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Clinical Pharmacokinetic and Pharmacodynamic Modelling for Precision Therapeutics: A Methodological Review of Identifiability, Transportability, and Decision Use

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ABSTRACT

Clinical pharmacokinetic and pharmacodynamic modelling can support precision therapeutics by connecting dose, exposure, response, patient characteristics, and uncertainty. However, a model that describes observed data adequately may still provide unreliable individual predictions or unsuitable dose recommendations when its parameters are non-identifiable, its evaluation is restricted to development data, or its assumptions do not transfer across populations and clinical settings. This methodological review examines the principal model classes used in clinical PK/PD research and evaluates how their assumptions, data requirements, identifiability, estimation procedures, validation strategies, calibration, transportability, and decision consequences affect their suitability for precision therapeutics. The proposed taxonomy distinguishes population and exposure–response models, semi-mechanistic and mechanistic models, physiologically based pharmacokinetic and systems models, Bayesian individual-prediction methods, and emerging data-adaptive or hybrid approaches. These classes are compared according to the questions they can answer rather than their mathematical complexity. Structural identifiability concerns whether model parameters are theoretically recoverable under defined observations, whereas practical identifiability concerns whether available clinical data support sufficiently precise and stable estimation. Internal diagnostics are distinguished from independent external validation, uncertainty calibration, and prospective evaluation of dose decisions. Transportability is treated as a conditional property determined by population characteristics, clinical context, measurement processes, therapeutic targets, and workflow rather than by model performance in the development dataset alone. The review argues that precision dosing requires an evidentiary chain linking interpretable model structure, stable estimation, externally evaluated prediction, calibrated uncertainty, and clinically meaningful decision consequences. Models may support therapy only within clearly defined contexts of use and should not be considered clinically ready merely because they fit data, reproduce expected simulations, or generate individualized recommendations.

Key words: *Clinical pharmacokinetics, Pharmacodynamics, PK/PD, Dose–exposure–response, Population modelling, Precision dosing*

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INTRODUCTION

Precision therapeutics seeks to match treatment intensity to the patient, disease state, therapeutic objective, and evolving response. Clinical pharmacokinetic and pharmacodynamic models can contribute by quantifying dose–

exposure–response relationships, separating population tendencies from individual variability, and updating predictions as new patient information becomes available. Nevertheless, model-informed precision dosing is not simply a computational exercise. It requires an integrated chain of model development, qualification, clinical interpretation, implementation, and continued evaluation appropriate to the intended decision [1].

This framing extends precision medicine beyond genomic stratification. Dose requirements may vary because of organ function, maturation, body composition, interacting medicines, disease progression, adherence, biomarkers, or time-varying physiological conditions. Exposure and response models can help translate such information into treatment hypotheses, but their relevance depends on whether the model represents the determinants of variability that matter for the proposed use. Precision therapeutics therefore concerns the reliability of dose-related inference and action, not merely the availability of individualized biological information [2].

Pharmacometric methods differ in their inferential targets and assumptions. Population models may estimate typical parameters and between-patient variability; PK/PD models may characterize temporal relationships between exposure and response; physiologically based models may support mechanistic extrapolation; and Bayesian or data-adaptive methods may update predictions or optimize sequential decisions. These approaches cannot be compared meaningfully through complexity alone because a method suitable for population description may be inadequate for individual forecasting, causal interpretation, extrapolation, or clinical dose selection [3].

The central problem is therefore methodological: under what conditions can a model move from plausible representation to transportable decision support? Routine implementation requires more than a published model or functioning dosing interface. Model structure, parameter information, validation, clinical targets, data turnaround, software, professional interpretation, and workflow must align with the intended use [4]. This methodological review examines those requirements through a structured comparison of model classes, identifiability, validation, transportability, uncertainty, and decision consequences. It provides an evidence-bounded synthesis rather than a clinical guideline, validated ranking, or claim that any model class is universally preferable.

