



Original Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Clinical PKPD Models Should Distinguish Structural Uncertainty from Patient Variability

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ABSTRACT

Clinical pharmacokinetic–pharmacodynamic models support increasingly individualized predictions of exposure, response, and dose requirements, yet uncertainty in those predictions is often summarized without distinguishing its origin. This can obscure a consequential methodological difference: uncertainty about whether the model adequately represents the system is not equivalent to variability among patients represented within that model. Structural misspecification, uncertain parameter estimates, between-patient variability, within-patient change, residual error, incomplete observations, and software implementation can all widen or distort individual predictions, but they imply different corrective actions. This Methodological Perspective argues for explicit separation of these sources before prediction error is interpreted as biological heterogeneity. Structural uncertainty should prompt model comparison, external evaluation, and challenge of assumptions; parameter uncertainty should be propagated; patient variability should remain conditional on the selected structure and measured covariates; and residual variability should undergo attribution rather than being treated automatically as irreducible noise. The proposed decomposition is intended as an inference and qualification architecture rather than a new statistical estimator. Its purpose is to make individual PKPD predictions more interpretable by showing what is known about the patient, what is uncertain about the model, what remains unresolved in the observations, and which uncertainty matters for the clinical decision at hand.

Keywords: Pharmacometrics, Population pharmacokinetics, PKPD modeling, Model uncertainty, Interindividual variability, Precision dosing

Received: 08 October 2025; **Revised:** 21 December 2025; **Accepted:** 25 December 2025

INTRODUCTION

Clinical PKPD models increasingly sit between heterogeneous patient data and decisions about dose, exposure, response, or monitoring. Model-informed precision dosing illustrates this transition particularly clearly: a population model provides a quantitative prior, patient characteristics condition that prior, observations can update individual parameters, and an implementation layer converts predictions into a clinical recommendation. Contemporary reviews and implementation guidance therefore treat model quality, patient information, measurement, validation, and clinical context as linked requirements rather than interchangeable ingredients [1-3]. The practical attraction is obvious, but so is the inferential risk. When an individualized prediction is uncertain or wrong, the observed discrepancy does not identify whether the patient is unusual, whether the model structure

is inadequate, whether parameters are imprecisely estimated, whether observations are poor, or whether the deployed implementation differs from the qualified model.

That distinction matters because predictive performance is not itself a clinical outcome. Even a technically sophisticated dosing system requires separate evidence that its use improves decisions or patient outcomes [4]. A methodology that treats every unexplained discrepancy as “patient variability” can therefore be doubly misleading: it can hide deficiencies in the model while simultaneously exaggerating the apparent unpredictability of the patient.

This Perspective develops a narrower proposition. Clinical PKPD analysis should separate uncertainty about the representation from variability represented by the representation. The separation is conceptual rather than an assertion that every component can be estimated independently from every dataset. Some components are statistically entangled, and the observable consequences of structural error, unmeasured physiology, sparse sampling, and residual noise can overlap. The methodological task is therefore not merely to calculate a larger uncertainty interval. It is to identify which explanations remain plausible, which can be tested, and which uncertainty source should govern confidence in the individual prediction.

Two different sources of uncertainty

A useful starting point is the intended use of the model. Systems-model evaluation frameworks emphasize that credibility is conditional on model purpose, scope, available evidence, and the consequence of being wrong [5]. The same principle applies to PKPD models. A structure adequate for population description may be inadequate for forecasting an individual concentration tomorrow; a model acceptable for interpolation may be fragile under an organ-function state absent from model development. Structural uncertainty is therefore uncertainty about the adequacy of the mathematical representation, its assumptions, and its transportability to the proposed decision context.

Patient variability occupies a different inferential level. Covariate modeling seeks to describe systematic relationships between patient characteristics and pharmacometric parameters, allowing predictable components of between-patient variability to be represented explicitly [6]. These relationships are useful without automatically being causal. Body size, renal function, genotype, disease state, concomitant therapy, or biomarkers may improve prediction because they carry information about parameter distributions; their presence in a model does not prove a complete biological mechanism.

Stochastic components also require separation. Simulation work comparing pharmacogenetic information with therapeutic drug monitoring demonstrates that interindividual variability, interoccasion variability, and residual unexplained variability can affect the value of patient information in different ways [7]. A large interindividual variance indicates dispersion of modeled patient parameters, whereas a large residual term concerns discrepancies remaining after the model and its individual predictions have been specified. Neither should be assumed to represent the same phenomenon.

