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Where Model-Informed Precision Dosing Changes Patient Care—and Where It Remains a Technical Exercise: A Global Evidence-Mapping Review of Implementation, Equity, and Outcomes, 2017–2025

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ABSTRACT

Model-informed precision dosing (MIPD) integrates pharmacometric models with patient-specific information to individualize treatment. Increasing availability of Bayesian dosing software has made bedside use technically feasible, but model validation, clinical implementation, pharmacokinetic target attainment, and improvement in patient outcomes represent different evidentiary levels. This evidence-mapping review examined where MIPD progressed into real clinical decisions during 2017–2025 and where evidence remained primarily technical. Literature searches used PubMed-indexed records, journal and publisher sources, targeted citation chaining, and iterative searches covering MIPD, Bayesian dosing, therapeutic drug monitoring, software, clinical decision support, implementation, access, and outcomes. The evidence-development search identified 66 candidate records. After removal of 20 duplicates, 46 records were screened; 11 were excluded at title/abstract screening. Thirty-five full-text reports were assessed and 11 were excluded, leaving 24 evidence units in the map. Evidence was coded by drug, population, geography, clinical decision use, implementation maturity, access requirements, and outcome level. Technical validation was kept separate from enacted patient care. Clinical implementation was concentrated in antimicrobial therapy, transplantation, hydroxyurea, and selected biologic applications, predominantly in specialist services in the United States and Western Europe, with additional pediatric antimicrobial implementation in Mexico. EHR integration, therapeutic-drug-monitoring infrastructure, model qualification, accessible software, trained personnel, and defined workflow ownership influenced implementation. Improvements in exposure or target attainment were more frequent than improvements in safety, efficacy, healthcare utilization, or survival. Randomized critical-care antibiotic evaluations supplied important null evidence, whereas selected transplant and hydroxyurea applications demonstrated stronger patient-facing consequences. MIPD changes patient care when patient-specific model output reaches an actionable treatment decision and is enacted within a functioning clinical service. Evidence from 2017–2025 demonstrates such implementation for selected therapies but does not justify treating technical model performance or pharmacokinetic target attainment as universal evidence of clinical benefit. Implementation capacity, transportability, infrastructure, and patient-outcome evaluation remain central constraints on broader adoption.

Keywords: Model-informed precision dosing (MIPD), Bayesian dosing, Clinical implementation, Therapeutic drug monitoring, Patient outcomes, Health equity

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Introduction

Model-informed precision dosing combines quantitative models with individual patient information to estimate drug exposure or response and support dose selection. Contemporary MIPD encompasses population pharmacokinetic and pharmacokinetic/pharmacodynamic models, Bayesian updating, biomarkers, clinical

measurements, and decision-support technologies. Recent syntheses describe substantial progress in the technical components of individualized dosing while continuing to identify implementation and outcome evaluation as major unresolved tasks [1–3].

The distinction between technical and clinical evidence is fundamental. A model may predict concentrations accurately in an external population without ever influencing a patient's treatment [4]. A software platform may produce individualized dosing recommendations while remaining outside normal clinical workflow [5]. Pharmacogenetic or other patient information can further contribute to individualized decisions, meaning that the operational intervention is often a clinical service rather than a model alone [6]. Model selection and validation must consequently be matched to the population and intended dosing task before prospective use [7].

Available software has widened the opportunity for clinical translation. Reviews identify numerous platforms capable of Bayesian estimation and individualized regimen prediction, but these tools differ in availability, model libraries, data handling, interoperability, regulation, and clinical functionality [8]. Antimicrobial dosing programs show similar heterogeneity, including substantial differences in EHR integration and the ability to use measured concentrations [9]. Software availability therefore describes technical opportunity rather than the maturity of implementation.

This review asks a narrower question than a conventional overview of pharmacometric methods: where did MIPD actually change patient care during 2017–2025, and where did evidence stop at technical capability? Evidence is mapped by decision use, workflow integration, population, geography, implementation maturity, equity and access requirements, and outcomes. A clinical implementation requires model-derived information to contribute to treatment or monitoring of an actual patient. Retrospective validation, simulation, and software testing remain relevant to readiness but are not classified as equivalent to enacted clinical dosing.

A second distinction separates pharmacokinetic success from patient benefit. Improving exposure can be clinically important, particularly for narrow-therapeutic-index drugs, but downstream effects depend on the validity of the exposure target, treatment timing, disease state, comparator care, pharmacodynamic variability, and other determinants of outcome. The review therefore preserves exposure attainment, process outcomes, safety, efficacy, healthcare use, economic consequences, and patient outcomes as separate evidence levels.

Materials and Methods

Review design and operational definition of implementation

An evidence-mapping review was undertaken for literature published from 2017 through 2025. The reporting approach was informed by principles of transparent scoping-review reporting [10].

