Digital Twins for Precision Pharmacology: An Integrative Review of Mechanistic Modeling, Virtual Patients, Pharmacokinetic Simulation, and Personalized Therapeutics

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ABSTRACT

Digital twins are emerging as computational representations that may support precision pharmacology by linking individual patient information with mechanistic models, virtual patient simulations, and longitudinal prediction. This integrative review examines how digital twin concepts intersect with systems pharmacology, physiologically based pharmacokinetic modeling, population pharmacokinetics, pharmacokinetic–pharmacodynamic integration, virtual populations, therapeutic drug monitoring, and personalized therapeutic decision support. The review integrates conceptual, methodological, and applied evidence according to model function, patient specificity, data requirements, updating capability, validation status, uncertainty handling, and intended clinical context. Mechanistic disease models and quantitative systems pharmacology can provide causal structures for representing biological and drug-response processes, whereas physiologically based and population pharmacokinetic models support individualized exposure prediction under explicit assumptions. Virtual patients and virtual populations enable scenario testing and heterogeneity analysis but should not be treated as equivalent to observed patients or clinical populations. Patient-specific simulation may assist therapeutic hypothesis generation, exposure interpretation, response assessment, and safety-oriented reasoning when models are appropriately calibrated and their uncertainty is communicated. However, pharmacokinetic simulation alone does not establish clinical benefit, dosing safety, or therapeutic effectiveness. Translation into personalized therapeutic decision support remains constrained by data quality, model identifiability, external and prospective validation, interoperability, workflow integration, governance, and human-factors requirements. Digital twins may therefore contribute to precision pharmacology only as bounded, evidence-qualified, and clinician-supervised systems. Responsible development requires transparent mechanistic assumptions, reliable patient-specific data, uncertainty-aware predictions, formal validation, auditability, and explicit decision boundaries.

Key Words: *Digital twins, Precision pharmacology, Virtual patients, Mechanistic modeling, Pharmacokinetic simulation, Personalized therapeutics*

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INTRODUCTION

Digital twins have been proposed as dynamic computational representations of individuals that integrate biological, clinical, and longitudinal information to simulate evolving health states and test patient-specific hypotheses. In contrast to a static risk score or a one-time predictive model, an idealized health digital twin is linked

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to an identifiable subject, incorporates multiple information streams, and can be updated when new observations become available [1]. This individual linkage creates distinctive ethical questions concerning consent, privacy, autonomy, data ownership, representation, accountability, and the consequences of acting on computational predictions [2]. These issues are particularly important in pharmacology because simulated exposure, response, or toxicity may influence decisions with immediate safety implications.

Precision pharmacology seeks to account for variability in drug exposure and response by integrating pharmacokinetic, pharmacodynamic, physiological, genomic, biomarker, disease-state, treatment, and contextual information. Digital twins may provide a conceptual framework for bringing these elements together, but their value depends on more than computational sophistication. Health digital twins intended for precision medicine require suitable data architectures, credible models, implementation pathways, and regulatory interpretation that reflect their intended context of use [3]. A model that performs adequately for retrospective exploration may not possess the evidentiary support required for prospective therapeutic decision support.

The digital twin literature nevertheless remains heterogeneous. The term has been applied to mechanistic physiological models, virtual patients, virtual populations, monitoring systems, artificial intelligence models, hospital process simulations, and clinical decision tools with widely different levels of individualization and validation. Reviews of recent health digital twin developments have identified persistent challenges involving data quality, interoperability, model updating, transparency, external validation, clinical integration, privacy, and governance [4]. Consequently, the label “digital twin” does not itself establish that a model is patient specific, dynamically updated, mechanistically interpretable, clinically validated, or suitable for therapeutic use.

An integrative pharmacological perspective is needed because the principal components of a potential drug-therapy digital twin are distributed across partially separate scholarly traditions. Mechanistic and systems pharmacology address biological causality and treatment response; physiologically based pharmacokinetic models represent drug disposition within physiological systems; population pharmacokinetic and pharmacodynamic models quantify variability and support Bayesian updating; virtual patients and virtual populations represent plausible individual and population trajectories; and model-informed precision dosing provides an operational example of how quantitative models may support clinical reasoning. This review therefore examines how these components can be integrated responsibly, identifies the boundaries separating digital twins from related computational models, and evaluates the validation, uncertainty, workflow, oversight, and governance requirements that must be satisfied before patient-specific simulations can support precision pharmacology.

Digital twins in precision pharmacology

Within precision pharmacology, a digital twin can be defined as a patient-linked computational representation that combines relevant biological mechanisms, drug disposition, disease processes, response relationships, and longitudinal observations for a specified predictive or decision-support purpose. A precision-pharmacology twin may operate across molecular, cellular, organ, and whole-body scales, particularly when drug effects arise from interactions among electrophysiology, physiology, pharmacokinetics, and disease mechanisms [5]. Cardiovascular digital twin scholarship illustrates how clinical measurements, imaging, biomarkers, physiological models, and repeated observations may be organized within a patient-specific architecture, while also showing that most proposed systems remain developmental rather than validated therapeutic tools [6].

This definition distinguishes precision-pharmacology twins from broader population, public-health, and health-system twins. A population twin may represent distributions, disease prevalence, or service demand, whereas a pharmacological patient twin must preserve a defensible connection between an individual’s data and a model of drug exposure or response. Digital twin concepts have been described across scales ranging from personalized medicine to precision public health, making explicit scale and purpose essential for interpreting any claimed twin [7]. A hospital workflow simulation, population surveillance model, or general clinical prediction algorithm may be valuable without constituting a patient-specific pharmacological digital twin.