The distinction becomes more important in adaptive PKPD simulations, where population variability, within-patient change, exposure, pharmacodynamic response, safety outcomes, covariates, and dose schedule can be perturbed separately [8]. Such frameworks demonstrate an analytical capability rather than clinical proof: different uncertainty sources can be carried through the same prediction problem without being collapsed into one generic error term. This Perspective extends that logic by proposing that interpretation should preserve the source label as long as the evidence permits.

Structural model uncertainty

Structural uncertainty concerns the possibility that the selected model is an incomplete or inappropriate description of the relevant PKPD system. It includes choices about compartmental structure, absorption or disposition processes, time-varying behavior, covariate relationships, response models, disease progression, delays, baseline functions, and the functional form of residual error. It also includes a broader transportability question: whether a structure developed in one population represents another sufficiently well for the intended prediction.

Residual behavior can provide evidence that model structure deserves re-examination. Kaikousidis and colleagues deliberately compared correctly specified and misspecified population PK settings and showed that structured information could remain in individual residuals; sufficiently flexible postprocessing could recover some of that predictable residual pattern [9]. The important implication is not that residual variability is equivalent to structural error. Rather, a residual component can absorb behavior that would be more appropriately represented in model

structure. Large or patterned residuals should therefore trigger attribution tests before being interpreted as irreducible patient noise.

Simulation-based automated model development makes the distinction clearer because the data-generating structure is known. Duvnjak and colleagues evaluated automated population PK model development against simulated “true” models, allowing structural recovery to be assessed directly [10]. Clinical datasets rarely offer that privilege. Several structures may describe available observations adequately while implying different individual predictions outside the observed region. Structural uncertainty therefore persists even after conventional goodness-of-fit criteria become acceptable.

External evaluation is one of the strongest available challenges to that uncertainty, but its interpretation is not standardized. El Hassani and Marsot noted substantial heterogeneity in the methods and criteria used to externally evaluate population PK models for precision dosing [11]. Consequently, “externally evaluated” is not a binary guarantee of transportability; the target population, observation design, error metrics, and intended use still matter. This becomes clinically tangible when multiple published models for the same drug are evaluated in the same external population. In critically ill adults receiving piperacillin, Greppmair and colleagues found substantial differences among 24 published models, while Bayesian forecasting with therapeutic drug monitoring improved predictions [12]. The result demonstrates that nominally relevant models can produce materially different performance in the same clinical context. It does not establish that every discrepancy is structural, because renal dynamics, treatment conditions, measurements, and other population features remain competing explanations.

Model uncertainty may also be local rather than global. Synthetic Model Combination was developed to weight pretrained pharmacometric models according to the patient’s position within their respective covariate domains [13]. The broader methodological lesson is that a model can be more credible for one patient state than another. Agreement between models can increase confidence, while disagreement can identify a region in which model-form uncertainty deserves explicit visibility rather than being hidden inside a patient random effect.

Parameter uncertainty

Even when the selected structure is treated as adequate, its parameters are not known without uncertainty. Fixed effects, variance components, covariate coefficients, correlation structures, and other model parameters are estimated from finite and imperfect data. Bayesian estimation makes this distinction particularly transparent because parameter knowledge can be represented as posterior distributions rather than as fixed point values [14]. Importantly, those distributions remain conditional on the model structure, likelihood, prior assumptions, and available data; they do not incorporate every plausible structural alternative automatically.

Parameter uncertainty matters because subsequent predictions and decisions inherit it. Simulation work on model-integrated evidence approaches for pharmacokinetic bioequivalence showed that inadequate characterization of parameter uncertainty can affect inferential operating characteristics, while resampling or importance-sampling approaches can improve uncertainty propagation in the studied designs [15]. The numerical results are specific to that setting, but the methodological principle is broader: a narrow individual prediction conditional on uncertain population parameters should not be interpreted as if those population quantities were known exactly.

Parameter uncertainty should therefore remain a separate channel in clinical PKPD interpretation. Increasing sample size, improving study design, adding informative observations, or refining estimation may reduce it. None of those actions is conceptually equivalent to explaining why two patients differ. Conversely, observing substantial patient heterogeneity does not justify treating uncertainty in the estimated population mean or covariate coefficient as biological variability.