Evidence was assigned to clinically interpretable implementation categories. Technical validation or simulation described evaluation of a model, algorithm, or dosing system without prospective enactment of its output. Patient-specific clinical decision support required generation of individualized dosing information for clinical interpretation. Enacted dosing required evidence that model-derived information changed a dose, interval, treatment plan, or monitoring decision in real patients. Routine workflow implementation required repeated operational use within an established service. Patient-facing outcome evaluation required evaluation extending beyond prediction itself, including safety, efficacy, utilization, patient outcomes, or economic consequences.

These categories describe different forms of evidence and are not intended as an obligatory sequential pathway. A technically sophisticated application can remain pre-implementation, whereas a comparatively simple validated Bayesian system can become clinically consequential when embedded in a reliable dosing service.

Search, eligibility, screening, and evidence-unit handling

Iterative literature searches combined terms for *model-informed precision dosing*, *model informed precision dosing*, *precision dosing*, *Bayesian dosing*, *therapeutic drug monitoring*, *clinical decision support*, *software*, *implementation*, *clinical practice*, *patient outcome*, *safety*, *efficacy*, *cost*, and relevant therapeutic areas. Searches used PubMed-indexed records, publisher and journal records, and citation chaining from relevant reviews and implementation studies.

Eligible reports were published from 2017 through 2025 and addressed at least one mapped dimension: model or software evaluation relevant to individualized dosing, patient-specific clinical decision support, enacted dosing or monitoring, routine workflow implementation, implementation or access requirements, or dosing, pharmacokinetic, clinical, utilization, or economic outcomes. Title/abstract screening preceded full-text

assessment. Reports were excluded when they fell outside the publication window, did not address the defined implementation, decision-use, or outcome question, or did not provide a distinct evidence function for the map.

The search process identified 66 candidate records before deduplication. Twenty duplicate records generated through overlapping search blocks or duplicate PubMed/publisher representations were removed, leaving 46 unique records for title/abstract screening. Eleven records were excluded at screening, primarily because their final publication year fell outside 2017–2025 or because the title and abstract did not address the defined implementation, decision-use, or outcome question.

The remaining 35 full-text reports were assessed. Eleven full-text reports were excluded: technical/model-development evidence without sufficient relevance to the implementation question (n=5); conceptual or guideline material used as background rather than an evidence-map unit (n=3); access or laboratory feasibility without clinical dosing implementation (n=1); an overlapping report from an already represented programme without a distinct evidence function (n=1); and a report insufficiently separable from general narrative background for independent mapping (n=1). The final evidence map contained 24 evidence units.

Multiple publications from the same implementation programme were linked. Thus, a clinical trial and an economic evaluation using the same programme were not treated as independent implementation settings, although they could contribute distinct evidence functions. The 24 mapped evidence units correspond to references 10–32 and 34 and are identified individually in **Table 1**. References 1–9, 33, and 35 were retained for background, contextual, methodological, validation, or reporting purposes and were not counted in the 24-unit evidence map.

The complete selection arithmetic is shown in **Figure 1**.

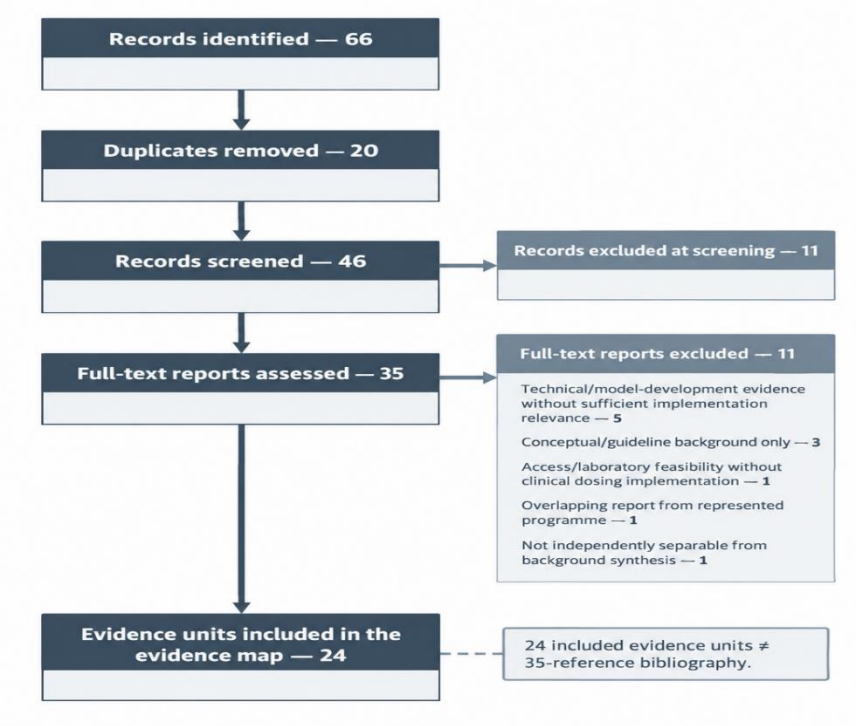

Figure 1. Selection of evidence units for the model-informed precision-dosing evidence map, 2017–2025

