



Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Model-Informed Precision Dosing Across Special Populations and Altered Physiology

Wouter De Smet^{1*}, Liesbeth Van Dam¹, Pieter Janssens²

¹Department of Model-Informed Drug Development, Faculty of Pharmaceutical Sciences, KU Leuven, Leuven, Belgium.

²Department of Precision Dosing and Special Populations, Faculty of Pharmacy, Ghent University, Ghent, Belgium.

*Email: wouter.desmet@kuleuven.be

ABSTRACT

Model-informed precision dosing (MIPD) is increasingly used to translate population pharmacokinetic, physiologically based pharmacokinetic, pharmacodynamic, biomarker, and therapeutic drug-monitoring information into patient-specific dose decisions. Its value is particularly compelling in patients whose physiology departs from that represented by conventional dosing studies, yet “special population” is an imprecise dosing construct. Childhood, ageing, pregnancy, renal or hepatic dysfunction, obesity, and critical illness alter different determinants of exposure and response, often dynamically and with drug-specific consequences. This State-of-the-Art Review examines how these sources of variability should be represented, transferred, updated, and interpreted within MIPD. We propose that population membership should be treated as a prior description of physiological state rather than a direct dose instruction. Four questions organize the synthesis: whether relevant physiology is represented, whether the model transports to the clinical state, whether individual observations can update the prior prediction, and whether the resulting recommendation improves a decision-relevant endpoint. This separation prevents model fit, exposure prediction, target attainment, and clinical benefit from being treated as interchangeable evidence. Across special populations, precision dosing is therefore best understood as a conditional inference process whose credibility depends on physiology, model validity, informative observations, and the clinical horizon over which the dose decision is made.

Keywords: Model-informed precision dosing, Special populations, Pharmacometrics, Physiologically based pharmacokinetics, Bayesian dosing, Therapeutic drug monitoring

INTRODUCTION

Model-informed precision dosing combines quantitative drug models with patient characteristics and, when available, measured drug or biomarker information to support individualized dosing. Contemporary MIPD extends beyond conventional therapeutic drug monitoring by allowing prior population knowledge, covariates, model-based predictions, and observations to contribute to a dose decision, but it requires rigorous model qualification for the intended use [1]. This distinction is especially important when physiology differs from the development population: a sophisticated prediction is not automatically a clinically useful recommendation.

Implementation also requires more than an accurate mathematical model. Clinical decision support, practical validation, workflow integration, health-economic considerations, and regulatory context are separable requirements for bringing MIPD into care [2]. Earlier assessments emphasized that large-scale evidence for clinical utility and cost-benefit remained limited despite successful local implementations [3]. More recent work

shows that pharmacogenetic information and PKPD models can be integrated into clinical decision support, while still making the resulting dose recommendation conditional on the information and infrastructure actually available [4].

The central problem addressed here is therefore not whether children, older adults, pregnant patients, patients with organ dysfunction, patients with obesity, or critically ill patients are “different.” They are. The problem is deciding which difference matters for a particular drug, whether that difference is represented in a model, whether it remains stable over the dosing horizon, and whether an observation can correct an inadequate prior estimate. We propose four linked but non-equivalent tests for MIPD across altered physiology: physiological-state representation, model transportability, individual updating, and decision utility. This is a proposed interpretive architecture, not an empirically validated universal algorithm.

Physiological sources of PKPD variability

Physiological variability enters PKPD models at several levels. In children, clearance cannot generally be represented by simple linear weight scaling because size and maturation contribute differently across development; pharmacodynamic maturation may also be relevant and is less completely characterized than pharmacokinetic maturation [5]. At the other end of life, quantitative repositories of ageing physiology show that organ size, blood flow, body composition, and other system parameters change across adulthood, while data density is uneven for some parameters and populations [6]. These examples illustrate why chronological age is often an index of physiology rather than the causal variable a model ultimately needs.

Organ dysfunction creates another representational problem. An industry evaluation of PBPK modeling in renal and hepatic impairment found generally stronger prediction for renal than hepatic impairment, with performance deteriorating in more severe hepatic dysfunction [7]. Thus, a covariate such as estimated renal function or an impairment category may be clinically convenient but may not uniquely identify the relevant pathway state for every drug. The model must represent the processes that dominate disposition in the drug and severity range of interest.

Obesity further demonstrates that body size is not a single pharmacokinetic quantity. PBPK modeling of fentanyl and methadone in children with obesity incorporated age, obesity-related physiology, and genotype to explore exposure and dosing, showing that these factors may act jointly rather than as interchangeable corrections [8]. The implication is not that every patient with obesity requires model-based dosing, but that a kilogram-based adjustment can be biologically under-specified when distribution, elimination, development, or genotype contribute differently.