Digital twins should also be distinguished from static virtual patients, virtual populations, and conventional simulation models. A virtual patient may be an internally coherent synthetic parameter set used to explore a model, and a virtual population may be calibrated to reproduce aggregate characteristics or variability. These constructs become closer to digital twins only when they are meaningfully matched to observed individuals, updated through new patient information, and evaluated for a clearly defined context of use. The health digital twin literature demonstrates substantial variation in whether systems include bidirectional data exchange, longitudinal updating, mechanistic structure, individual calibration, uncertainty assessment, or clinical validation [8]. These dimensions should therefore be reported separately rather than inferred from terminology.

For precision pharmacology, digital twin status is best treated as a graded property rather than a categorical marketing label. At one end are generic mechanistic or statistical models that represent a disease, drug, or population. More advanced configurations incorporate patient covariates, therapeutic drug monitoring measurements, organ function, biomarkers, pharmacogenomic information where supported, and longitudinal disease observations. A mature pharmacological twin would additionally include controlled updating, prediction intervals or other uncertainty measures, independent validation, an auditable model history, and explicit human-review requirements. Even then, the system would support rather than replace pharmacological and clinical judgment, and its conclusions would remain limited to the therapeutic questions for which its models, data, and workflow have been evaluated.

Integrative review approach

This article uses an integrative review approach to connect evidence from digital health, clinical pharmacology, pharmacometrics, systems pharmacology, pharmacokinetic simulation, virtual patient research, and therapeutic decision support. The review is not presented as a systematic review, scoping review, or meta-analysis, and no quantitative estimate of pooled effect is attempted. Conceptual boundaries were established by separating patient-focused pharmacological modeling from operational digital twins designed primarily for hospital management, resource allocation, or organizational process simulation, which constitute a related but distinct evidence domain [9].

The search concepts encompassed digital twins in medicine and pharmacology; quantitative systems pharmacology; mechanistic disease modeling; virtual patients and virtual populations; physiologically based pharmacokinetic modeling; population pharmacokinetics; pharmacokinetic–pharmacodynamic integration; model-informed precision dosing; therapeutic drug monitoring; individualized exposure, response, and toxicity simulation; decision-support implementation; uncertainty; validation; ethics; governance; and regulatory alignment. Because digital twin terminology is fragmented across disciplines, evidence was synthesized by functional characteristics rather than by terminology alone. This approach is consistent with literature showing that healthcare digital twin publications vary markedly in definitions, technical architectures, clinical domains, and claimed applications [10].

Evidence extraction focused on the pharmacology question addressed, model class, mechanistic content, input data, patient-specific features, virtual patient or virtual population construction, pharmacokinetic and pharmacodynamic functions, updating capability, predicted output, uncertainty treatment, calibration and validation approach, implementation context, governance issues, and stated limitations. Particular attention was given to distinguishing model verification and calibration from external or prospective validation. The review also separated technical performance from clinical utility because a model may reproduce observed data without demonstrating that its use improves therapeutic decisions or patient outcomes. Conceptual healthcare digital twin frameworks support organizing evidence according to data inputs, computational representation, simulation function, feedback processes, and intended clinical use [11].

The synthesis was conducted across six linked domains: conceptual definition, mechanistic modeling, virtual patient representation, pharmacokinetic simulation, personalized therapeutic decision support, and translational governance. Evidence was interpreted conservatively. A simulation was not considered clinically useful solely because it was individualized; a virtual population was not assumed to reproduce real-world representativeness; and a digital twin label was not treated as evidence of updating, validation, safety, or regulatory readiness. **Table 1** summarises the integrative review approach, evidence domains, synthesis logic, and interpretation boundaries used to evaluate digital twins in precision pharmacology.

Table 1. Integrative Review Approach for Digital Twins in Precision Pharmacology: Evidence Domains, Search Concepts, Inclusion Logic, Extraction Fields, Synthesis Themes, Validation Appraisal, and Interpretation Boundaries

Review component	Specification	Purpose	Evidence captured	Synthesis output	Interpretation boundary
Review design	Original integrative review linking conceptual, methodological, pharmacometric, and translational literature	Connect evidence distributed across disciplines without implying quantitative evidence pooling	Reviews, perspectives, methodological articles, modeling applications, validation studies, and bounded implementation reports	Narrative and matrix-based cross-domain synthesis	Not a systematic review, scoping review, or meta-analysis

Core search concepts	Digital twins, precision pharmacology, mechanistic modeling, QSP, PBPK, population PK, PK/PD, virtual patients, virtual populations, MIPD, TDM, decision support, validation, governance	Capture literature that may not use identical terminology	Digital twin and related computational-pharmacology constructs	Function-based rather than label-based evidence map	Use of the term "digital twin" does not establish patient specificity or clinical maturity
Pharmacological relevance	Evidence had to inform drug exposure, drug response, toxicity, disease–drug interaction, therapeutic monitoring, or pharmacological decision support	Exclude unrelated engineering and operational applications	Patient-focused and drug-focused modeling evidence	Precision-pharmacology-specific conceptual boundaries	General digital health evidence was included only when it supported implementation, validation, or governance analysis
Modeling domains	Systems pharmacology, mechanistic disease models, PBPK, population PK, PK/PD, biomarker and toxicity models	Identify complementary computational foundations	Biological mechanisms, physiological disposition, variability, exposure–response, and safety representations	Layered model architecture	No single model class is assumed to provide a complete digital twin
Patient representation	Patient-specific calibration, avatars, virtual patients, virtual populations, longitudinal states	Distinguish observed individuals from synthetic representations	Individual parameter sets, population distributions, biomarkers, covariates, and repeated observations	Taxonomy of patient linkage and updating	Synthetic plausibility is not equivalent to clinical representativeness
Data inputs	Demographics, clinical variables, laboratory values, organ function, biomarkers, TDM, medication history, omics or pharmacogenomics where supported	Assess whether inputs can support intended personalization	Static and longitudinal patient information	Data-to-model mapping	Additional data do not automatically improve prediction if parameters are unidentifiable or measurements are unreliable
Simulation functions	Exposure prediction, response prediction, toxicity-risk hypothesis, scenario testing, disease progression, variability assessment	Clarify what the model actually produces	Pharmacokinetic, pharmacodynamic, mechanistic, and uncertainty outputs	Functional classification of twin capabilities	Simulation output is not equivalent to a therapeutic recommendation
Validation appraisal	Verification, calibration, internal checks, external validation, prospective validation, uncertainty	Separate model construction from evidence of trustworthy use	Model diagnostics, independent evaluation, transportability, and implementation evidence	Credibility and readiness assessment	Successful calibration does not establish external validity or clinical utility