Review methodology and model-class taxonomy

A structured methodological-review design was used to compare modelling approaches according to the questions they address and the evidence required to justify their use. The review questions concerned relevant method classes, distinguishing assumptions and data requirements, approaches to identifiability and estimation, standards for validation and transportability, relationships between modelling and dose decisions, and priorities for reporting and evaluation. Information was sought from peer-reviewed clinical pharmacology, pharmacometrics, systems pharmacology, therapeutic-monitoring, and quantitative-methods literature using combinations of clinical PK/PD, population modelling, mechanistic modelling, precision dosing, covariate analysis, identifiability, validation, calibration, extrapolation, uncertainty, and decision-use terminology.

Eligible articles had to contribute extractable methodological, validation, transportability, implementation, or decision-use evidence. Sources were retained when they supported a defined claim, comparison criterion, table construct, figure relationship, limitation, or research priority. Articles were excluded when they addressed an adjacent topic without direct relevance, lacked sufficient methodological detail, or would require interpretation beyond the population, model, validation context, or decision actually examined. Extraction considered model class, intended use, assumptions, data requirements, identifiability, estimation or training, internal evaluation, independent validation, calibration, transportability, decision use, and principal limitations.

Synthesis was qualitative and comparative. Models were organized into empirical population and exposure–response approaches, semi-mechanistic and mechanistic models, physiologically based and systems models, Bayesian individual-prediction approaches, and data-adaptive or hybrid methods. These categories may overlap; for example, mechanistic structures may be estimated through mixed-effects methods, while machine learning may support covariate exploration or combine predictions from pharmacometric models. The taxonomy therefore describes methodological functions rather than mutually exclusive labels, consistent with the need to interpret modelling and simulation according to their research or clinical purpose [3].

Figure 1 presents the original conceptual synthesis for taxonomy of clinical pk/pd modelling approaches, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