We therefore propose that residual between-patient variability should not automatically be interpreted as unmeasured physiology. It can also reflect measurement error, model misspecification, incomplete covariate trajectories, adherence, or unrepresented disease dynamics. Precision dosing becomes more defensible when the model separates what is measured, what is physiologically represented, what is empirically estimated, and what remains unexplained.

Paediatric and geriatric populations

Paediatric MIPD is a natural test of this principle because both data scarcity and developmental change are prominent. Recent pharmacometric work supports PBPK and population approaches as complementary methods for translating existing information to children, provided that developmental physiology, pathway maturation, and model qualification are explicit rather than assumed [9–11]. PBPK is particularly attractive when direct clinical data are sparse, whereas population PK can efficiently estimate covariate relationships from observed paediatric data; neither approach is intrinsically superior for every question.

The clinical significance of this distinction is illustrated by disease-specific decision support. HdxSim was developed for hydroxyurea dosing in children with sickle cell anaemia and validated against clinical-trial datasets and comparator approaches. It reproduced clinically relevant exposure and maximum-tolerated-dose estimates with useful agreement, while some exposure estimates differed between software approaches [12]. This supports the feasibility of tightly specified MIPD, not transfer of the tool or its performance to unrelated drugs or diseases. Older adults present an inverse but equally heterogeneous problem. A systematic review of β -lactam pharmacokinetics in older people found renal function to be an important determinant of clearance in many studies, while evidence on pharmacodynamic target attainment and evidence-based dosing recommendations remained incomplete and heterogeneous [13]. Chronological age therefore cannot substitute automatically for renal function, frailty, body composition, comorbidity, or interacting treatment effects.

Geriatric PBPK has consequently been proposed as a way to combine ageing physiology with disease-related impairment rather than treating “elderly” as a single covariate [14]. That approach is conceptually attractive but remains dependent on the quality and representativeness of the system parameters used to construct the virtual population. Across both ends of the age spectrum, the strongest role for MIPD is not to replace direct evidence but to state explicitly how developmental or ageing information changes the prior expectation and where individual observations are needed to correct it.

Pregnancy

Pregnancy exposes the limitations of static special-population categories because physiology changes along a gestational trajectory rather than switching once from a non-pregnant to a pregnant state. Published pregnancy PBPK models demonstrate the feasibility of representing gestation-dependent physiology, while also revealing heterogeneity in model structures, drug pathways, and verification strategies. Recent dolutegravir modeling further shows how verified PBPK can supplement observed pregnancy and lactation data and explore clinically unobserved UGT1A1 phenotype scenarios [15, 16]. The critical boundary is that a simulated scenario remains a prediction even when neighboring model states have been verified.

For dosing, physiological change and dose change should not be treated as synonyms. A model may predict altered exposure while still supporting an unchanged regimen for the endpoint and drug under consideration [16]. Conversely, an apparently adequate prediction at one gestational state should not simply be carried forward when the model represents time-varying physiology. The dose decision is therefore indexed to both gestational state and decision horizon.

We propose a pregnancy-specific inference sequence in which the clinician first identifies whether the relevant maternal physiology and drug pathway are represented, then asks whether the model has been verified in a sufficiently similar gestational and clinical context, and only then considers whether observed concentrations or other patient-specific information should update the prediction. Maternal, fetal, neonatal, and lactational predictions must remain analytically distinct when their evidentiary support differs.

The design-space implications are easier to compare simultaneously than sequentially in prose, particularly because the same physiological trajectory can justify observation, model reassessment, or no dose change depending on the drug-specific endpoint.

Table 1. Gestation-Dependent Dose-Adaptation Design Space Under Sparse and Time-Varying Evidence

Dose-adaptation decision	Pregnancy inference situation	Temporal feedback	Evolving covariate state	Model assumption under test	Dominant uncertainty	Decision endpoint
Preserve the current regimen	Predicted exposure changes but remains compatible with the drug-specific therapeutic objective	Reassess as gestational state changes	Maternal state remains within represented model space	Verified model remains applicable across the decision interval	Unmeasured individual deviation from the virtual population	Continued regimen without assuming physiological invariance
Re-evaluate before changing dose	Physiological trajectory has moved beyond the state directly supported by observations	New clinical or concentration information should shorten the inference lag	Gestational descriptors have changed since the prior prediction	Transport between gestational states is adequate	Extrapolation beyond verified state	Updated prediction before dose alteration
Use patient observation to challenge the prior	Measured exposure is discordant with model expectation	Observation provides patient-specific feedback	Covariates alone do not explain the discrepancy	Measurement and model structure are sufficiently credible for comparison	Sampling, adherence, measurement, or structural-model error	Individualized reassessment rather than automatic model acceptance
Explore an unobserved phenotype only as a scenario	Genotype or phenotype combination is not represented directly in clinical observations	No empirical feedback exists for the exact state	Genotype and gestation may vary jointly	Pathway contribution is sufficiently represented for simulation	Unverified phenotype transfer	Scenario analysis rather than a stand-alone dosing mandate

Keep maternal and offspring inference separate	Maternal exposure prediction is supported more strongly than downstream transfer predictions	Evidence may update each biological level at different times	Maternal and offspring states are not interchangeable	Cross-compartment transfer is adequately represented	Sparse downstream observations	Level-specific interpretation rather than one composite pregnancy dose
--	--	--	---	--	--------------------------------	--

Note: The decision categories are proposed synthesis derived from the pregnancy evidence discussed in the text. They are not validated scoring rules and do not specify numerical dose thresholds.

