it may be to preserve the current regimen or defer change until uncertainty is reduced.

The framework is not a validated algorithm and does not specify universal signal weights, thresholds, or reassessment intervals. Its usefulness will depend on drug-specific evidence, credible therapeutic targets, adequate measurements, patient context, implementable workflows, and prospective evaluation. Precision dosing should therefore be judged not by how many patient variables can enter a model, but by whether the resulting evidence can be interpreted, challenged, updated, and translated into a proportionate patient-specific decision.

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