Evidence extraction and implementation-maturity coding

Each evidence unit was characterized by medicine or technology, population, setting, geography where applicable, study design, information used for dosing, comparator, model or software role, clinical decision supported, workflow characteristics, and consequence measured. Outcome evidence was separated into dosing performance, pharmacokinetic exposure or target attainment, clinical process, safety, efficacy, healthcare utilization, patient outcome, and economic outcome.

Implementation status was determined by reported activity rather than by the terminology used in article titles. A prospective external-validation study remained technical when recommendations were not enacted. Conversely,

a clinical service using an established Bayesian model was classified as implemented when individualized recommendations altered real treatment.

Appraisal and synthesis

The synthesis was design aware. Randomized evidence was given greatest weight for comparative claims concerning patient outcomes, while implementation and observational studies were used to characterize workflow, adoption, feasibility, and service consequences. Simulation and model-validation studies informed technical readiness but were not treated as proof of patient benefit. Formal risk-of-bias tools were used only where the information reported in the article supported a defensible study-level judgment. The nonrandomized comparative studies in references 10 and 19 were judged at serious risk of bias under ROBINS-I because treatment/comparator allocation was nonrandomized and confounding could not be excluded. RoB 2 judgments were not assigned to the randomized studies in references 17, 28, and 29 because the domain-level information required for a valid RoB 2 judgment was not reported here.

Where an explicit numerator and denominator were available, proportions and 95% confidence intervals were calculated with the Wilson method. Absolute percentage-point differences were calculated directly from percentages reported in the included evidence. No quantitative pooling was undertaken because drugs, populations, targets, interventions, comparators, and outcomes were substantially heterogeneous. The evidence map instead examined where technical capability became an enacted clinical decision and whether consequences remained proximal to dosing or extended to patient-facing outcomes.

Results and Discussion

From model output to enacted clinical decisions

Antimicrobial therapy supplied the clearest concentration of implemented MIPD [11]. In hospitalized adults receiving vancomycin, Bayesian AUC-guided dosing was associated with reductions in sampling and nephrotoxicity relative to a preceding trough-guided strategy while maintaining treatment effectiveness [12]. Prospective ICU validation demonstrated that a model-informed tool could predict vancomycin exposure under real clinical conditions, although prospective prediction should not itself be equated with comparative effectiveness [13].

Pediatric implementation provides evidence of routine workflow use. At an academic children's hospital, a commercial Bayesian tool was integrated with the EHR, clinical data were transferred automatically, pharmacists became primary users, and MIPD expanded from a neonatal pilot to hospital-wide availability [14]. In children with cystic fibrosis, implementation improved initial AUC target attainment from 39% to 71% (absolute increase, 32 percentage points) and post-adjustment attainment from 57% to 86% (absolute increase, 29 percentage points), while acute kidney injury remained similar [15].

Clinical use was not restricted to vancomycin. A Mexican pediatric programme evaluated 43 antimicrobial regimens and recommended adjustment in 27 (62.8%; 95% CI, 47.9%–75.6%), demonstrating patient-specific use across several antimicrobial agents [16]. A Swedish programme defined responsibilities, sampling procedures, data-transfer processes, dosing-software instructions, staff education, and recurring MIPD rounds, emphasizing that implementation consists of a service as well as an algorithm [17].

Transplantation showed a similar separation between pharmacokinetic and clinical outcomes. A randomized kidney-transplant study found that Bayesian tacrolimus dosing improved early target attainment and reduced dose modifications, but significant differences in measured clinical outcomes were not demonstrated [18]. Tacrolimus model benchmarking also showed that published models and software cannot be assumed to perform interchangeably across populations [19].

Patient-facing outcome evidence was stronger for mycophenolate, although less resistant to confounding. In a multicentre cohort, three-year rejection-free survival was 91.2% among patients managed with MIPD compared with 80.6% without MIPD (absolute difference, 10.6 percentage points) [20]. Because treatment allocation was not randomized, this association supports clinical relevance without establishing the same causal certainty as a randomized outcome trial.