Between-patient variability

Between-patient variability is the component most easily invoked when individualized predictions differ, yet it is meaningful only relative to a model that defines what is allowed to vary. Clinical precision-dosing literature emphasizes that genetics, physiology, disease, body composition, organ function, concomitant treatment, and environmental or behavioral factors can contribute to heterogeneous drug exposure or response [16-18]. These sources support individualized modeling, but their effects remain drug-, population-, time-, and endpoint-specific. Some heterogeneity is predictable. In overweight and obese patients receiving vancomycin, population PK analysis identified bodyweight, renal function, and intensive-care status as determinants associated with clearance in the studied population [17]. In a different modeling paradigm, geriatric physiology was incorporated into PBPK models for apixaban and rivaroxaban and prospectively compared with concentrations from hospitalized patients

[18]. These examples illustrate the same conceptual point from different directions: patient heterogeneity can be represented through measured characteristics when the relationship is supported and externally challenged. However, the estimated magnitude of “between-patient variability” is itself model conditional. A systematic review and benchmark of tacrolimus population PK models identified a large landscape of alternative structures, covariate relationships, and software implementations [19]. A variance component estimated under one structural representation cannot automatically be interpreted as the same biological quantity under another. Structural assumptions determine which systematic patterns are modeled explicitly and which are left to random effects. Patient observations can reduce uncertainty after a population model has been chosen. In external evaluation of posaconazole models, prior concentration information improved individual prediction under the selected fit-for-purpose model [20]. Simulation of amikacin model-informed dosing likewise showed that individual prediction depended on the amount and timing of concentration information and on the underlying population model [21]. Bayesian updating therefore addresses one important source of patient-level uncertainty, but it cannot guarantee that the population prior or model structure is appropriate.

A practical consequence is that apparent “patient uniqueness” should be treated as a hypothesis rather than a default diagnosis. A changing creatinine value, evolving inflammation, altered target expression, new interacting therapy, or other time-varying state may represent real biological heterogeneity. Yet the same observation can also expose an omitted covariate, an inadequate time-varying structure, insufficient sampling, or model transportability failure. **Table 1** converts this distinction into a claim-to-test format so that patient variability is accepted only to the extent supported by observations that distinguish it from competing model explanations.

Table 1. Adjudicating claims of between-patient variability before assigning individual PKPD deviation to biology

Monitoring signal Exposure measure	Validation criterion	Clinical state PK driver PD Permitted interpretation
Variability claim or patient state Stable measured physiology explains a persistent exposure shift		
Monitoring signal Repeated covariates and concentrations move consistently with the modeled relationship Exposure measure Individual concentration profile or exposure summary	Prediction improves when the supported covariate is included and remains stable on repeat observation	Clinical state Clinically stable PK driver Measured physiologic determinant PD or target response Response remains coherent with predicted exposure Permitted interpretation Represented between-patient variability is plausible within the qualified population
Variability claim or patient state Organ function or disease state is changing during therapy		
Monitoring signal Covariate trajectory changes on the same time scale as exposure Exposure measure Serial exposure estimates	A time-varying relationship explains sequential observations better than a fixed baseline value	Clinical state Dynamically changing PK driver Time-varying clearance or distribution determinant PD or target response Response trajectory follows or lags the changing exposure as biologically plausible Permitted interpretation Dynamic patient state should be separated from static interindividual variability
Variability claim or patient state Patient is sparsely observed after a population prior is applied		

Monitoring signal Wide individual prediction uncertainty before informative measurement Exposure measure Sparse concentration or biomarker data	Additional appropriately timed observation materially narrows prediction uncertainty without requiring structural change	Clinical state Incompletely observed PK driver Population prior dominates individual estimate PD or target response PD estimate remains weakly informed Permitted interpretation Limited information should not be relabelled as biological unpredictability
Variability claim or patient state Repeated patient data remain systematically discordant with the model		
Monitoring signal Directionally persistent prediction error despite reliable measurements Exposure measure Repeated exposure discrepancy	Alternative structures or external models reduce the discordance more than additional random-effect freedom	Clinical state Stable or reproducibly discordant PK driver Candidate omitted process or incorrect structural relation PD or target response Response inconsistency may or may not accompany PK error Permitted interpretation Structural uncertainty remains active and the deviation should not be assigned solely to patient variability
Variability claim or patient state Exposure is predicted adequately but response differs		
Monitoring signal PK observations fit while PD observations remain discordant Exposure measure Exposure reproduced	Response-model alternatives, endpoint quality, disease state, or target dynamics are tested separately	Clinical state PK stable, PD heterogeneous PK driver PK driver adequately represented PD or target response Target or clinical response differs from expectation Permitted interpretation Heterogeneity may reside in PD biology or response-model structure rather than PK variability

The table distinguishes observations that support represented patient heterogeneity from observations that should reopen the model or information assumptions. **Figure 1** places those tests within the full exposure–response feedback loop, where therapeutic drug monitoring can reduce uncertainty about an individual state but cannot cross a structural-validation boundary by itself.