	quantification, workflow evaluation				
Decision-support appraisal	Interface design, uncertainty communication, workflow fit, expert review, auditability, override mechanisms	Evaluate translation from model output to professional reasoning	Software, workflow, human-factors, and implementation evidence	Bounded decision-support framework	Digital twin outputs should support rather than replace professional judgment
Governance appraisal	Privacy, consent, ownership, accountability, bias, cybersecurity, change control, post-deployment monitoring	Extend evaluation beyond predictive performance	Ethical, legal, organizational, and lifecycle issues	Governance requirements and research priorities	Technical validity alone is insufficient for responsible clinical adoption
Integrative synthesis	Comparison of evidence patterns, limitations, validation gaps, barriers, and future needs	Produce a unified precision-pharmacology interpretation	Cross-cutting findings from all model and application domains	Conceptual architecture and synthesis map	Conclusions are limited to the reviewed evidence and do not imply regulatory approval or routine clinical readiness

Mechanistic modeling and virtual patients

Mechanistic modeling provides the causal and physiological substrate required for a digital twin to do more than associate patient features with outcomes. Quantitative systems pharmacology models can represent interacting pathways, cellular processes, disease mechanisms, drug targets, biomarkers, and treatment effects, whereas physiologically based pharmacokinetic models describe drug absorption, distribution, metabolism, and excretion through anatomically and physiologically structured compartments. Virtual populations generated from QSP models can explore mechanistic heterogeneity, but their construction requires disciplined parameter selection, calibration targets, distributional constraints, and checks against population-level observations [12]. Translational QSP guidance similarly emphasizes that mechanistic richness must be aligned with the pharmacological question, available evidence, and intended use rather than pursued as an end in itself [13].

A pharmacological digital twin architecture may therefore combine multiple model classes rather than rely on a single comprehensive model. Systems pharmacology may represent causal disease and drug-action mechanisms; PBPK may provide individual or population exposure predictions; population pharmacokinetics may quantify variability and update individual parameter estimates; and PK/PD models may connect exposure to biomarkers, efficacy-related endpoints, or toxicity hypotheses. Credibility depends on transparent assumptions, parameter provenance, documentation, version control, reproducibility, and procedures for model reuse and modification [14]. Applied QSP work using systems-based twins has demonstrated how mechanistic virtual populations may be used to investigate heterogeneous dose–response patterns and candidate predictive biomarkers, although such analyses remain hypothesis-generating and do not by themselves establish clinical decision utility [15]. **Figure 1** illustrates a conceptual digital twin architecture for precision pharmacology, linking patient-specific data, mechanistic modeling, virtual patients, pharmacokinetic simulation, uncertainty assessment, and clinical oversight.

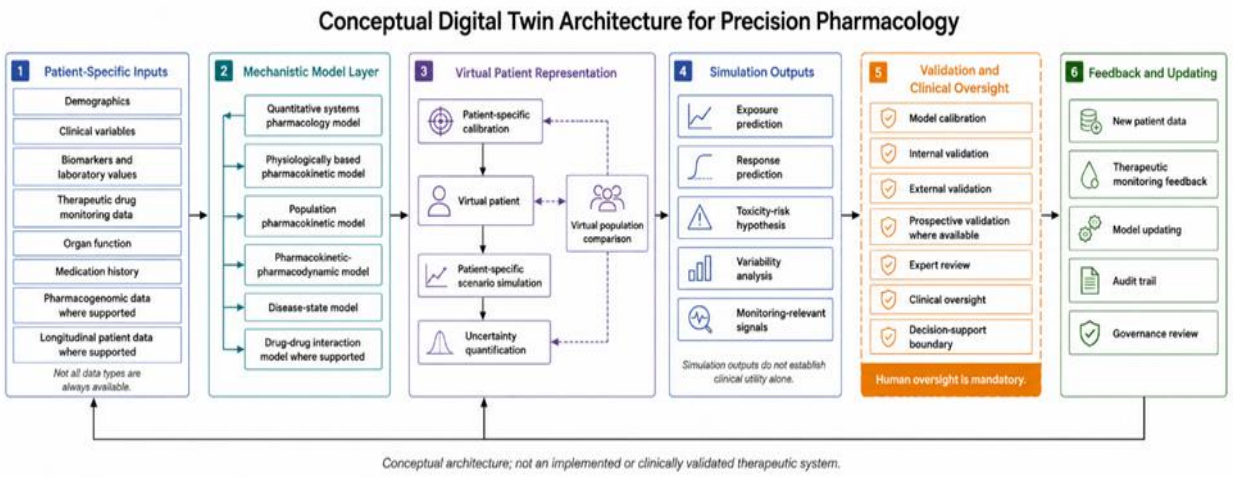

Figure 1. Conceptual Digital Twin Architecture for Precision Pharmacology

Alt-text description

A conceptual architecture diagram showing patient data flowing into mechanistic models, virtual patient simulation, pharmacokinetic and pharmacodynamic prediction, calibration, uncertainty assessment, validation, decision-support boundaries, clinician oversight, and feedback updating.