Other specialist applications illustrate widening therapeutic scope. Biologic precision dosing was incorporated into an EHR-linked clinical environment for inflammatory bowel disease [21]. HdxSim was designed to convert hydroxyurea pharmacokinetic calculations into accessible patient-specific decision support [22], while

prospective pharmacokinetically guided hydroxyurea dosing shortened the pathway to maximum tolerated dose and produced robust hematologic responses in young children with sickle cell anemia [23]. Model-informed dosing has also been applied to eculizumab in transplant-associated thrombotic microangiopathy [24].
Table 1 provides the complete identity-level ledger of the 24 mapped evidence units and shows the evidence role used in the synthesis.

Table 1. Complete identity-level ledger of the 24 mapped model-informed precision-dosing evidence units

Ref.	Evidence unit	Design / map position	Key outcome and formal appraisal
10	Neely *et al*., 2018 — vancomycin AUC-guided dosing	Prospective nonrandomized comparative dosing study; enacted dosing with safety/process outcomes	Lower sampling and nephrotoxicity reported versus preceding trough strategy. ROBINS-I: serious risk (nonrandomized allocation/confounding).
11	Ter Heine *et al*., 2020 — ICU vancomycin MIPD tool	Prospective validation; technical model/tool performance in real clinical conditions	Prediction/validation evidence; not treated as comparative clinical benefit.
12	Frymoyer *et al*., 2020 — pediatric vancomycin CDS	Implementation/adoption study; EHR-linked Bayesian TDM in hospitalized children	Routine workflow implementation with pharmacist-led use.
13	Wicha *et al*., 2021 — antibiotics TDM-to-MIPD synthesis	Antimicrobial/TDM evidence synthesis; multi-setting methodological evidence	Supports antimicrobial implementation context; RoB 2/ROBINS-I not applicable to this evidence role.
14	Frymoyer *et al*., 2023 — vancomycin in pediatric cystic fibrosis	Implementation outcome evaluation; enacted AUC-guided individualization	Initial target attainment 39%→71% (+32 pp); post-adjustment 57%→86% (+29 pp); AKI similar.
15	Velarde-Salcedo *et al*., 2023 — pediatric multi-antimicrobial MIPD	Pilot clinical implementation; patient-specific dose/infusion adjustment	Adjustment recommended in 27/43 regimens: 62.8% (95% CI 47.9%–75.6%).
16	Swartling *et al*., 2025 — vancomycin clinical-practice workflow	Intervention-development/implementation study; standardized MIPD service	Defines workflow ownership, sampling, software procedures, training, and recurring rounds.
17	Lloberas *et al*., 2023 — Bayesian tacrolimus dosing	Prospective controlled randomized trial; enacted dosing and target-attainment evaluation	Improved early target attainment and fewer dose modifications; no significant clinical-outcome difference. RoB 2 not assigned from available domain information.
18	Hoffert *et al*., 2024 — tacrolimus models/software benchmark	Systematic review and benchmark study; technical validation/transportability	Demonstrates non-interchangeability of published models/software across populations.
19	Villeneuve *et al*., 2024 — mycophenolate MIPD	Multicentre observational cohort; patient-facing outcome evaluation	3-y rejection-free survival 91.2% vs 80.6% (+10.6 pp). ROBINS-I: serious risk (nonrandomized allocation/confounding).
20	Colman *et al*., 2023 — biologic MIPD in inflammatory bowel disease	Bedside/EHR-linked clinical decision support	Patient-specific biologic dose support incorporated into a clinical environment.
21	Power-Hays *et al*., 2024 — HdxSim hydroxyurea CDS	Clinical decision-support development and validation	Patient-specific hydroxyurea dosing capability; technical/decision-support evidence.
22	McGann *et al*., 2019 — PK-guided hydroxyurea dosing	Prospective enacted dosing in young children with sickle cell anemia	Shorter pathway to maximum tolerated dose and robust hematologic response reported.
23	Jodele *et al*., 2023 — eculizumab precision dosing	Specialist clinical application of model-informed dosing	Enacted/patient-specific dosing application in transplant-associated thrombotic microangiopathy.
24	Janssen Daalen *et al*., 2024 — levothyroxine machine-learning MIPD	Development, validation, and clinical simulation trial	Improved simulated dose selection; classified as technical/simulation rather than routine implementation.
25	Centanni *et al*., 2024 — vincristine PK/PD simulation	PK/PD modeling and simulation	Predicted neuropathy reduction; no prospectively observed clinical effect.