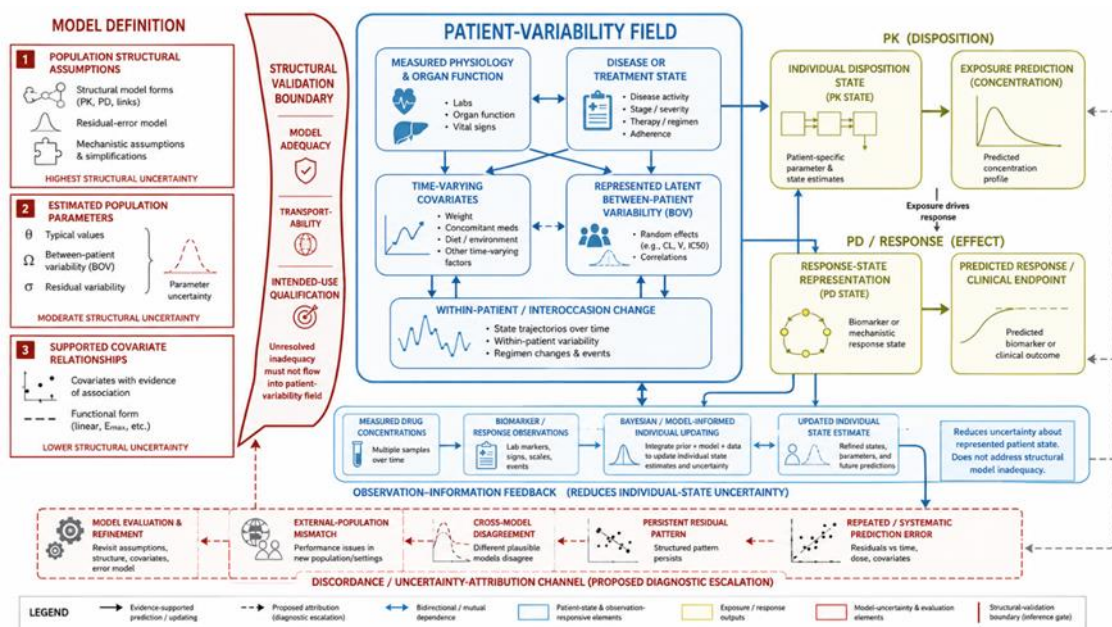


Figure 1. Locating patient heterogeneity within the feedback loop of individualized PKPD prediction

Residual variability

Residual variability is often described operationally as the discrepancy remaining between model prediction and observation after structural, covariate, and individual effects have been specified. That definition is statistically useful but scientifically agnostic. The residual can contain analytical measurement error, recording mistakes, dose-history errors, sampling-time error, short-timescale biological fluctuation, omitted covariates, inappropriate residual-error form, unmodeled temporal processes, and structural misspecification. Treating the estimated residual term as one biological entity therefore exceeds what the model has established.

Problematic pharmacology data provide a direct illustration. Missing or incorrect dose information, sampling times, concentrations, and covariate records can bias pharmacokinetic analysis in different ways, and appropriate handling depends on the error mechanism [22]. Such errors concern the observation process, not necessarily the underlying patient. They should therefore remain analytically separate from biological heterogeneity wherever data provenance permits.

Implementation adds another layer. A scoping review of model-informed precision-dosing software identified substantial heterogeneity in available tools and emphasized continuing needs for standardization, validation, and evaluation in real patients [23]. Software differences are not residual variability in the narrow statistical sense, but they can create discrepancies between a qualified model and its deployed prediction. Clinical interpretation should therefore distinguish model residual error from computational or implementation divergence.

The statistical components themselves also remain conceptually different. Interindividual variability, interoccasion variability, and residual unexplained variability can alter the value of patient measurements differently [7]. A patient whose clearance changes across treatment occasions should not automatically be described by the same random component as assay imprecision. Likewise, predictable structure remaining in residuals can be a signal that the fitted model has left systematic behavior unexplained [9].

The appropriate response is therefore exception-first rather than variance-first. Before accepting a large residual component as irreducible noise, analysts should ask whether the pattern is related to time, concentration, patient state, occasion, data provenance, model domain, or software implementation. **Table 2** organizes these failure modes around the observation that would discriminate among them.