Virtual patients and virtual populations occupy different positions within this architecture. A virtual patient may represent one internally consistent parameter set, while a virtual population comprises multiple plausible parameterizations selected to reproduce specified aggregate characteristics. Neither construct should be assumed to correspond to an observed individual unless explicit patient matching and updating have been performed. Verification, validation, and uncertainty quantification are therefore necessary to evaluate numerical correctness, structural assumptions, parameter uncertainty, model-form uncertainty, and performance within a stated context of use [16]. Pharmacometric avatars provide a useful intermediate concept because they can generate plausible individual profiles from population models, but their interpretation remains dependent on the underlying model, construction algorithm, and intended application [17].

Patient-specific calibration converts a generic or population model into an individualized representation by conditioning parameters or latent states on observed information. Depending on the application, relevant data may include demographics, body size, organ function, genotype, biomarkers, disease severity, treatment history, drug concentrations, adherence information, and longitudinal clinical measurements. Rare-disease applications have shown how patient-matched QSP twins may supplement interpretation of limited trial observations by linking disease mechanisms, biomarkers, treatment effects, and pharmacokinetic exposure, while remaining dependent on model assumptions and available calibration data [18]. Longitudinal updating could strengthen such representations by allowing new observations to revise parameter estimates and forecasts, but repeated updating also introduces risks involving measurement error, unstable feedback, model drift, and false precision. **Table 2** maps mechanistic modeling and virtual patient components relevant to digital twins for precision pharmacology.

Table 2. Mechanistic Modeling and Virtual Patient Components in Digital Twins for Precision Pharmacology: Systems Models, PBPK Models, PK/PD Integration, Virtual Populations, Biomarker Inputs, Patient-Specific Calibration, Uncertainty, and Validation Requirements

Modeling component	Core pharmacology question	Required input data	Modeling function	Patient-specific relevance	Validation requirement	Failure risk	Integrative synthesis role
Mechanistic disease model	Which biological processes generate disease progression and	Pathway, cellular, tissue, biomarker, natural-history, and	Represents causal or semi-mechanistic disease dynamics	Patient states or selected parameters may be individualized	Structural plausibility, sensitivity analysis, calibration, and independent	Omitted mechanisms, nonidentifiability, oversimplified disease dynamics	Provides the disease-process foundation for therapeutic

	treatment response?	intervention data			outcome checks		scenario testing
Quantitative systems pharmacology model	How does a drug perturb interacting biological systems across scales?	Target biology, pathway kinetics, biomarkers, exposure, disease-state, and response data	Links drug action to multiscale biological effects	Covariates and biomarkers may personalize mechanisms or baseline states	Context-of-use qualification, predictive checks, parameter identifiability, and uncertainty assessment	Excessive complexity, parameter compensation, weak data support	Connects mechanism, biomarkers, response, and toxicity hypotheses
Physiologically based pharmacokinetic model	How do drug properties and physiology determine plasma and tissue exposure?	Anatomy, physiology, organ function, enzyme and transporter information, physicochemical properties, and clinical PK data	Simulates absorption, distribution, metabolism, and excretion	Physiology, organ function, genotype, and interacting drugs may be individualized	Mass-balance checks, parameter verification, comparison with observed concentrations, and external scenario testing	Incorrect physiology, uncertain parameters, and extrapolation beyond verified populations	Supplies the mechanistic exposure layer
Population pharmacokinetic model	How does drug exposure vary between and within patients?	Dosing histories, concentration-time measurements, covariates, and residual-error information	Estimates typical parameters, variability, and covariate relationships	Bayesian updating can produce individual posterior estimates	Goodness-of-fit evaluation, simulation-based diagnostics, forecasting performance, and external validation	Sparse sampling, biased covariates, misspecified variability, and incorrect dosing histories	Supplies a statistical-pharmacometric individualization layer
Pharmacokinetic–pharmacodynamic model	How does exposure relate over time to biomarkers, response, or toxicity?	PK observations, biomarkers, response or safety endpoints, treatment timing, and disease information	Links exposure or effect-site concentration to dynamic outcomes	Individual PK and response parameters may be estimated or updated	Temporal predictive checks, endpoint validation, external evaluation, and prospective assessment where appropriate	Incorrect exposure–response assumptions, surrogate endpoint misuse, and timing misspecification	Connects drug exposure with therapeutic interpretation
Drug–drug interaction model	How may co-administered agents alter exposure or response?	Enzyme, transporter, physiological, dosing-schedule, and interaction data	Simulates perpetrator–victim interactions and time-varying effects	Patient medication history and physiology can define individual scenarios	Comparison with observed interaction studies and complex-regimen testing	Unmodeled mechanisms, uncertain adherence, and polypharmacy complexity	Extends the twin to treatment-context effects