26	Mahomedradja *et al*., 2025 — busulfan MIPD evaluation	Critical evaluation of PK models and dose recommendations	Initial model-guided dosing alone was less compelling than iterative TDM/individual feedback.
27	De Cock *et al*., 2024 — BENEFICIAL vancomycin trial	Multicentre randomized controlled trial protocol	Defines bedside MIPD comparison with exposure and clinical endpoints; outcome RoB judgment not applicable to protocol evidence.
28	Roggeveen *et al*., 2022 — AutoKinetics antibiotic dosing	Two-centre randomized clinical trial; enacted bedside individualized dosing	Feasible; early ciprofloxacin target attainment improved; major clinical outcomes neutral. RoB 2 not assigned from available domain information.
29	Ewoldt *et al*., 2022 — beta-lactam/ciprofloxacin MIPD	Multicentre randomized clinical trial; patient-facing outcome evaluation	No significant reduction in ICU length of stay or improvement in assessed secondary outcomes. RoB 2 not assigned from available domain information.
30	Broulikova *et al*., 2025 — personalized antibiotic dosing economics	Economic evaluation linked to the personalized-dosing programme	Greater target attainment with higher intervention costs; no convincing cost-effectiveness case.
31	Thomas *et al*., 2025 — psoriasis precision-dosing dashboard	Development, validation, and user testing; patient-specific decision support	Usable validated dashboard; prospective health/cost benefit not established.
32	Dibbets *et al*., 2025 — barriers and facilitators for bedside MIPD	Systematic review of implementation barriers and facilitators; implementation/access evidence	Identifies validation, usability, education, measurements, stakeholder collaboration, and governance as recurrent determinants of bedside implementation.
34	Freriksen *et al*., 2023 — pediatric PBPK-informed dosing	Model-informed dosing guidance for a special population	Technical/transportability evidence for pediatric dosing; assumptions about transferability remain important.

Evidence-unit count: references 10–32 and 34 (24 units). Sources retained in the bibliography but excluded from the 24-unit map were Minichmayr *et al*. [1], Darwich *et al*. [2], Polasek *et al*. [3], Keizer *et al*. [4], Vinks *et al*. [5], Mizuno *et al*. [6], Taylor *et al*. [7], Del Valle-Moreno *et al*. [8], Jager *et al*. [9], Turner *et al*. [25], and Tricco et al. [10]; these served background, contextual, methodological, validation, or reporting functions. Publications from the same programme were interpreted as linked when relevant; the economic analysis in reference 30 is linked to the personalized critical-care antibiotic programme rather than representing a separate implementation setting.

Implementation maturity is heterogeneous

The evidence map contained technically advanced systems that had not yet crossed into routine treatment. Levothyroxine MIPD used machine learning and was evaluated with general practitioners in a clinical simulation; improved simulated dose selection did not establish routine patient-level implementation [26]. Vincristine PK/PD modeling predicted that exposure-guided dosing could reduce neuropathy risk, but the clinical consequence remained simulated rather than prospectively demonstrated [27].

Busulfan illustrates the importance of feedback. Critical evaluation of existing models found that model-guided initial dosing did not necessarily outperform established recommendations, whereas incorporation of TDM and individual feedback produced stronger exposure control [28]. Thus, a model may have limited clinical value when used once but greater value when embedded in an iterative monitoring process.

Prospective trials have tested more complete implementation systems. The BENEFICIAL protocol specified bedside vancomycin MIPD with exposure and clinical endpoints in severely ill children, marking a transition from implementation rationale to comparative testing [29]. In critically ill adults, the AutoKinetics trial showed that bedside individualized antibiotic dosing was feasible and improved early target attainment for ciprofloxacin, but benefits were not uniform across antibiotics and major clinical outcomes were neutral [30].

A separate eight-hospital randomized trial provides an especially important limiting case. Model-informed beta-lactam and ciprofloxacin dosing did not significantly reduce ICU length of stay and did not improve the assessed secondary clinical outcomes [31]. The accompanying economic evidence from the broader personalized-dosing

programme showed greater target attainment but higher intervention costs and no sufficiently convincing probability of cost-effectiveness [32].

A United Kingdom psoriasis dashboard occupied another intermediate state: real-world data were used for validation and healthcare professionals rated the interface as usable, yet prospective evidence that the system improves health or cost outcomes was still lacking [33].

Implementation evidence therefore spans several qualitatively different states rather than a simple implemented/not-implemented dichotomy.

Table 2. Implementation maturity represented in the 2017–2025 evidence

Implementation maturity	**Evidence signature**		**Inference permitted**
Evidence state	**Defining observation**	**Typical examples**	**What it permits**
Technical validation/simulation	Model or software performance tested without enacted patient dosing	Levothyroxine simulation; vincristine simulation	Readiness or hypothesis
Patient-specific decision support	Individual recommendation generated for clinical interpretation	Hydroxyurea/biologic dashboards	Decision capability
Enacted dosing	Recommendation changes treatment in real patients	Pediatric antimicrobials; tacrolimus	Clinical implementation
Routine workflow use	Repeated use embedded in service processes	Pediatric vancomycin CDS	Operational adoption
Patient-facing outcome evaluation	Safety, efficacy, utilization or economic outcome evaluated	Mycophenolate; ICU antibiotic trials	Comparative clinical-value evidence

Exposure success is more common than patient-outcome success

The outcome map showed a pronounced gradient. Dosing efficiency and target attainment were the most consistently favorable endpoints because they lie closest to the MIPD intervention. Clinical outcomes were evaluated less frequently and were less consistently improved.