Table 2. Failure-mode triage for residual patterns that should not be accepted automatically as irreducible PKPD noise

Isolated implausible concentration or abrupt outlier Residuals drift systematically with time		
Misleading residual pattern	Isolated implausible concentration or abrupt outlier	Residuals drift systematically with time
Classification basis and likely origin	Observation-process error is plausible	Unmodeled temporal process or changing patient state is plausible
PK driver implicated	Dose record, sampling time, assay, transcription	Time-varying clearance, absorption, distribution or physiology
Observable exposure signature	Single point inconsistent with adjacent trajectory	Directional error across serial samples
PD or target-response implication	Usually indeterminate unless response data are independently affected	Response may drift in parallel or with delay
Competing diagnosis and decisive check	Check source record, timing, dose history, assay and repeat data	Compare time-varying covariate or structural models with a static random-effect explanation
Synthesis consequence	Do not expand biological variability before data integrity is tested	Persistent temporal structure should reopen model specification
Residual magnitude changes with concentration Prediction resets poorly between treatment occasions		
Misleading residual pattern	Residual magnitude changes with concentration	Prediction resets poorly between treatment occasions
Classification basis and likely origin	Residual-error form may be inadequate	Interoccasion change is plausible

PK driver implicated	PK driver may be correctly centered but error model misspecified	Dynamic physiology, adherence, interacting treatment, episodic clearance shift
Observable exposure signature	Heteroscedastic discrepancy across exposure range	Within-patient profiles differ reproducibly by occasion
PD or target-response implication	Apparent PD heterogeneity can be amplified at poorly modeled concentrations	Response may change between occasions despite similar baseline covariates
Competing diagnosis and decisive check	Compare additive, proportional or combined observation-error descriptions without changing patient effects first	Model occasion effects or measured state changes and test reproducibility
Synthesis consequence	Error-model inadequacy should be distinguished from patient heterogeneity	Within-patient variability should not be absorbed into static between-patient variance
Residual pattern persists across reliable measurements Model output changes across implementations using nominally the same inputs		
Misleading residual pattern	Residual pattern persists across reliable measurements	Model output changes across implementations using nominally the same inputs
Classification basis and likely origin	Structural misspecification or population mismatch remains plausible	Computational or software-layer divergence is plausible
PK driver implicated	Omitted PK process or unsupported covariate relation	Model coding, parameter mapping, units, solver or data pipeline
Observable exposure signature	Repeated directionally coherent prediction error	Prediction differs before new biological data are introduced
PD or target-response implication	PD discordance may emerge secondarily if exposure is wrong	Derived response recommendation may differ despite identical patient state
Competing diagnosis and decisive check	Compare alternative qualified structures and external-population performance	Reproduce the calculation in a reference implementation and audit model version and input transformation
Synthesis consequence	Residual variance cannot be interpreted as irreducible until model alternatives are challenged	Deployment discrepancy belongs to qualification, not to patient variability

Model misspecification versus biological heterogeneity

The hardest practical cases arise when model misspecification and genuine biological heterogeneity generate similar observable behavior. Both can appear as biased individual predictions, unusually large random effects, poor predictive checks, or persistent residuals. The inferential mistake is to decide from the magnitude of disagreement alone.

Derived endpoints demonstrate why localization matters. Prybylski showed through simulation and a pharmacometric case example that discrepancies in predictive checks for derived outcomes can arise even when the underlying directly modeled quantities behave adequately [24]. A diagnostic failure therefore needs to be traced through the transformation from model state to reported endpoint. Rejecting the structure immediately may be as inappropriate as declaring the discrepancy biological.

Conversely, allowing increasingly flexible patient random effects can conceal an inadequate structure. If a model consistently underpredicts exposure in one population, the additional variance may improve apparent fit while leaving the reason for the bias unresolved. Model ensembling and external model-selection studies reinforce this point: in vancomycin and imatinib applications, the best-performing model or ensemble strategy depended on the studied cohort, and no single approach established universal superiority [25]. Patient-level performance is consequently conditional on which model structures have been admitted as credible candidates.

The proposed distinction is therefore diagnostic rather than ontological. “Structural uncertainty” does not mean that the model is known to be wrong, and “biological heterogeneity” does not mean that every patient difference

has a measured mechanism. They are competing explanatory classes. Structural uncertainty becomes more plausible when errors are systematic across individuals, concentrations, time, or model domains; biological heterogeneity becomes more plausible when reliable repeated observations identify reproducible patient-state differences that are coherent with supported physiology or response biology. Parameter uncertainty, sparse sampling, data error, and implementation discrepancies remain additional explanations rather than forced members of either class.