Virtual patient	What trajectory is plausible for one internally consistent model-defined individual?	Coherent parameter set, baseline state, disease characteristics, and treatment scenario	Simulates an individual trajectory under model assumptions	High only when meaningfully linked to an observed patient	Plausibility checks and comparison with withheld observations when patient matched	Treating a synthetic individual as a real patient	Supports individual scenario testing while clarifying representational limits
Virtual population	How can plausible heterogeneity and population outcomes be represented?	Parameter distributions, correlations, prevalence information, and calibration constraints	Generates multiple plausible individuals matching aggregate evidence	Represents variability but not necessarily identifiable patients	Population-distribution checks, subgroup evaluation, and independent calibration targets	Nonunique populations, implausible parameter combinations, and poor subgroup coverage	Supports heterogeneity, uncertainty, and trial-simulation analyses
Biomarker-linked simulation	Can biomarkers inform hidden disease states, response, or toxicity?	Longitudinal biomarkers, exposure, disease, and outcome information	Links measured biomarkers with mechanistic or latent model states	Enables updating when biomarkers are sufficiently informative	Analytical validity, temporal predictive validation, and incremental-value assessment	Measurement error, biomarker nonspecificity, and surrogate overinterpretation	Provides a bridge between observed patient state and mechanistic prediction
Patient-specific calibration	Which model parameters or states are consistent with the individual's observations?	Patient covariates, measurements, priors, model constraints, and calibration objectives	Estimates patient-specific states or parameters	Central to individualized representation	Identifiability assessment, posterior predictive checking, and separation of calibration from evaluation data	Overfitting, parameter compensation, and data leakage	Converts generic models into bounded individualized representations
Longitudinal updating	How should new observations revise the twin and its predictions?	Time-stamped dosing, concentrations, biomarkers, organ function, clinical events, and adherence information	Sequential Bayesian estimation, data assimilation, or state updating	Defining feature of a dynamically linked patient model	Forecasting on future observations, temporal calibration, stability testing, and drift assessment	Feedback instability, stale data, measurement error, and model drift	Distinguishes dynamic twins from one-time patient simulations
Uncertainty quantification	How uncertain is the predicted exposure, response, or	Parameter, measurement, numerical, model-form, and scenario uncertainty	Propagates uncertainty into predicted outcomes and	Enables patient-specific risk communication and abstention	Coverage, calibration, sensitivity analysis, and stress testing	False precision and omission of model-form uncertainty	Establishes responsible interpretation boundaries

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	safety signal?		confidence bounds				
Model calibration	Which parameter values make the model consistent with relevant evidence?	Calibration datasets, priors, constraints, and objective functions	Estimates parameters or selects plausible virtual subjects	May personalize baseline states and individual trajectories	Identifiability checks, cross-validation, and posterior predictive assessment	Overfitting, nonunique solutions, and reuse of evaluation data	Establishes the evidence-to-model connection
External validation	Does performance persist in independent patients, institutions, or settings?	Independent observations not used in model development or calibration	Tests transportability, robustness, and generalizability	Essential before patient-level clinical reliance	Prespecified endpoints, subgroup analysis, calibration assessment, and dataset-shift evaluation	Hidden sample overlap, selective reporting, and poor transportability	Separates internal model plausibility from transferable performance
Prospective validation where available	Does the model function safely and usefully within its intended future workflow?	Prospectively collected patient data, predefined workflow, and clinical review procedures	Evaluates real-time prediction, usability, safety, and decision consequences	Highest relevance for clinical translation	Prespecified protocol, comparator, human-factors assessment, and safety monitoring	Workflow confounding, alert fatigue, overreliance, and local-only validity	Represents a necessary stage toward bounded clinical utility

Pharmacokinetic simulation

Pharmacokinetic simulation provides a central quantitative layer through which a digital twin may translate patient characteristics into hypotheses about drug exposure. Model-informed precision dosing has developed from population pharmacokinetics, Bayesian forecasting, therapeutic drug monitoring, and exposure–response analysis, yet its limited routine adoption demonstrates that model availability alone is insufficient. Persistent barriers include inconsistent clinical evidence, fragmented workflows, limited interoperability, variable professional expertise, software constraints, unclear responsibilities, and uncertain regulatory pathways [19]. Within a digital twin framework, pharmacokinetic simulation should therefore be treated as one component of a broader evidence and decision process rather than as an autonomous optimization mechanism.

Individualized pharmacokinetic interpretation requires an appropriate model, reliable patient measurements, explicit therapeutic objectives, computational infrastructure, and a clearly bounded clinical context. Contemporary model-informed precision dosing frameworks emphasize that model qualification, data quality, Bayesian updating, uncertainty assessment, and implementation design must be considered together before individual predictions are used to support treatment decisions [20]. Bedside translation also raises scientific challenges involving sparse or mistimed samples, uncertain adherence, changing physiology, population-model transportability, and the validity of pharmacodynamic targets [21]. A digital twin that generates a precise exposure estimate from incomplete or unreliable inputs may therefore communicate greater certainty than the underlying evidence warrants.

Physiologically based pharmacokinetic modeling offers a mechanistic approach to individualization by representing organ volumes, tissue composition, blood flows, enzymes, transporters, renal and hepatic function, and drug-specific physicochemical properties. Systematic assessment of individualized PBPK models has shown that incorporating patient measurements can improve prediction only when those measurements meaningfully identify influential physiological or biochemical parameters [22]. The addition of patient-specific variables is not inherently beneficial when parameter effects are weak, correlated, or poorly measured. PBPK models can also be linked with quantitative systems toxicology to examine how variability in exposure may influence mechanistic safety hypotheses, but such outputs remain conditional predictions rather than demonstrations of individual safety [23].

Pharmacogenomic factors, drug–drug interactions, organ impairment, disease-related physiological changes, and longitudinal therapeutic drug monitoring may further

refine exposure simulations when their effects are supported by evidence. PBPK network models can represent interacting medicines, genotype-dependent metabolism, transporter activity, and physiological variation within the same mechanistic structure [24]. Models of renal impairment similarly demonstrate how altered organ function can be incorporated into exposure prediction, although credible application requires comparison with observed pharmacokinetic data across relevant levels of impairment [25]. These approaches may help define plausible exposure scenarios, identify monitoring needs, and clarify sources of variability, but they should not be converted directly into dose recommendations without validated therapeutic targets, qualified models, and professional review. **Table 3** summarises pharmacokinetic simulation domains that connect digital twins with precision pharmacology and personalized therapeutic interpretation.