The tacrolimus randomized study exemplifies this separation: Bayesian dosing improved target achievement without a corresponding significant difference in the reported clinical outcomes. Mycophenolate provided a more favorable downstream signal, with improved rejection-free survival in observational practice. The randomized critical-care antibiotic trial, by contrast, showed neither the anticipated improvement in ICU length of stay nor convincing improvement in secondary outcomes [18, 20, 31].

Safety evidence was similarly medicine specific. Adult Bayesian AUC-guided vancomycin management was associated with lower nephrotoxicity [12], whereas improved exposure attainment in pediatric cystic fibrosis did not produce a detectable difference in acute kidney injury [15]. Hydroxyurea pharmacokinetic-guided dosing produced clinically meaningful treatment responses without evidence that precision dosing was intrinsically safer across unrelated therapies [23].

Healthcare-use and economic endpoints were particularly resistant to generalization. Improved pharmacokinetic target attainment in the AutoKinetics programme did not translate into a clear cost-effectiveness case [32]. This pattern argues against using exposure success as an automatic surrogate for value.

Table 3. Outcome levels represented in model-informed precision-dosing studies

Outcome level	**Examples of measures**	**Overall evidence pattern**
Proximal dosing and model-linked performance		
Dose performance	Starting dose, adjustment, number of modifications	Frequently favorable
Pharmacokinetic performance	AUC or concentration target attainment	Most consistently favorable
Clinical process	Sampling, workflow uptake, treatment duration	Favorable in selected services
Patient safety and efficacy		
Safety	Nephrotoxicity, AKI, treatment toxicity	Mixed and medicine dependent

Efficacy	Rejection, infection response, treatment response	Positive in selected applications; null in others
Major patient outcomes	Survival or rejection-free survival	Sparse
	Health-system and economic value	
Healthcare use	ICU/hospital length of stay	Limited and often neutral
Economic outcomes	Costs, QALYs, cost-effectiveness	Insufficient evidence for general benefit

Geographic concentration of implementation evidence

Mapped clinical evidence was concentrated in the United States and Western Europe. The United States contributed pediatric and adult vancomycin implementation, hydroxyurea dosing, biologic decision support, and other specialist applications. The Netherlands contributed model validation, general-practice simulation, technical evaluations, and randomized critical-care antibiotic programmes. Spain and France supplied major transplant evidence, Sweden contributed an implementation-development programme, and the United Kingdom contributed biologic dashboard evidence. Mexico provided an important pediatric antimicrobial implementation outside the most densely represented settings.

The distribution should not be interpreted as prevalence of MIPD practice. Published evidence can be affected by research infrastructure, indexing, publication patterns, and the availability of clinical pharmacology groups. Absence from the map therefore means that a country was not represented in the completed mapped evidence, not that MIPD is absent there.

Figure 2 encodes implementation status without using marker size to imply clinical superiority.

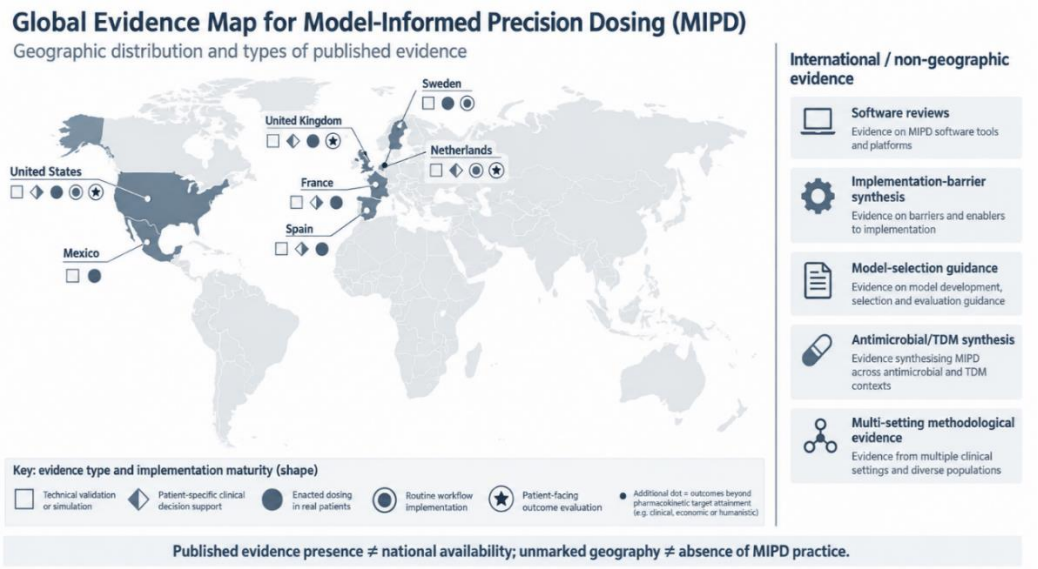

Figure 2. Geographic distribution and implementation maturity of published model-informed precision-dosing evidence