This distinction also limits what random effects should be asked to accomplish. Random effects are powerful representations of population dispersion, but they should not function as sinks for every form of model inadequacy. A clinically useful PKPD analysis should preserve uncertainty about why an individual prediction is discordant until discriminating evidence is available. That discipline is essential before uncertainty is propagated into individual decisions, because the corrective action depends on its source: obtain another observation, update the patient state, revise a parameter distribution, challenge model structure, select a better-transported model, or withhold a confident individualized recommendation.

Consequences for individual predictions

The distinction between model uncertainty and patient variability becomes most consequential when the model is used to predict an individual rather than summarize a population. A population model can perform acceptably on average while failing systematically in a clinically relevant subgroup, and an individual prediction can appear precise because conditional uncertainty has narrowed even though the selected structure is poorly transported.

External validation of infliximab population PK models in Korean patients with inflammatory bowel disease illustrates this problem. Adult and pediatric models did not transfer equivalently, and incorporating prior concentration information did not remove all inadequacy in the pediatric setting [26]. The methodological implication is narrow but important: a model–patient mismatch should not be relabelled automatically as unusually large patient variability. Population transferability, age-dependent model structure, available covariates, assay context, and prior-information content remain competing explanations.

The choice of prediction architecture can also alter individual classification even when the same clinical problem is being addressed. In chemotherapy-associated neutropenia, a hybrid approach combining pharmacodynamic-model information with machine learning improved predictive metrics relative to component approaches in the analyzed real-world dataset [27]. This does not establish clinical superiority, but it demonstrates that model form influences which patients are classified as high or low risk. Individual uncertainty therefore includes uncertainty about the representation used to generate the risk estimate, not only uncertainty in the patient-specific parameter values conditional on that representation.

Bedside implementation sharpens this requirement. Model-informed dosing tools need diagnostics appropriate to individual predictive performance rather than relying exclusively on population-level goodness of fit [28]. For a clinician, the relevant question is not merely whether the population model was once acceptable. It is whether the current patient lies inside a domain in which the model, observations, parameter uncertainty, and implementation support the intended decision.

The practical implication is a shift from a single prediction to a **decision state**. A point estimate should be accompanied conceptually by information about what is observed, which uncertainty remains unresolved, what action is permissible, and what new observation would justify reassessment. **Table 3** summarizes this decision logic without assigning universal numerical thresholds.

Table 3. Decision states for individual PKPD predictions when uncertainty sources remain incompletely resolved

Individual decision state	Evidence structure	Individual decision state	Decision structure
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Population prior only	Information currently available Qualified population model and baseline patient characteristics Dominant unresolved uncertainty Individual parameter state and unmeasured patient-specific determinants Permissible action Use only a conservative population-informed prediction within the validated domain Reassessment trigger First informative concentration, biomarker, response measure, or major clinical-state change Interpretation for individualized dosing Prediction remains predominantly population conditional	Patient data support the population model	Information currently available Reliable observations agree with the predicted trajectory Dominant unresolved uncertainty Residual parameter and observation uncertainty Permissible action Update the individual estimate and use model-informed prediction if the clinical context is qualified Reassessment trigger New discordant data, changing organ function, treatment interaction, or disease-state transition Interpretation for individualized dosing Confidence can increase without implying structural certainty
Patient observations are sparse or poorly timed	Information currently available Limited individual data with high dependence on the prior Dominant unresolved uncertainty Individual state versus information deficiency Permissible action Avoid overinterpreting an extreme individual estimate; obtain informative measurements where feasible Reassessment trigger Additional appropriately timed observation Interpretation for individualized dosing Lack of information should not be described as biological unpredictability	Repeated observations remain directionally discordant	Information currently available Reliable longitudinal data repeatedly disagree with the selected model Dominant unresolved uncertainty Structural adequacy, population transferability, omitted temporal process, or patient heterogeneity Permissible action Withhold high-confidence individualized inference and compare plausible model explanations Reassessment trigger Alternative-model evaluation, corrected data, or external-population evidence Interpretation for individualized dosing Random effects should not absorb unresolved model failure automatically
Competing models produce materially different individual recommendations	Information currently available Multiple plausible qualified structures remain Dominant unresolved uncertainty Model-form uncertainty Permissible action Report conditional predictions or use a conservative decision rule appropriate to consequence Reassessment trigger New discriminating data or model qualification in the relevant population Interpretation for individualized dosing Model disagreement is itself decision-relevant uncertainty	Prediction is technically stable but clinical consequence is uncertain	Information currently available Model and patient data support a reproducible estimate Dominant unresolved uncertainty Link between predicted exposure/response and meaningful clinical benefit or harm Permissible action Separate predictive confidence from treatment-effect confidence Reassessment trigger Prospective outcome evidence or clinically validated decision threshold Interpretation for individualized dosing Accurate prediction does not establish clinical utility