Table 3. Pharmacokinetic Simulation Domains for Digital Twins in Precision Pharmacology: Exposure Prediction, PBPK Simulation, Population Pharmacokinetics, PK/PD Integration, Therapeutic Drug Monitoring, Drug–Drug Interaction Simulation, Organ Function Modeling, and Decision Boundaries

Simulation domain	Core question	Input requirements	Potential output	Clinical interpretation boundary	Validation need	Human oversight need	Failure risk
Drug exposure prediction	What concentration–time profile is plausible under a specified treatment scenario?	Drug properties, regimen history, physiology, covariates, concentrations where available, and uncertainty assumptions	Plasma or tissue exposure trajectories with uncertainty intervals	Exposure prediction does not establish efficacy, safety, or an appropriate treatment change	Comparison with observed pharmacokinetics, predictive checks, and independent-population assessment	Clinician or pharmacologist must assess model relevance and data reliability	Model misspecification, inaccurate dosing history, and extrapolation beyond supported populations
Physiologically based pharmacokinetic simulation	How do physiology and drug properties jointly determine disposition?	Anatomical, physiological, biochemical, physicochemical, enzyme, transporter, and clinical PK information	Mechanistic predictions of absorption, distribution, metabolism, excretion, and tissue exposure	Mechanistic detail does not guarantee patient-level accuracy	Verification of system and drug parameters, mass-balance checks, and external clinical comparison	Expert review of physiological assumptions and intended context	Incorrect system parameters, uncertain tissue partitioning, and unverified extrapolation
Population pharmacokinetics	How does exposure vary between and within patients?	Concentration-time data, dosing history, covariates, residual-error structure, and sampling information	Typical PK parameters, variability estimates, covariate effects, and individual posterior estimates	Population associations should not be interpreted as deterministic patient predictions	Goodness-of-fit evaluation, simulation-based diagnostics, forecasting assessment, and external validation	Clinical review of covariate relevance and posterior plausibility	Sparse sampling, model-selection bias, unrecorded adherence, and unsuitable population priors
Pharmacokinetic–pharmacodynamic integration	How does exposure relate to biomarker change,	PK profiles, biomarkers, clinical endpoints, adverse	Dynamic exposure–response or exposure–	A modeled association does not establish causal	Temporal predictive checks, endpoint validity	Expert interpretation of endpoint relevance	Surrogate endpoint misuse, incorrect delay

	therapeutic response, or toxicity?	events, disease-state information, and timing data	toxicity predictions	clinical benefit or safety	assessment, and independent evaluation	and competing clinical factors	structure, and misspecified exposure–response relationships
Therapeutic drug monitoring integration	How should measured drug concentrations revise individual exposure estimates?	Accurate sample time, assay result, dosing history, covariates, organ function, and a qualified population model	Updated posterior parameters, exposure estimates, and uncertainty	Interpretation is valid only when sampling, assay, dosing, and model assumptions are credible	Forecasting accuracy, assay validation, timing-error sensitivity, and external evaluation	Pharmacist or clinician must review data quality and clinical context	Incorrect timestamps, assay error, missing doses, contamination, and automation bias
Drug–drug interaction simulation	How may concomitant medicines alter drug exposure over time?	Interaction mechanisms, perpetrator and victim properties, administration schedules, enzyme and transporter information, and physiology	Predicted interaction magnitude and time course	Simulation cannot account automatically for all mechanisms or complex polypharmacy	Verification against observed interaction studies and assessment in complex regimens	Medication reconciliation and expert review are essential	Unmodeled interaction mechanisms, adherence uncertainty, and cumulative polypharmacy effects
Organ function modeling	How may renal or hepatic dysfunction alter clearance and exposure?	Longitudinal organ-function measurements, disease severity, elimination pathways, physiology, and relevant covariates	Exposure predictions across modeled impairment states	A single laboratory value may not represent dynamic organ function or overall clinical status	Evaluation across impairment strata and independent clinical datasets	Clinicians must interpret changing physiology and competing risks	Static measurements, acute deterioration, inappropriate categorical assumptions, and extrapolation
Pharmacogenomic-informed simulation	How may a supported genetic variant alter metabolism, transport, or exposure?	Validated genotype, functional phenotype, drug pathway, interacting medicines, ancestry context, and physiology	Genotype-conditioned exposure distributions and uncertainty	Applicable only when gene–drug relationships and clinical relevance are established	Genotype–phenotype verification, multi-population assessment, and transportability analysis	Genetics and pharmacology expertise may be required	Deterministic interpretation, population bias, phenoconversion, and omission of non-genetic effects
Toxicity-risk simulation	What exposure-related or mechanistic safety signal may be plausible?	PK, off-target mechanisms, physiological models, biomarkers, safety endpoints, and patient	Modeled toxicity trajectory or relative risk hypothesis	A simulated safety signal is not proof that a treatment is safe or unsafe for an individual	Independent endpoint validation, uncertainty calibration, and prospective monitoring	Professional review must consider unmodeled risks and observed	False reassurance, poor endpoint validity, omitted mechanisms, and compounded

		susceptibility factors				clinical findings	model uncertainty
Model-informed precision dosing concept	How can models and patient observations assist consideration of treatment alternatives?	Qualified model, patient measurements, therapeutic target, treatment history, and appropriate software	Comparative exposure projections under prespecified scenarios	Output must remain advisory and bounded by validated targets, evidence, and clinical responsibility	Drug-, population-, endpoint-, and workflow-specific validation	Accountable clinical review and documented decision-making are indispensable	Automation bias, inappropriate targets, unsuitable patient matching, and unsupported extrapolation
Real-time pharmacokinetic updating	When should new observations revise the patient representation?	Time-stamped concentrations, dosing events, organ function, biomarkers, adherence, and clinical events	Updated exposure forecasts and patient-state estimates	Updating is appropriate only when incoming data are reliable, timely, and informative	Temporal calibration, stability testing, latency assessment, and drift monitoring	Review of anomalous data and clinically meaningful changes	Unstable feedback, sensor or transcription errors, model drift, and excessive alerting
Decision boundary	What can reasonably be concluded from a pharmacokinetic simulation?	Model purpose, validation evidence, prediction uncertainty, patient context, and therapeutic evidence	Explicitly bounded interpretation, warnings, and escalation criteria	Pharmacokinetic simulation alone cannot establish therapeutic effectiveness, clinical benefit, or safe treatment modification	Context-of-use qualification and outcome-oriented evaluation	Final interpretation remains with accountable health professionals	Unqualified translation of simulated exposure into treatment action