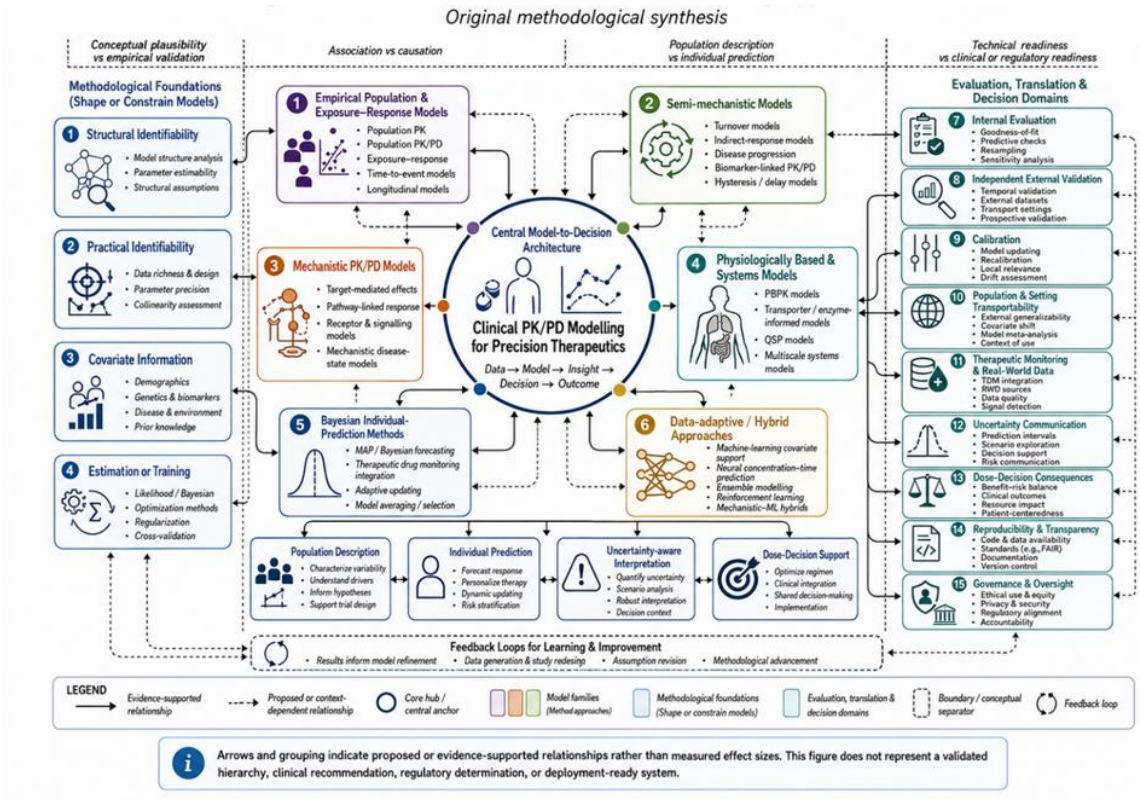

Figure 1. Taxonomy of Clinical PK/PD Modelling Approaches.

The figure is an original conceptual synthesis developed for "Clinical Pharmacokinetic and Pharmacodynamic Modelling for Precision Therapeutics: A Methodological Review of Identifiability, Transportability, and Decision Use." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Structural and practical identifiability

Identifiability determines whether the parameters or latent mechanisms invoked by a model can be distinguished using its mathematical structure and observation process. Structural identifiability asks whether unique parameter values could theoretically be recovered under ideal, noise-free observations. Practical identifiability asks whether the available sampling design, measurement precision, parameter correlations, and data volume support sufficiently stable estimation in practice [5]. The distinction is essential because a structurally identifiable model may remain weakly informed by clinical data, whereas good numerical convergence cannot demonstrate theoretical uniqueness.

Identifiability is not an intrinsic property of equations considered in isolation. It depends on model parameterization, known inputs, measured outputs, initial conditions, sampling schedule, observation error, and which parameters are fixed or estimated. Consequently, changing the biomarker, sampling window, dose design, or assumed parameter values may alter what can be learned. Sensitivity analysis can indicate which outputs respond to parameters, but sensitivity alone does not prove that correlated parameter effects can be separated [6]. Method selection should therefore follow the model and intended interpretation. Symbolic or algebraic methods can investigate theoretical uniqueness, while profile likelihoods, information-based analyses, simulation–estimation exercises, posterior distributions, and parameter-correlation diagnostics can examine practical information and stability. These approaches answer related but non-identical questions, and agreement across complementary diagnostics provides stronger support than reliance on one numerical indicator [7]. Identifiability assessment should also be repeated after meaningful changes to structure, data, constraints, or intended use.

A model may appear estimable during development yet become unstable when reused with a smaller dataset, altered sampling, different initialization, updated software, or a population providing less parameter information. Such instability should not automatically be labelled structural non-identifiability; it may instead reflect weak practical information, parameter scaling, numerical optimization, model misspecification, or incompatibility

between the reused model and new data [8]. Identifiability analysis constrains which parameters and mechanisms can be interpreted, but it cannot independently establish predictive validity, population transportability, or clinical decision benefit.

Population, mechanistic, and physiologically based models

Population pharmacokinetic and PK/PD models commonly use nonlinear mixed-effects structures to estimate typical parameter values, between-patient variability, covariate relationships, and residual unexplained error. Individual parameters or responses may then be estimated conditionally from the population distribution and patient observations. This structure is well suited to sparse and unbalanced clinical data, but conclusions depend on the chosen structural model, variability distributions, residual-error specification, covariate representation, and estimation procedure [9]. Adequate population fit does not ensure reliable prediction for every individual.

Mechanistic models represent biological or physiological processes more explicitly. Physiologically based pharmacokinetic models, for example, may combine anatomical compartments, blood flows, tissue composition, enzyme or transporter information, physicochemical properties, and in-vitro evidence. Their potential value lies in structured extrapolation to scenarios not observed directly, but credibility depends on parameter provenance, biological assumptions, verification, sensitivity analysis, and qualification for a defined context of use [10]. Physiological detail alone does not demonstrate that all parameters or mechanisms are identifiable.