Figure 2 extends this ledger by placing individual prediction behind successive validation gates. The central point is that more patient data can narrow uncertainty inside a chosen model while leaving model-form, population-transfer, or clinical-decision uncertainty unresolved.

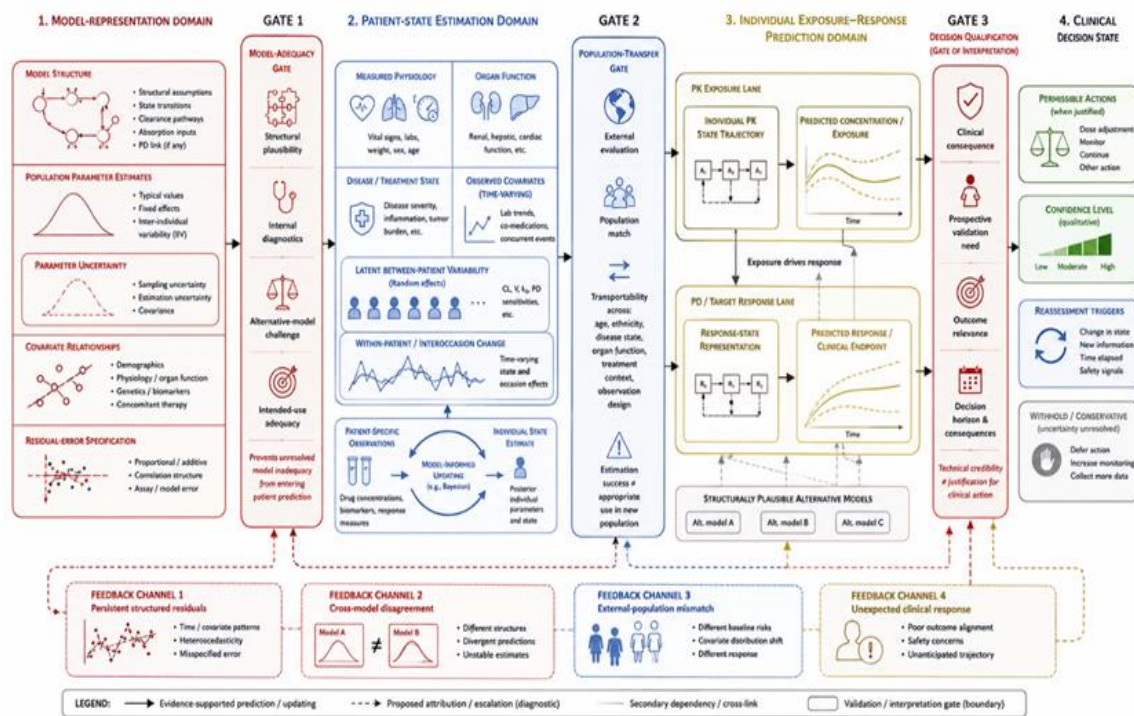


Figure 2. Cross-scale validation gates separating individual prediction confidence from decision confidence

An uncertainty-decomposition framework

The central proposal of this Perspective is an uncertainty-decomposition framework for interpreting clinical PKPD predictions. It is not a claim that every variance component can be estimated independently or that a unique decomposition exists for every dataset. Instead, it is an analytical sequence that preserves competing explanations long enough to identify the corrective action appropriate to each.

The first component is structural uncertainty: uncertainty that the mathematical representation, covariate structure, temporal assumptions, response model, or transportability domain is inadequate. Model evaluation should therefore begin from intended use and the consequence of incorrect prediction rather than from goodness-of-fit statistics alone [5]. Structural uncertainty is reduced by alternative-model challenge, mechanistic or empirical justification, external evaluation, and testing in the target population—not merely by increasing an individual random effect.