The same reasoning is represented in **Figure 1** as a longitudinal state-space in which gestational physiology, drug disposition, observation, and dosing decisions remain connected without erasing the boundary between measured evidence and extrapolation.

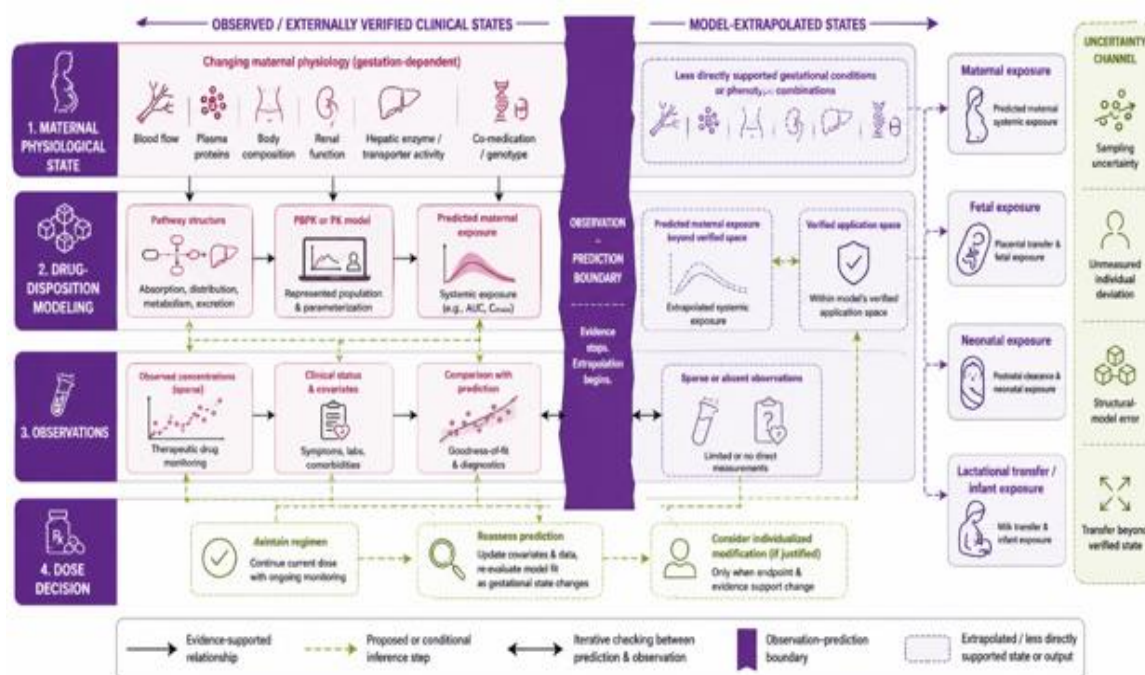


Figure 1. Gestational State Updating Across the Observation–Prediction Boundary in Precision Dosing

Renal and hepatic dysfunction

Renal and hepatic dysfunction illustrate why routinely recorded organ-function categories can be useful covariates yet incomplete mechanistic descriptors. For renally secreted drugs, chronic kidney disease may alter transporter-mediated secretion in ways not captured by glomerular filtration alone. Analysis of OAT1/3 substrates suggested that severe kidney disease can reduce secretory activity beyond a simple proportional reduction with glomerular filtration, making pathway-aware modeling relevant for suitable substrates [17]. This should not be generalized to every renally cleared drug because filtration, secretion, reabsorption, metabolism, protein binding, and nonrenal clearance contribute in drug-specific proportions.

Hepatic impairment is still more structurally challenging when uptake, metabolism, biliary handling, and sinusoidal efflux contribute jointly. Mechanistic modeling of OATP substrates showed that the accuracy and direction of hepatic-impairment predictions depend on the relative contributions of uptake and CYP3A-mediated metabolism, with underprediction remaining for some dual OATP/CYP3A substrates [18]. A single impairment category can therefore conceal multiple mechanistic states that produce similar clinical labels.