Quantitative systems pharmacology and related mechanistic PK/PD models may connect drug action to pathway activity, disease progression, biomarkers, and clinical outcomes across scales. Their evaluation must account for the decision they are intended to influence and the consequences of incorrect conclusions. A model used to generate exploratory hypotheses may require a different evidentiary standard from one used to select a trial regimen or support patient-level dosing [11]. Verification, calibration, validation, and uncertainty analysis should therefore be proportional to model influence and risk rather than treated as uniform procedural requirements.

Transporter-mediated drug-interaction modelling illustrates the limitations of mechanistic extrapolation. Predictions may depend on uncertain transporter abundance, substrate specificity, tissue localization, in-vitro experimental systems, scaling relationships, and interactions among transport and metabolism. A physiologically plausible structure cannot compensate automatically for poorly informed system or drug parameters [12]. Such examples do not invalidate PBPK methodology; they show that mechanistic interpretation is conditional on the quality and relevance of component evidence.

Population and mechanistic models should therefore be regarded as complementary rather than opposing approaches. Population models can characterize variability observed in clinical data, while mechanistic models can organize prior biological knowledge and explore extrapolation. Hybrid approaches may combine these strengths, but they also inherit assumptions and failure modes from each component. Greater complexity is justified only when it improves the answer to a defined question and remains supported by identifiable parameters, relevant data, transparent evaluation, and an explicitly bounded context of use.

Covariate modelling and individual prediction

Covariate modelling seeks to explain systematic variability in pharmacokinetic or pharmacodynamic parameters through measurable patient characteristics. Its conclusions depend on the underlying random-effects structure because misspecified between-patient variability can alter apparent covariate relationships, uncertainty, and individual predictions [13].

Data-adaptive methods may help identify nonlinear candidate relationships. Explainability techniques such as SHAP values can reveal how a fitted predictor associates covariates with model output and may guide selection of functional forms [14]. These associations remain model-dependent and cannot establish causation or biological mechanism.

Covariate preselection may reduce computational burden in complex repeated-event or longitudinal models. However, screening procedures can amplify instability, multiplicity, confounding, and dependence on the sampled population [15]. Covariates should therefore be judged by predictive relevance, physiological plausibility, parameter uncertainty, and performance beyond the development data.

Neural models can reproduce concentration–time patterns without requiring the same structural assumptions as conventional pharmacometric models [16]. Their flexibility may benefit prediction in information-rich settings, but training-distribution dependence, limited mechanistic interpretability, calibration, and domain shift remain important constraints.

Individual prediction consequently requires more than adding patient variables to a population model. It depends on population relevance, observation timing, assay reliability, parameter information, residual-error assumptions, and the stability of Bayesian or data-driven updating. A selected covariate is not necessarily causal, transportable, or useful for dose modification.

Table 1 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for method classes, assumptions, data requirements, and intended uses in clinical pharmacokinetic and pharmacodynamic modelling for precision therapeutics.

Table 1. Method classes, assumptions, data requirements, and intended uses in Clinical Pharmacokinetic and Pharmacodynamic Modelling for Precision Therapeutics