Equity and access: Implementation depends on service capacity

MIPD is often presented as a computational intervention, but clinical implementation depends on a chain of resources. EHR-integrated decision support can reduce manual data transfer and place individualized predictions inside the clinical encounter [5]. Where EHR connectivity is unavailable, the same dosing process may require repeated manual entry of drug administration times, laboratory measurements, demographics, renal function, and other covariates.

Software reviews and validation studies reinforce this distinction. Available programs vary in accessibility, model libraries, data requirements, interface design, regulatory status, interoperability, and implementation of dosing equations [8, 9, 25]. The implementation-barrier synthesis similarly identifies validation, usability, education, measurements, stakeholder collaboration, and governance as determinants of bedside use [34]. A software license or downloadable model does not therefore establish equivalent access to a functioning MIPD service.

The Swedish vancomycin programme shows how infrastructure and personnel become part of the intervention. Sampling instructions, documentation, software procedures, clinical routines, training, communication, and

recurring dosing rounds were deliberately defined [17]. Clinical implementation thus requires ownership of tasks that occur before and after the model calculation.

Population representation creates a separate access problem. A model may be technically available but poorly supported for a patient whose age, organ function, disease state, ancestry, treatment context, or interacting therapies were underrepresented during model development or validation. Pediatric PBPK-informed dosing illustrates how model-based approaches can address evidence gaps in special populations, while also requiring explicit assumptions about transferability [35].

The evidence map cannot quantify global inequity from geography alone. It can identify an important evidence gap: routine implementation is best documented in institutions with therapeutic monitoring, clinical-pharmacology or pharmacy expertise, and digital infrastructure. Whether comparable benefit can be achieved where these resources are constrained remains insufficiently tested.

Table 4. Access and service requirements that condition MIPD implementation

Implementation requirement	Clinical function	Consequence when constrained
	Data and model prerequisites	
Reliable patient/dosing data	Individual prediction	Biased or unusable estimates
Timely drug/biomarker measurement	Bayesian updating	Delayed or impossible adjustment
Appropriate model	Population-specific inference	Poor transportability
	Technical and workflow delivery	
Usable dosing software	Decision delivery	Low adoption or workflow burden
EHR/data connectivity	Automated information transfer	Manual-entry workload and error
Trained clinical users	Interpretation and enactment	Recommendation not translated into care
Defined workflow ownership	Accountability	Delayed or missed decisions
	Governance and reach	
Governance/regulation	Sustained deployment	Restricted routine use
Representative populations	Generalizability	Uncertain performance in underserved groups

Null, conditional, and non-transferable evidence

Failure cases are essential for determining what MIPD can and cannot be expected to accomplish. Model performance can deteriorate when transported to populations differing from development cohorts, and software platforms may implement different models or assumptions. Tacrolimus benchmarking and Bayesian software comparisons demonstrate that apparently similar tools are not automatically interchangeable [19, 25].

Busulfan provides a clinically relevant example of conditional value. Model-guided initial dosing alone did not provide the same benefit as a strategy incorporating patient measurements and subsequent adaptation [28]. This indicates that the value of MIPD may lie in iterative learning rather than merely replacing one initial dosing equation with another.

Simulation should also be distinguished from observed clinical benefit. The vincristine analysis predicted that individualized exposure management could reduce neuropathy [27]. Such work is valuable for trial design, but prospective enactment is required before the predicted reduction can be treated as an observed clinical effect.

Randomized ICU evidence provides a stronger test because recommendations were enacted. The AutoKinetics programme demonstrated technical and operational feasibility, yet pharmacokinetic improvement varied by drug and major clinical outcomes remained neutral [30]. The multicentre beta-lactam/ciprofloxacin trial likewise failed to demonstrate improvement in ICU length of stay or secondary outcomes [31].

These studies do not establish that MIPD is ineffective in critical care. They establish that individualization is conditional. Standard care may already perform adequately; samples may arrive too late; a target may have an uncertain causal relationship with the clinical endpoint; or disease-related factors may dominate the effect of exposure optimization.

What constitutes a genuine change in patient care?

The completed evidence map suggests a useful threshold: MIPD changes patient care when patient-specific model output becomes an enacted treatment or monitoring decision. The threshold is behavioral and clinical rather than

computational. It is crossed when a recommended dose or interval is actually prescribed, administered, or used to alter monitoring.