Personalized therapeutic decision support

Personalized therapeutic decision support represents the point at which digital twin outputs may begin to influence clinical reasoning. Precision dosing has been described as a process that combines quantitative models, patient characteristics, measured drug concentrations, pharmacodynamic evidence, and professional interpretation to reduce avoidable variability in exposure [26]. This process is fundamentally different from autonomous treatment selection. A clinically responsible system should present the assumptions, patient data, model provenance, predicted range, uncertainty, and relevant alternatives while preserving the clinician's ability to reject, defer, or request further evaluation.

Therapeutic drug monitoring offers a practical pathway for linking longitudinal patient observations with individualized model updating. In antimicrobial therapy, population pharmacokinetic models and Bayesian forecasting can combine concentration measurements with dosing histories, organ function, pathogen information, and pharmacokinetic–pharmacodynamic targets to support exposure interpretation [27]. Such integration resembles a restricted pharmacological twin because the patient representation changes when new measurements become available. Nevertheless, the quality of the output remains dependent on accurate sampling times, validated assays, correct medication histories, model suitability, and clinically credible exposure targets.

Evidence that individualized modeling improves clinical outcomes is less mature than evidence that it can improve exposure estimation. Randomized studies of individualized antimicrobial dosing have shown benefits for selected pharmacokinetic target-attainment measures and some clinical outcomes, but findings vary across medicines, populations, interventions, and endpoints [28]. This variability supports a cautious interpretation: a successful model prediction does not automatically demonstrate that a decision-support intervention improves safety or therapeutic effectiveness. Clinical utility must be evaluated separately through appropriately designed prospective studies that account for workflow, competing

interventions, user behavior, treatment complexity, and patient-important outcomes.

Implementation barriers extend across model validation, software engineering, interoperability, professional education, governance, staffing, and organizational responsibility. Reviews of bedside model-informed precision dosing have identified both facilitators and obstacles involving evidence credibility, workflow alignment, regulatory expectations, training, local leadership, and multidisciplinary collaboration [29]. Available software platforms also differ in supported models, user interfaces, transparency, data exchange, reporting, and clinical integration [30]. Routine-care experience with a model-informed platform for busulfan demonstrates that individualized modeling can be incorporated into a bounded specialist workflow, but such experience remains drug specific, population specific, and institution dependent [31]. Digital twin outputs should consequently support structured clinical reasoning within defined boundaries rather than replace the judgment of clinicians, clinical pharmacologists, pharmacists, or therapeutic drug monitoring services.

Integrative synthesis

The integrative evidence indicates that a precision-pharmacology digital twin is not a single model but a coordinated lifecycle of data acquisition, patient representation, simulation, validation, interpretation, updating, and governance. Ethical evaluation must therefore extend across the entire lifecycle, including the acquisition and reuse of patient data, the construction of computational representations, the generation of predictions, and the allocation of responsibility when outputs influence care [32]. Consent, privacy, data ownership, bias, access, cybersecurity, accountability, and the right to challenge or override computational conclusions are not secondary concerns; they shape whether a technically credible model can be used responsibly.

Across the reviewed domains, mechanistic models contribute causal and physiological structure, virtual patients represent plausible individualized states, pharmacokinetic models estimate drug exposure, and PK/PD models connect exposure with response or toxicity hypotheses. Health digital twin scholarship in life science and pharmacology increasingly treats these components as an interconnected research and care infrastructure rather than as isolated algorithms [33]. The principal scholarly contribution of the digital twin concept is therefore integrative: it emphasizes continuity between patient data, mechanistic reasoning, model updating, uncertainty, and the context in which predictions are interpreted.

Artificial intelligence may strengthen this infrastructure by assisting multimodal data integration, representation learning, parameter estimation, emulation of computationally intensive models, anomaly detection, and generation of candidate virtual populations. Generative methods may also help explore plausible patient trajectories or trial scenarios, but they introduce additional problems involving data provenance, reproducibility, hallucinated structure, distributional bias, interpretability, and validation [34]. Hybrid systems should not allow data-driven components to obscure mechanistic assumptions or create the appearance of biological credibility without evidence.

A central conceptual distinction remains the relationship among a virtual patient, a virtual population, a causal disease model, and a digital twin. Virtual patients may be synthetic model realizations, and virtual populations may reproduce aggregate constraints without corresponding to actual individuals. Causal disease models can represent treatment mechanisms without being patient specific. A stronger digital twin claim requires defensible patient linkage, longitudinal updating where relevant, a specified predictive purpose, uncertainty communication, and validation proportional to the consequences of use [35]. This distinction prevents in silico experiments from being interpreted as direct substitutes for clinical trials or clinical observation.

Taken together, the evidence supports a staged interpretation of readiness. Generic models support mechanistic understanding; calibrated virtual populations support heterogeneity analysis; patient-conditioned models support individualized hypotheses; dynamically updated systems support longitudinal prediction; and externally and prospectively evaluated interfaces may support bounded clinical decisions. Progress between these stages requires stronger evidence rather than a change in terminology. **Table 4** presents the integrative synthesis of digital twin opportunities, limitations, validation gaps, implementation barriers, and future research priorities in precision pharmacology.