Evidence domain or review construct	Review question	Eligible evidence type	Key extraction fields	Appraisal or relevance criterion	Synthesis role	Main limitation	Interpretation boundary
Population and mixed-effects modelling	How are population tendency and individual variability represented?	Methods studies and applied pharmacometric analyses	Structural model, random effects, residual error, covariates	Alignment between model structure, data, and intended prediction [9]	Defines empirical population modelling	Distributional and structural misspecification	Population fit does not ensure individual accuracy
Mechanistic and PBPK modelling	Which biological assumptions support extrapolation?	Qualification frameworks and mechanistic applications	Physiological structure, parameter provenance, sensitivity, context of use	Traceability and evidence supporting model components [10]	Defines mechanistic extrapolation	Weakly informed or correlated parameters	Biological complexity does not prove validity
Structural and practical identifiability	Which quantities can be uniquely and stably estimated?	Identifiability analyses and workflows	Inputs, outputs, parameters, sampling, uncertainty	Compatibility between parameterization and observation design [7]	Constrains interpretation of parameters	Method-dependent diagnoses	Identifiability does not establish transportability
Covariate modelling	Which patient factors explain relevant variability?	Covariate-method comparisons and case studies	Candidate variables, functional form, selection method, uncertainty	Stability, plausibility, and performance outside selection data [15]	Links population variability to prediction	Multiplicity and confounding	Statistical association is not causation
Data-adaptive prediction	Can flexible models improve individual forecasts?	Neural or machine-learning proof-of-concept studies	Training domain, features, target, calibration, interpretability	Evaluation relative to the intended prediction task [16]	Represents emerging predictive methods	Domain shift and opacity	Predictive fit does not establish clinical utility
Hybrid modelling	How can empirical, mechanistic, and data-adaptive components interact?	Integrative methodological evidence	Component roles, interfaces, updating, inherited assumptions	Explicit justification for each component	**Proposed review construct**	Compounded assumptions and failure modes	Hybrid complexity is not evidence of superiority

Internal evaluation, external validation, and calibration

Internal evaluation examines whether a model reproduces relevant features of its development data. Diagnostic plots, residual analyses, simulations, and numerical summaries provide complementary information because no single metric establishes adequacy [17]. Internal consistency cannot determine performance in a new population. External validation requires data independent of model development and analyses matched to the intended use. Population prediction, simulation behavior, Bayesian forecasting, and calibration answer different questions and should not be treated as interchangeable [18].

Independent evaluations illustrate that models developed for the same drug can differ materially when applied to new cohorts. Vancomycin models, for example, showed variable predictive performance in critically ill populations, demonstrating that pharmacological relevance alone does not ensure transportability [19].

Evaluation depth should be proportional to context of use, model influence, and the consequence of an incorrect conclusion [20]. A model used for exploration requires different evidence from one informing patient-level dosing. Credibility assessment nevertheless remains distinct from clinical validation or regulatory acceptance.

Transportability across populations and clinical settings

Transportability concerns whether model relationships remain adequate when population characteristics, disease severity, care processes, assays, sampling, concomitant treatment, or covariate distributions change. External evaluations of antibiotic models indicate that extrapolation is conditional rather than automatic [21].

Tacrolimus models developed in apparently related populations have shown inadequate performance on independent liver-transplant data [22]. Nominal similarity in drug and indication therefore cannot substitute for empirical assessment of the target population and observation process.

Bayesian updating with patient observations may improve individual forecasting, as shown in external evaluation of ciclosporin models [23]. It cannot reliably repair an unsuitable structural model, invalid covariate relationship, or prior distribution that conflicts with the target context.

Continued learning may update population parameters as clinical data accumulate [24]. Such adaptation may improve local relevance but introduces risks of drift, biased feedback, changing measurement practices, and deterioration in underrepresented subgroups. Updating therefore requires version control, monitoring, and periodic independent evaluation.

Model-informed dose selection and therapeutic monitoring

Model-informed precision dosing combines a prior population model, patient covariates, measured concentrations or biomarkers, a therapeutic target, and an actionable dosing rule [25]. Its credibility depends on every component, including assay turnaround, target validity, data timing, software implementation, and professional interpretation.

Model averaging or selection may reduce dependence on one prior model when candidate models produce different individual predictions [26]. Improved predictive performance does not by itself establish better treatment outcomes. In a multicentre randomized trial of antimicrobial dosing, implementation did not improve the primary clinical endpoint, showing that timing, targets, workflow, and downstream actions mediate value [27].

Observational implementation research has reported improved outcomes in patients receiving model-informed vancomycin dosing [28]. Such findings provide practice-relevant evidence but remain vulnerable to confounding and setting effects. Together, the evidence suggests that dosing systems should be evaluated as clinical decision interventions rather than as prediction algorithms alone.

Table 2 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for evaluation dimensions, validation strategies, and reporting requirements for clinical pharmacokinetic and pharmacodynamic modelling for precision therapeutics.