This definition avoids two opposite errors. It prevents retrospective validation from being labeled clinical implementation, but it does not require mortality improvement before an intervention can legitimately be described as implemented. EHR-linked pediatric vancomycin, pediatric antimicrobial dose adjustment, tacrolimus Bayesian dosing, mycophenolate exposure-guided dosing, hydroxyurea PK-guided treatment, and selected biologic applications all demonstrate varying forms of enacted decision use.

A further evidence level begins when the consequences of enactment are evaluated. Pharmacokinetic improvement is meaningful but should be reported as such. Safety, efficacy, patient experience, utilization, and economic outcomes require separate evidence.

Why pharmacokinetic target attainment is insufficient as a universal surrogate

The evidence is strongest closest to the mechanism of intervention. MIPD changes dose; changed dose alters exposure; therefore exposure-related endpoints are the outcomes most likely to respond. Movement from exposure to clinical outcome introduces additional causal steps.

This explains why the mapped literature contains clear improvements in target attainment alongside neutral clinical results. The cystic-fibrosis vancomycin study markedly improved AUC attainment without detecting a difference in AKI [15]. Tacrolimus Bayesian dosing improved early exposure control without significant clinical-outcome differences [18]. Conversely, observational mycophenolate evidence linked MIPD to improved rejection-free survival [20].

Critical-care antibiotic trials demonstrate why a single general claim is untenable. Better individualized dosing did not reliably improve ICU utilization or mortality. The clinical value of a target depends on the drug, pathogen, disease state, timing, competing care, and strength of the exposure-response relationship.

Target attainment should consequently be treated as an intermediate endpoint whose importance depends on validated therapeutic context, not as automatic proof that MIPD improves patient health.

Generalizability and implementation burden

Scaling MIPD requires transfer of both the quantitative model and the surrounding service. Model-selection guidance emphasizes qualification for the intended population and dosing purpose [7]. Software studies document differences in technical capabilities and integration [8]. Implementation synthesis identifies regulation, validation, usability, education, measurements, and stakeholder collaboration as recurrent determinants [34].

These observations make implementation burden part of effectiveness. A system that provides excellent dose predictions but requires unsustainable manual data entry, specialist oversight, or delayed measurements may perform poorly outside an expert centre. Conversely, automation can improve feasibility while creating new dependencies on informatics infrastructure and governance.

Equitable implementation will therefore require studies in different service environments, not merely larger model-development datasets. Reporting should make the resource requirements of a successful programme visible.

Research priorities

Future MIPD studies should report the complete chain from input to consequence. At minimum, evaluations should distinguish model validity, recommendation generation, clinician acceptance, enacted dosing, exposure change, and the outcome the intervention is intended to improve.

Implementation-effectiveness trials should document unsuccessful as well as successful recommendations: recommendations not accepted, missing concentrations, software failures, delayed sampling, deviations from proposed doses, and reasons for non-use. These observations can explain why an apparently effective algorithm does or does not change care.

Outcome selection should remain drug specific. Mortality is inappropriate as a universal benchmark for MIPD. For some therapies, toxicity reduction, faster stabilization, fewer samples, fewer dose modifications, prevention of rejection, or reduced treatment burden may be more plausible and clinically useful outcomes.

Economic evaluation should accompany resource-intensive systems. The critical-care economic analysis shows that pharmacokinetic improvement can coexist with higher costs and uncertain value [32]. Future analyses should incorporate assay costs, software, implementation effort, clinician time, informatics, and downstream care.

Finally, prospective evidence should expand beyond specialist early-adopter institutions. Evidence of successful implementation in tertiary centres establishes possibility; it does not establish transportability. Comparative research across hospitals, regions, and populations with different infrastructure would clarify whether precision dosing can become a broadly deployable clinical service rather than a capability concentrated in selected centres.

Conclusion

Model-informed precision dosing has moved beyond technical development in selected areas of patient care. Its strongest implementations combine an appropriate model with patient-specific data, timely measurement when required, usable decision support, defined clinical responsibility, and a mechanism for translating recommendations into treatment.

The evidence is less mature as outcomes move further downstream. Pharmacokinetic target attainment improves relatively often; safety, efficacy, utilization, economic value, and major patient outcomes are less consistently demonstrated. Null randomized evidence in critical care is therefore as important to the field as successful implementation examples.

The answer to where MIPD changes patient care is conditional. It changes care when individualized predictions are converted into timely clinical action and that action addresses an exposure-response relationship that matters for the therapeutic objective. Where evidence ends at model validation, simulation, software performance, or untested target attainment, MIPD remains principally a technical capability. The next phase of the field depends on comparative outcome evidence, implementation science, transportable models, and demonstration that effective precision-dosing services can function across a broader range of healthcare environments.

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