The second component is parameter uncertainty. Population parameters and variance components are estimated rather than known. Bayesian methods provide one explicit representation of that uncertainty through posterior distributions [14]. Parameter uncertainty should therefore propagate into predictions while remaining labelled as uncertainty about estimated quantities conditional on the structure. It should not be converted conceptually into patient heterogeneity merely because both increase predictive dispersion.

The third component is represented patient variability. Supported covariates, interindividual random effects, interoccasion effects, and longitudinal state changes describe differences among or within patients conditional on the selected model. Their interpretation should remain conditional on population domain, time scale, dose, organ function, disease state, treatment history, and available observations. Bayesian updating can reduce uncertainty about the individual state, but only within the assumed representation.

The fourth component is residual and observation uncertainty. Persistent residual patterns should be subjected to attribution rather than accepted immediately as irreducible noise. Data defects, measurement processes, omitted time dependence, unsupported error models, and structural misspecification remain plausible origins [24]. The decomposition therefore contains a feedback rule: unresolved residual structure moves backward toward model or data evaluation rather than forward into an expanded estimate of biological variability.

The framework's practical output is not a single total uncertainty number. It is a statement of where confidence is conditional. An individualized estimate may have low parameter uncertainty but high structural uncertainty; strong population transportability but poor patient observation; or excellent predictive reproducibility but weak evidence linking the predicted endpoint to clinical benefit. Combining those states into one interval would conceal distinctions that determine what should happen next.

Model qualification and decision thresholds

Model qualification should consequently extend beyond the fitted pharmacometric model. Software evaluations, EHR integration work, and implementation roadmaps show that model-informed dosing operates through multiple technical and clinical layers [29-31]. A model can be statistically credible yet incorrectly implemented, poorly integrated into workflow, used outside its validated population, or attached to a decision rule whose clinical consequence has not been established.

Decision thresholds therefore require a different level of evidence from prediction thresholds. A concentration or response can be predicted with technical confidence without establishing that crossing a particular value warrants a dose change. Precision-dosing frameworks have accordingly called for prospective evaluation of implementation and patient outcomes rather than assuming that individualized prediction automatically creates clinical benefit [32].

The proposed decision rule is qualitative: the amount and type of uncertainty that can be tolerated should depend on the consequence of being wrong. Low-consequence exploratory predictions may remain useful despite structural alternatives. High-consequence individualized dosing, toxicity avoidance, or treatment escalation should require stronger evidence that the structure is transported, parameters are adequately characterized, patient observations are informative, residual anomalies have been investigated, and the clinical action itself is justified. This is not an argument for universal numerical cutoffs. The approved evidence does not establish a single acceptable prediction error, variance component, external-validation criterion, or confidence probability applicable to all PKPD decisions. Qualification should instead be fit for purpose. A decision boundary should identify which uncertainty source would materially alter the action, which evidence could reduce that uncertainty, and when uncertainty remains too consequential for a confident individualized recommendation.

The methodological advantage of decomposition is therefore operational. Structural uncertainty calls for model challenge; parameter uncertainty calls for propagation or additional information; patient variability calls for characterization and updating; residual uncertainty calls for attribution; implementation uncertainty calls for technical qualification; and clinical-action uncertainty calls for outcome evidence. Treating these as one undifferentiated error term removes precisely the information needed to decide what to do next.

CONCLUSION

Clinical PKPD models can support increasingly individualized predictions, but individualized prediction becomes less interpretable when every unexplained discrepancy is treated as patient variability. Structural assumptions, uncertain parameters, represented between-patient differences, within-patient change, residual error, observation quality, software implementation, and clinical decision evidence occupy different inferential levels.

This Perspective proposes preserving those levels through an uncertainty-decomposition architecture. The framework does not assume that every source is statistically independent or uniquely identifiable. Its purpose is diagnostic: persistent disagreement should remain attributable to competing model, patient, data, and implementation explanations until evidence discriminates among them.

The central practical implication is that confidence in an individual prediction should state what it is conditional on. More patient data may reduce uncertainty about an individual state without establishing structural correctness. External validation may support transportability without proving clinical benefit. Accurate exposure prediction may still leave response or treatment-action uncertainty unresolved.

Clinical pharmacometrics therefore benefits from replacing the question “How variable is this patient?” with a more discriminating sequence: what is uncertain about the model, what is uncertain about its parameters, what variability is genuinely represented among patients, what remains unexplained in the observations, and which of those uncertainties matters for the clinical decision. That distinction offers a more defensible basis for model qualification, precision dosing, and interpretation of individual PKPD predictions.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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