Table 2. Evaluation dimensions, validation strategies, and reporting requirements for Clinical Pharmacokinetic and Pharmacodynamic Modelling for Precision Therapeutics

Method, platform, or evidence category	Representative application	Reported strength	Validation context	Generalization concern	Contradictory evidence	Evidence gap	Review interpretation
Internal pharmacometric evaluation	Development-data diagnostics	Detects model–data inconsistency [17]	Original dataset and simulations	Optimism and reuse of development information	Adequate fit may coexist with poor external prediction	No universal adequacy threshold	Necessary but insufficient
Independent external evaluation	Population and Bayesian prediction	Tests performance in new observations [18]	Separate population or dataset	Differences in design, assay, covariates, and care	Models for the same drug may perform differently [19]	Inconsistent calibration reporting	Must match intended use

Context-of-use credibility	Empirical or mechanistic decision support	Aligns evidence burden with model influence [20]	Defined question and consequence	Context may be specified too broadly	Technical verification may be mistaken for decision validity	Limited prospective assessment	Credibility is use-specific
Transportability assessment	Extrapolation across clinical populations	Identifies domain-dependent performance [21]	New population and setting	Nominal similarity may conceal relevant shift	External failure despite related indications	Sparse evaluation across health systems	Transfer must be demonstrated
Continued learning	Local updating of population parameters	May adapt models to accumulating data [24]	Sequential clinical data	Drift, feedback bias, subgroup deterioration	Adaptation may preserve local errors	Limited prospective governance evidence	Updating requires monitoring
Prospective decision evaluation	Randomized MIPD intervention	Measures downstream clinical consequences [27]	Clinical workflow and patient outcomes	One trial may not transfer across drugs or targets	Predictive sophistication may not improve outcomes	Few adequately powered comparative trials	Decision benefit is not implied by prediction
Observational implementation	Routine-care MIPD	Provides real-world feasibility and outcome signals [28]	Implemented clinical service	Confounding and secular change	Associations may differ from randomized evidence	Limited causal attribution	Useful but not definitive

Uncertainty communication and decision consequences

Sequential dose policies may incorporate changing observations and delayed outcomes. Reinforcement learning combined with Bayesian data assimilation illustrates this possibility, but results depend on the simulated disease process, observation model, reward definition, and assumed treatment consequences [29].

Parameter confidence intervals, uncertainty in mean predictions, and prediction intervals for future observations represent different quantities [30]. Reporting them interchangeably can conceal whether uncertainty concerns parameter knowledge, expected response, unexplained variability, or a future patient measurement.

Uncertainty displays should support a concrete action, such as additional sampling, cautious dose adjustment, deferral, or clinical override. They should also distinguish uncertainty that may be reduced through additional information from uncertainty arising through misspecification or domain shift [31].

Uncertainty becomes decision-relevant only when model evaluation, independent performance, and context-of-use credibility are considered jointly [17, 18, 20]. A narrow interval from a poorly transported model may be more misleading than a visibly uncertain estimate. Decision systems should therefore communicate both predictive uncertainty and the boundary of justified use.

Comparative methodological strengths and weaknesses

Methodological strength is conditional on purpose. Population models are efficient for quantifying variability; mechanistic models may support structured extrapolation; Bayesian methods enable individual updating; and adaptive methods can represent complex prediction or sequential decisions. None is preferable independently of data, target, workflow, validation, and decision consequence [32].

Reinforcement learning reframes dosing as policy optimization but introduces dependence on reward definition, simulated states, exploration assumptions, and safety constraints [33]. Model ensembles may reduce sensitivity to selection of one model, although their performance remains limited by component relevance and may obscure the origin of failure [34].

Failure can arise from nonunique structure, inadequate information, or instability during reuse [5, 7, 8]. These mechanisms require different remedies: structural revision, improved experimental design, stronger parameter information, recalibration, or withdrawal of the intended use. Complexity should not be added merely to conceal unresolved ambiguity.

Table 3 organizes the evidence, constructs, relationships, uncertainties, and boundary conditions required for methodological strengths, failure modes, transportability, and decision-use implications.