Direct clinical pharmacokinetic data remain essential for anchoring these models. In a single-dose study of milvexian, renal impairment increased overall exposure while peak concentration remained comparatively similar [19]. That pattern demonstrates why “exposure change” itself requires specification: area under the concentration–time curve, peak concentration, trough concentration, and pharmacodynamic response are not interchangeable endpoints. For precision dosing, organ dysfunction should therefore modify the prior prediction only to the extent justified by the drug’s elimination pathways, impairment severity, available observations, and dosing horizon.

Obesity and body-composition extremes

Obesity challenges dose scaling because total body weight can encode different mixtures of lean mass, adipose tissue, organ size, blood flow, and developmental state. A population analysis of midazolam found higher clearance in obese adolescents than in morbidly obese adults, demonstrating that obesity and age cannot be collapsed into a single total-body-weight relationship for a CYP3A substrate [20]. This does not establish a universal alternative size descriptor; rather, it shows that the clinically relevant descriptor is model- and drug-dependent.

PBPK offers a way to test interacting hypotheses when sufficient physiological and pathway information is available. For pantoprazole in children, modeling incorporated obesity and CYP2C19 variation and compared alternative dosing strategies against an adult exposure reference, with weight-tiered dosing giving the most favorable simulated exposure distribution [21]. The endpoint was simulated exposure relative to a reference range, not demonstrated improvement in symptoms or safety. Accordingly, body-composition modeling should be interpreted as support for a dosing hypothesis whose clinical meaning still depends on the exposure–response relationship and the population in which it is applied.

Critical illness

Critical illness is a stress test for the assumption that a model-qualified prior remains useful over the next dosing interval. Patient state may evolve on a timescale comparable with therapeutic decision-making, while a model may have been developed in patients whose covariate distributions or clinical trajectories differ from the patient now being treated. The central question is therefore temporal: whether physiology, observations, and model assumptions remain sufficiently aligned for the next decision.

The strongest caution comes from clinical-outcome evidence. In a multicentre randomized trial of model-informed dosing of β -lactam antibiotics and ciprofloxacin in critically ill patients, MIPD did not significantly improve ICU length of stay or the reported secondary outcomes [22]. This result does not establish that MIPD is ineffective in all critical-care settings; it establishes that technically individualized dosing cannot be assumed to produce patient-level benefit merely because the dose is model informed.

External model evaluation makes the complementary methodological point. Across multiple published piperacillin models in critically ill adults, predictive performance varied substantially, while incorporation of measured concentrations through Bayesian forecasting generally improved prediction [23]. Improvement after updating does not make the prior model irrelevant: structural misspecification, transfer to a different clinical state, or observations with limited information can still constrain the individualized recommendation.

The resulting boundaries are more informative when organized as patient-state scenarios than as generic advantages and disadvantages, because each scenario identifies both what can be observed and what remains inferential.

Table 2. Boundary Conditions for Model-Guided Antibiotic Dose Adaptation During Rapid Physiological Change in Critical Illness

Patient-variability scenario	Covariate trajectory and boundary	Model assumption requiring scrutiny	Main uncertainty	What is observable now	Decision-relevant endpoint
Current state remains close to the model's validated ICU population	Clinically important covariates remain sufficiently stable over the immediate dosing horizon	External transportability is adequate for the drug and setting	Residual individual variability	Recent covariates and, when available, concentrations	Model-guided next-dose estimate with explicit uncertainty
Physiology is changing faster than model input is refreshed	Recorded covariates lag behind the state affecting exposure	A static covariate snapshot remains representative	Temporal mismatch	A new clinical state may be apparent before its PK consequence is fully observed	Reassessment rather than automatic continuation of the prior recommendation
A priori prediction conflicts with	Individual data challenge the population expectation	The selected population model remains an adequate prior	Structural misspecification versus patient-	Concentration–time observations	Bayesian updating may improve prediction without

measured concentrations		specific deviation		removing model-selection concern	
Exposure appears adequate while clinical benefit remains uncertain	Pharmacokinetic success and patient response occupy different evidentiary levels	Target attainment is an adequate surrogate for benefit	Endpoint validity	Exposure is more directly observable than clinical utility	No inference of outcome superiority from exposure adequacy alone
Observations are sparse or poorly timed	Feedback contains limited information about the evolving state	Available samples identify the patient-specific parameters required for dosing	Identifiability and measurement timing	Partial concentration information	Qualified uncertainty or acquisition of more informative data before strong individualization

Note: The boundary scenarios are a proposed synthesis of the critical-illness evidence. They are not a validated triage score and do not imply a universal sampling schedule, exposure target, or dose threshold.

PBPK and population PK approaches

PBPK and population PK models address overlapping but distinct inference problems. PBPK can encode system physiology, pathway contributions, and anticipated changes in organ function, maturation, pregnancy, or body composition, whereas population PK estimates variability and covariate relationships from observed concentration–time data. For MIPD, however, the clinically decisive question is not which model class is intrinsically preferable, but whether the selected model is qualified for the patient state, drug, endpoint, and decision horizon. Model-selection tutorials, model-ensembling studies, and tacrolimus benchmarking consistently show that model choice, external validation, covariate structure, and software implementation can materially alter predicted dosing outputs [24–26].