Table 3. Methodological strengths, failure modes, transportability, and decision-use implications

Cross-study pattern or configuration	Context or boundary condition	Mechanism or explanatory factor	Observed or reported outcome	Rival explanation	Certainty or rigour concern	Implication	Research priority
Population models support sparse-data inference	Representative population and correct error structure	Hierarchical pooling	Population and individual estimates can be generated [9]	Apparent precision from restrictive assumptions	Dependence on structural specification	Evaluate individual as well as population prediction	Compare alternative variability structures
Mechanistic detail supports extrapolation conditionally	Component parameters and biology are evidenced	Physiological constraints	Simulation beyond observed settings may be possible [10]	Added detail may compensate numerically for weak information	Partial identifiability	Tie qualification to context of use	Develop observation designs for key mechanisms
Bayesian updating improves patient prediction	Prior model is relevant and observations are informative	Combination of prior and individual data	Forecasting may improve after measurements [23]	Improvement may reflect measurement density	Drug- and setting-specific evidence	Do not treat updating as structural correction	Identify conditions under which priors fail
Continued learning improves local adaptation	Stable data generation and governance	Sequential parameter updating	Population estimates may change with practice data [24]	Drift may reflect changing treatment or sampling	Limited prospective evidence	Monitor subgroup performance and version changes	Develop drift-sensitive validation
RL enables sequential optimization	Valid state, transition, and reward definitions	Policy learning over time	Simulated policies may adapt doses [29]	Benefit may arise from unrealistic simulation assumptions	Absence of clinical validation	Restrict claims to evaluated environments	Prospective safety and utility testing
Ensembles reduce single-model dependence	Component models remain relevant	Combination of predictions	Predictive robustness may improve [34]	Averaging may hide shared misspecification	Proof-of-concept evidence	Examine transparency and component failure	Validate under domain shift
Implementation does not guarantee benefit	Model output must alter timely clinical action	Workflow and target mediation	Clinical outcomes may remain unchanged [27]	Intervention intensity or endpoint may be inadequate	Limited number of randomized evaluations	Evaluate the complete decision pathway	Link predictive, process, and patient outcomes

Reporting recommendations and research gaps

Reproducibility requires more than a verbal model description. Equations, parameter values, initial conditions, data provenance, test cases, code, software dependencies, and computational settings should be sufficiently accessible to permit scrutiny and re-execution [35].

Model reuse additionally requires documentation of purpose, assumptions, version history, parameter sources, verification tests, and the domain in which performance has been examined [36]. Transparent reporting is necessary but cannot replace external validation or evidence of decision benefit.

Independent reconstruction can reveal ambiguities in data handling, code, model specification, and computational environment that conventional narrative reporting leaves unresolved [37]. Research should connect reproducibility with identifiability, calibration, domain-shift detection, subgroup transportability, and prospective decision consequences.

Figure 2 presents the original conceptual synthesis for pathway from model identifiability to transportable dose decisions, showing how the article's principal components, evidence relationships, uncertainties, and decision boundaries are connected.

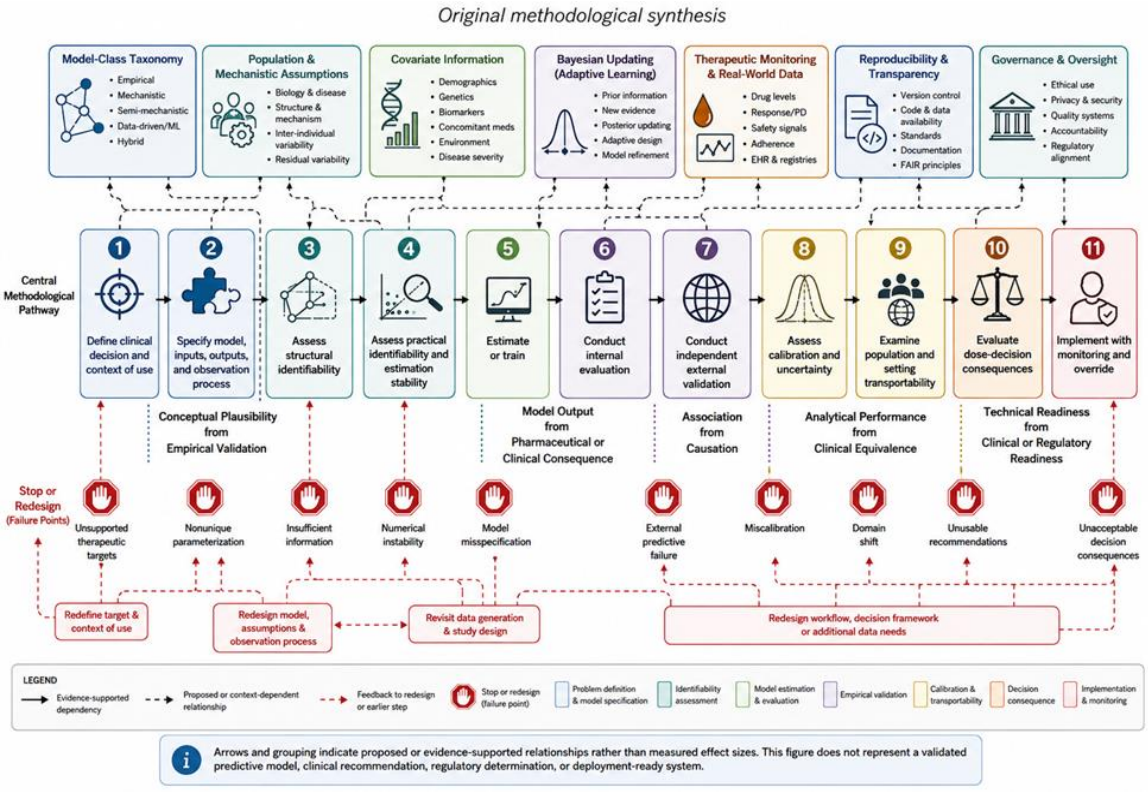

Figure 2. Pathway from Model Identifiability to Transportable Dose Decisions.

The figure is an original conceptual synthesis developed for "Clinical Pharmacokinetic and Pharmacodynamic Modelling for Precision Therapeutics: A Methodological Review of Identifiability, Transportability, and Decision Use." Arrows and grouping indicate proposed or evidence-supported relationships rather than measured effect sizes. The figure does not represent a validated predictive model, clinical recommendation, regulatory determination, or deployment-ready system.

Review limitations

The evidence spans heterogeneous drugs, populations, model classes, endpoints, sampling designs, and intended uses. Direct comparison is therefore methodological rather than quantitative, and findings from one application cannot be converted into universal performance estimates.

External-validation practices are inconsistent in data independence, diagnostic selection, Bayesian forecasting, and calibration reporting. This limits comparison among apparently similar evaluations and may favor models tested under less demanding conditions.

The literature may overrepresent successful model development, positive implementation, and technically reproducible applications. Failed models, abandoned dosing systems, negative transfer studies, and unsuccessful clinical workflows may be less visible.

The proposed taxonomy and model-to-decision pathway are interpretive syntheses. They organize evidence and expose boundaries but have not themselves been prospectively validated. This review cannot certify a method for a specific medicine, patient, population, or clinical decision.

CONCLUSION

Clinical PK/PD modelling can support precision therapeutics only when the evidentiary chain from model structure to decision consequence remains explicit. Structural plausibility, successful estimation, or internal fit cannot substitute for identifiability, independent validation, calibration, transportability, target justification, and prospective evaluation of clinical use. Population, mechanistic, Bayesian, and data-adaptive models offer complementary capabilities but also distinct assumptions and failure modes. Their value is therefore conditional on the question, data, population, workflow, and consequence of error. The principal methodological priority is not selection of a universally superior model class, but development of transparent, reproducible, externally evaluated, and uncertainty-aware approaches whose decision domain is clearly bounded.

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