External transportability therefore deserves greater weight than apparent fit within a development dataset. A model can describe its source population well yet become unreliable when disease severity, covariate distributions, concomitant treatment, assay conditions, or sampling schedules change. The piperacillin evaluation in critically ill adults illustrates that Bayesian observations may improve forecasting while substantial differences among candidate prior models remain [23]. Model updating should consequently be understood as conditional correction of an informative prior rather than immunity from structural misspecification.

We propose an exception-first model-selection logic: before accepting a dose recommendation, identify the principal way in which the model could be wrong for the current physiological state, seek an observable signature of that failure, and determine whether available data can discriminate patient-specific deviation from model inadequacy. **Table 3** operationalizes this proposed triage without assigning numerical scores or universal acceptability thresholds.

Table 3. Failure-Mode Triage for Translating PBPK and Population PK Predictions into Individual Dose Decisions

Misleading modeling pattern	Classification basis	Dose consequence if ignored	Observable monitoring signal	Corrective validation test	Residual decision consequence
Development–population fit is mistaken for transportability	Patient physiology or covariate distribution differs from the model-development state	Dose may be shifted on the basis of an inapplicable prior	Systematic prediction–observation discordance after transfer	External evaluation in the intended population and clinical setting	Restrict model use if transport remains uncertain
A plausible mechanistic structure is treated as sufficient qualification	PBPK pathways are biologically credible but incompletely verified for the drug or impairment state	Mechanistic plausibility may be converted prematurely into a dose adjustment	Exposure differs from the expected pathway-driven pattern	Compare predictions with independent clinical PK data across relevant states	Preserve mechanistic interpretation as conditional
A strong population model is assumed to	Population-level variability is well described but	Apparent precision exceeds the information	Wide or unstable individual	Examine predictive diagnostics and	Maintain explicit

identify the individual patient	individual information remains sparse	carried by the patient data	posterior prediction	information contributed by new samples	individualized uncertainty
Bayesian updating masks an unsuitable prior	Measured concentrations improve local prediction while the prior model remains structurally weak	A revised dose may appear reliable despite persistent model bias	Improvement depends strongly on sample number or timing	Compare alternative qualified priors and external prediction performance	Updating cannot substitute for model selection
Target attainment is treated as clinical effectiveness	Model predicts exposure within a prespecified target	Dose recommendation is interpreted as proven patient benefit	Exposure objective is met without corresponding outcome evidence	Validate the exposure–response link and clinically relevant endpoint	Keep pharmacometric success separate from outcome superiority

Note: The failure modes and decision consequences are proposed synthesis. They are not a validated scoring system, and the table does not define universal model-performance or dose-adjustment thresholds.

The distinction among prior model, patient observation, posterior prediction, and clinical endpoint is central enough to require a second visual representation. **Figure 2** therefore separates model construction from individual updating and places explicit validation gates between population prediction, patient-specific inference, and clinical action.

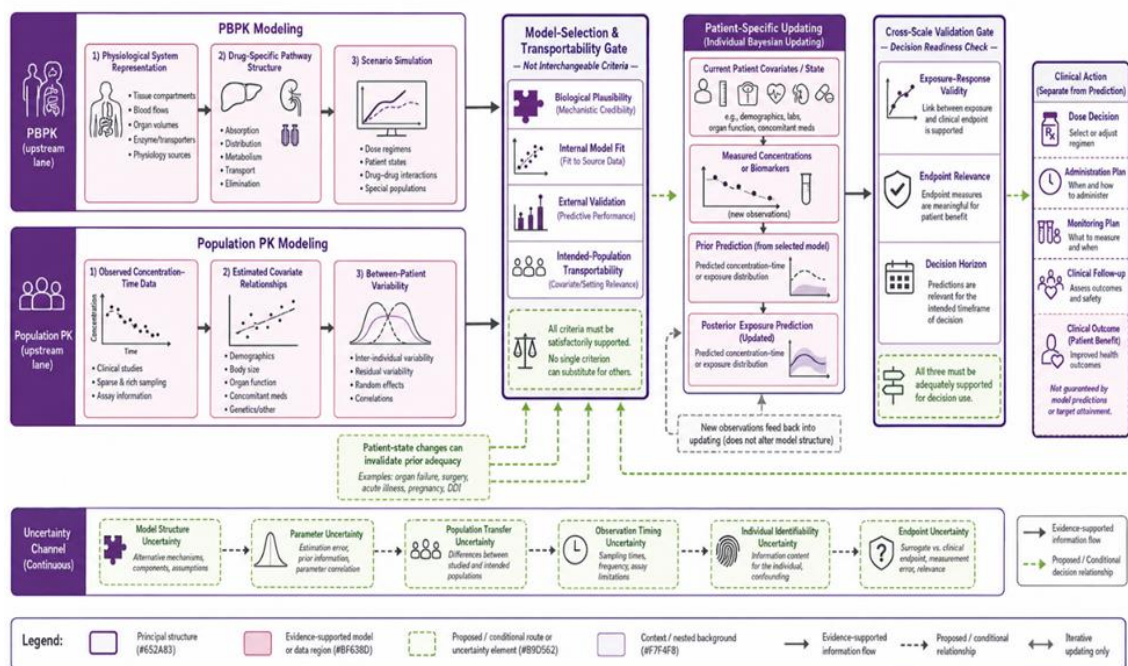


Figure 2. Validation Gates That Prevent Model Updating from Becoming Unqualified Dose Certainty

Bayesian updating and therapeutic drug monitoring

Therapeutic drug monitoring becomes model informed when measured concentrations are interpreted through a population prior rather than against a concentration threshold alone. In antibiotic therapy, Bayesian MIPD can use sparse observations, patient covariates, and prior PK information to estimate individualized exposure and support subsequent dosing [27]. Its principal advantage is therefore not simply more measurement but more structured use of the information contained in each measurement.

That advantage is conditional. Bedside MIPD depends on adequate predictive performance, appropriate data capture, and recognition of model limitations [28]. Sample timing, assay quality, adherence, rapidly changing physiology, and the choice of prior model determine how much information a concentration contributes. A precise posterior estimate can still be misleading if the prior model is poorly transported or the observations do not identify the patient-specific parameters relevant to the next dose.

We therefore propose that Bayesian updating be treated as an evidence transition rather than a validation endpoint. The prior prediction becomes more patient specific when informative observations are added, but the clinician must still ask whether the resulting exposure estimate is linked adequately to the intended pharmacodynamic or clinical objective.

Clinical implementation

Clinical implementation converts a quantitative prediction into a sociotechnical intervention. Evaluation of MIPD software has shown substantial variation in validation, functionality, electronic-health-record integration, security, and user support, indicating that model quality alone does not determine implementation readiness [29]. A clinically useful system must preserve model provenance, patient-state inputs, observation timing, uncertainty, and the rationale for a recommendation in a form that can be acted upon safely.

Recent assessments of precision dosing identify continued challenges in biomarker development, clinical trials, implementation, regulatory pathways, and health-system adoption [30]. These constraints argue against treating implementation as a binary condition. We propose instead that readiness be judged separately at model, data, workflow, endpoint, and governance levels.

Decision support can still be useful before broad outcome superiority is established. A machine-learning dosing tool for levothyroxine improved simulated starting-dose selection in a large primary-care dataset and clinician simulation, but it was not a prospective demonstration of improved patient outcomes [31]. The same distinction applies to disease-specific tools such as HdxSim: successful prediction or simulated decision improvement should support implementation research, not be inflated into universal effectiveness.

Evidence gaps

The most important evidence gap is the distance between prediction and consequence. Better model fit, lower concentration-prediction error, more frequent exposure-target attainment, and a different prescribed dose are increasingly measurable outcomes, yet none is automatically equivalent to improved symptoms, toxicity, length of stay, or survival. The null critical-care trial result makes that separation empirically consequential.

A second gap concerns transportability across dynamic physiology. External validation is often performed at the population level, whereas the clinical question is whether a model remains informative for a particular patient whose renal function, inflammatory state, body composition, pregnancy state, or treatment context may be changing. Prospective studies should therefore prespecify the physiological state represented, the model version, observation schedule, updating method, exposure–response target, and clinical decision horizon.

Third, MIPD needs clearer failure reporting. Studies should report when a priori prediction fails, whether Bayesian updating rescues prediction, whether an alternative model performs differently, and whether improved exposure prediction changes a clinically meaningful endpoint. Negative and context-dependent results are especially valuable because they identify where model-based individualization should stop rather than merely where it can be applied.

Finally, implementation research requires version control, reproducible model qualification, interoperable data capture, transparent uncertainty communication, and health-economic evaluation. Without these layers, technically sophisticated models may remain difficult to audit or safely transfer between institutions.

CONCLUSION

Model-informed precision dosing across altered physiology is best treated as a conditional inference process rather than a catalogue of special-population dose adjustments. Childhood, ageing, pregnancy, organ dysfunction, obesity, and critical illness change different determinants of exposure and response, often on different timescales. The proposed synthesis separates four questions: whether relevant physiology is represented, whether the model transports to the current patient state, whether individual observations meaningfully update the prior prediction, and whether the resulting recommendation improves a decision-relevant endpoint. This separation prevents physiological plausibility, predictive performance, target attainment, and clinical benefit from being treated as equivalent evidence. The next advance in precision dosing will therefore depend not only on more models, but on sharper validation boundaries, informative patient updating, explicit uncertainty, and prospective tests of whether better pharmacometric inference produces better clinical decisions.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Minichmayr IK, Dreesen E, Centanni M, Wang Z, Hoffert Y, Friberg LE, et al. Model-informed precision dosing: State of the art and future perspectives. *Adv Drug Deliv Rev.* 2024;215:115421. doi:10.1016/j.addr.2024.115421
2. Darwich AS, Polasek TM, Aronson JK, Ogungbenro K, Wright DFB, Achour B, et al. Model-informed precision dosing: Background, requirements, validation, implementation, and forward trajectory of individualizing drug therapy. *Annu Rev Pharmacol Toxicol.* 2021;61:225-45. doi:10.1146/annurev-pharmtox-033020-113257
3. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny JL, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther.* 2017;101(5):646-56. doi:10.1002/cpt.659
4. Mizuno T, Dong M, Taylor ZL, Ramsey LB, Vinks AA. Clinical implementation of pharmacogenetics and model-informed precision dosing to improve patient care. *Br J Clin Pharmacol.* 2022;88(4):1418-26. doi:10.1111/bcp.14426
5. Germovsek E, Barker CIS, Sharland M, Standing JF. Pharmacokinetic-pharmacodynamic modeling in pediatric drug development, and the importance of standardized scaling of clearance. *Clin Pharmacokinet.* 2019;58(1):39-52. doi:10.1007/s40262-018-0659-0
6. Stader F, Siccardi M, Battegay M, Kinvig H, Penny MA, Marzolini C. Repository describing an aging population to inform physiologically based pharmacokinetic models considering anatomical, physiological, and biological age-dependent changes. *Clin Pharmacokinet.* 2019;58(4):483-501. doi:10.1007/s40262-018-0709-7
7. Heimbach T, Chen Y, Chen J, Dixit V, Parrott N, Peters SA, et al. Physiologically-based pharmacokinetic modeling in renal and hepatic impairment populations: A pharmaceutical industry perspective. *Clin Pharmacol Ther.* 2021;110(2):297-310. doi:10.1002/cpt.2125
8. Gerhart JG, Carreño FO, Ford JL, Edginton AN, Perrin EM, Watt KM, et al. Use of physiologically-based pharmacokinetic modeling to inform dosing of the opioid analgesics fentanyl and methadone in children with obesity. *CPT Pharmacometrics Syst Pharmacol.* 2022;11(6):778-91. doi:10.1002/psp4.12793
9. Freriksen JJM, van der Heijden JEM, de Hoop-Sommen MA, Greupink R, de Wildt SN. Physiologically based pharmacokinetic (PBPK) model-informed dosing guidelines for pediatric clinical care: A pragmatic approach for a special population. *Paediatr Drugs.* 2023;25(1):5-11. doi:10.1007/s40272-022-00535-w
10. Small BG, Johnson TN, Rowland Yeo K. Another step toward qualification of pediatric physiologically based pharmacokinetic models to facilitate inclusivity and diversity in pediatric clinical studies. *Clin Pharmacol Ther.* 2023;113(3):735-45. doi:10.1002/cpt.2777
11. Meesters K, Balbas-Martinez V, Allegaert K, Downes KJ, Michelet R. Personalized dosing of medicines for children: A primer on pediatric pharmacometrics for clinicians. *Paediatr Drugs.* 2024;26(4):365-79. doi:10.1007/s40272-024-00633-x
12. Power-Hays A, Dong M, Punt N, Mizuno T, Smart LR, Vinks AA, et al. Rationale, development, and validation of HdxSim, a clinical decision support tool for model-informed precision dosing of hydroxyurea for children with sickle cell anemia. *Clin Pharmacol Ther.* 2024;116(3):670-7. doi:10.1002/cpt.3119
13. Vervaecke J, De Clercq A, De Paepe P, Petrovic M, Desmet T, De Cock PA. Pharmacokinetics and target attainment of β -lactam antibiotics in older people: A systematic review of current literature. *Clin Pharmacokinet.* 2023;62(1):1-43. doi:10.1007/s40262-022-01196-1
14. Qian L, Wang Z, Paine MF, Chan ECY, Zhou Z. Application of physiologically-based pharmacokinetic modeling to inform dosing decisions for geriatric patients. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(12):2031-5. doi:10.1002/psp4.13241
15. Dallmann A, Pfister M, van den Anker J, Eissing T. Physiologically based pharmacokinetic modeling in pregnancy: A systematic review of published models. *Clin Pharmacol Ther.* 2018;104(6):1110-24. doi:10.1002/cpt.1084

16. Ning J, Pansari A, Rowland Yeo K, Heikkinen AT, Waitt C, Almond LM. Using PBPK modeling to supplement clinical data and support the safe and effective use of dolutegravir in pregnant and lactating women. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(11):1924-38. doi:10.1002/psp4.13251
17. Tan SPF, Scotcher D, Rostami-Hodjegan A, Galetin A. Effect of chronic kidney disease on the renal secretion via organic anion transporters 1/3: Implications for physiologically-based pharmacokinetic modeling and dose adjustment. *Clin Pharmacol Ther.* 2022;112(3):643-52. doi:10.1002/cpt.2642
18. Storelli F, Ladumor MK, Liang X, Lai Y, Chothe PP, Enogieru OJ, et al. Toward improved predictions of pharmacokinetics of transported drugs in hepatic impairment: Insights from the extended clearance model. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(1):118-31. doi:10.1002/psp4.13062
19. Perera V, Abelian G, Li D, Wang Z, Zhang L, Lubin S, et al. Single-dose pharmacokinetics of milvexian in participants with normal renal function and participants with moderate or severe renal impairment. *Clin Pharmacokinet.* 2022;61(10):1405-16. doi:10.1007/s40262-022-01150-1
20. van Rongen A, Brill MJE, Vaughns JD, Väitalo PAJ, van Dongen EPA, van Ramshorst B, et al. Higher midazolam clearance in obese adolescents compared with morbidly obese adults. *Clin Pharmacokinet.* 2018;57(5):601-11. doi:10.1007/s40262-017-0579-4
21. Thompson EJ, Jeong A, Helfer VE, Shakhnovich V, Edginton AN, Balevic SJ, et al. Physiologically-based pharmacokinetic modeling of pantoprazole to evaluate the role of CYP2C19 genetic variation and obesity in the pediatric population. *CPT Pharmacometrics Syst Pharmacol.* 2024;13(8):1394-408. doi:10.1002/psp4.13167
22. Ewoldt TMJ, Abdulla A, Rietdijk WJR, Muller AE, de Winter BCM, Hunfeld NGM, et al. Model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin in critically ill patients: A multicentre randomised clinical trial. *Intensive Care Med.* 2022;48(12):1760-71. doi:10.1007/s00134-022-06921-9
23. Greppmair S, Brinkmann A, Roehr A, Frey O, Hagel S, Dorn C, et al. Towards model-informed precision dosing of piperacillin: Multicenter systematic external evaluation of pharmacokinetic models in critically ill adults with a focus on Bayesian forecasting. *Intensive Care Med.* 2023;49(8):966-76. doi:10.1007/s00134-023-07154-0
24. Taylor ZL, Poweleit EA, Paice K, Somers KM, Pavia K, Vinks AA, et al. Tutorial on model selection and validation of model input into precision dosing software for model-informed precision dosing. *CPT Pharmacometrics Syst Pharmacol.* 2023;12(12):1827-45. doi:10.1002/psp4.13056
25. Agema BC, Kocher T, Öztürk AB, Giraud EL, van Erp NP, de Winter BCM, et al. Selecting the best pharmacokinetic models for a priori model-informed precision dosing with model ensembling. *Clin Pharmacokinet.* 2024;63(10):1449-61. doi:10.1007/s40262-024-01425-9
26. Hoffert Y, Dia N, Vanuytsel T, Vos R, Kuypers D, Van Cleemput J, et al. Model-informed precision dosing of tacrolimus: A systematic review of population pharmacokinetic models and a benchmark study of software tools. *Clin Pharmacokinet.* 2024;63(10):1407-21. doi:10.1007/s40262-024-01414-y
27. Wicha SG, Mårtson AG, Nielsen EI, Koch BCP, Friberg LE, Alfenaar JWC, et al. From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clin Pharmacol Ther.* 2021;109(4):928-41. doi:10.1002/cpt.2202
28. Keizer RJ, Ter Heine R, Frymoyer A, Lesko LJ, Mangat R, Goswami S. Model-informed precision dosing at the bedside: Scientific challenges and opportunities. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(12):785-7. doi:10.1002/psp4.12353
29. Kantasiripitak W, Van Daele R, Gijzen M, Ferrante M, Spriet I, Dreesen E. Software tools for model-informed precision dosing: How well do they satisfy the needs? *Front Pharmacol.* 2020;11:620. doi:10.3389/fphar.2020.00620
30. Minichmayr IK, Mizuno T, Goswami S, Peck RW, Polasek TM; American Society of Clinical Pharmacology and Therapeutics Precision Dosing Community. Recent advances addressing the challenges of precision dosing. *Clin Pharmacol Ther.* 2024;116(3):527-30. doi:10.1002/cpt.3365
31. Janssen Daalen JM, Doesburg D, Hunik L, Kessel R, Herngreen T, Knol D, et al. Model-informed precision dosing using machine learning for levothyroxine in general practice: Development, validation and clinical simulation trial. *Clin Pharmacol Ther.* 2024;116(3):824-33. doi:10.1002/cpt.3293