Table 4. Integrative Synthesis of Digital Twins for Precision Pharmacology: Mechanistic Modeling, Virtual Patients, Pharmacokinetic Simulation, Personalized Decision Support, Validation Gaps, Workflow Barriers, Governance Needs, and Future Research Priorities

Synthesis theme	Main contribution	Evidence pattern	Main limitation	Validation gap	Implementation barrier	Governance need	Future research priority

Digital twin definitions	Provides a unifying concept for patient-linked, updateable, predictive models	Terminology ranges from static simulations to dynamically linked patient representations	No universally accepted pharmacology-specific definition	Few studies verify whether claimed twins satisfy patient-linkage and updating criteria	Inconsistent terminology obscures maturity and intended use	Reporting standards for data linkage, updating, model purpose, and decision scope	Consensus definition and minimum reporting criteria for pharmacological digital twins
Mechanistic modeling foundations	Connects biological causality, physiology, disease progression, and drug action	QSP, PBPK, population PK, PK/PD, and disease models provide complementary functions	Complex models may be weakly identifiable or supported by sparse data	Linked submodels are rarely validated independently and jointly	Specialized expertise, computational burden, model maintenance, and limited reuse	Transparent assumptions, provenance, version control, reproducibility, and change management	Modular interoperable models with formal context-of-use credibility assessment
Virtual patients	Enables individual-level scenario testing under explicit model assumptions	Virtual patients range from synthetic avatars to calibrated patient-matched models	Synthetic plausibility may be mistaken for clinical identity	Individual trajectories are infrequently validated against withheld longitudinal observations	Difficulty matching sparse clinical data to high-dimensional models	Clear labeling of synthetic, calibrated, matched, and dynamically updated representations	Methods for patient matching, identifiability assessment, and longitudinal validation
Virtual populations	Represents heterogeneity and supports population-level simulation	Populations are calibrated to selected distributions, outcomes, or biomarkers	Multiple parameter populations may satisfy the same calibration constraints	Correlations, subgroup coverage, and transportability are often insufficiently tested	High computational cost and limited representative calibration data	Documentation of construction algorithms, constraints, exclusions, and uncertainty	Independent validation of subgroup distributions and parameter dependencies
Pharmacokinetic simulation	Provides quantitative predictions of plasma or tissue exposure	PBPK and population PK capture complementary physiological and statistical variability	Prediction quality depends on model structure, drug knowledge, and patient data	External validation is limited in complex, changing, or underrepresented patients	Missing dosing histories, sampling errors, EHR fragmentation, and assay delays	Drug- and population-specific qualification and audit trails	Longitudinal hybrid pharmacokinetic models with reliable real-time updating
PK/PD integration	Relates exposure to response, biomarker change, or toxicity	Mechanistic and empirical exposure–response models are available in selected domains	Endpoints may be surrogate, delayed, or context dependent	Patient-specific response predictions are rarely validated prospectively	Sparse longitudinal outcomes and heterogeneous endpoint definitions	Explicit endpoint justification and communication of uncertainty	Multimodal response models evaluated against patient-important outcomes

Therapeutic drug monitoring	Supplies longitudinal measurements for Bayesian model updating	TDM is the most established patient-feedback mechanism in precision pharmacology	Applicability is limited to medicines with informative concentrations and validated targets	Effects on clinical outcomes remain inconsistent across settings	Sampling logistics, assay turnaround, missing data, and staffing	Quality control for sample timing, assays, data transfer, and model updates	Interoperable TDM workflows with prospective effectiveness evaluation
Model-informed precision dosing	Provides an operational analogue for bounded pharmacological decision support	Applications are more mature for selected medicines and specialist populations	Evidence and implementation are highly context specific	Limited comparative evidence for patient-important benefits	Software, education, workflow fit, target agreement, and resource requirements	Accountable review, documentation, override functions, and post-use audit	Pragmatic multicenter studies of outcomes, workload, equity, and cost
Personalized decision support	Translates simulation outputs into structured clinical interpretation	Systems may display individualized exposure, uncertainty, and treatment scenarios	Interfaces may conceal assumptions or encourage automation bias	Human-factors, comprehension, and error-recovery testing are limited	Poor usability, alert fatigue, latency, and lack of interoperability	Clear accountability, escalation rules, explainability, and user override	Standardized uncertainty displays and comparative interface evaluation
Validation and uncertainty	Defines whether model outputs are credible for a specified use	Verification, calibration, external validation, prospective evaluation, and uncertainty quantification are recognized requirements	No single validation approach fits all model types and risk levels	Model-form uncertainty, calibration drift, and abstention are rarely evaluated	Independent data and prospective testing are resource intensive	Tiered evidence thresholds proportional to therapeutic risk	Component-, system-, workflow-, and outcome-level validation frameworks
Clinical workflow integration	Connects patient data, model execution, expert review, and documentation	Bounded implementations demonstrate local feasibility	Local feasibility does not establish transportability	Multisite and cross-system workflow studies remain scarce	EHR heterogeneity, unclear ownership, staffing, and turnaround time	Defined roles, maintenance responsibility, failure procedures, and change control	Interoperable architectures tested across varied institutions
Human oversight	Protects against overreliance and unmodeled clinical circumstances	Expert interpretation is consistently identified as necessary	Oversight can add workload and may be inconsistently applied	Limited evidence on trust, override behavior, and uncertainty comprehension	Training gaps and ambiguous professional responsibilities	Competency standards, accountability, escalation, and documentation	Human–model interaction research in realistic therapeutic workflows
Ethical governance	Extends evaluation beyond technical performance	Privacy, consent, bias, ownership, accountability, and access	Governance approaches are mainly conceptual	Few empirical studies assess governance effectiveness	Fragmented legal and institutional requirements	Lifecycle data stewardship, equity monitoring, cybersecurit	Evaluated governance frameworks tailored to patient-specific

		recur across the literature				y, and redress mechanisms	pharmacological models
Regulatory alignment	Links model evidence to intended clinical function and risk	Context-of-use concepts are applicable to biomedical simulations and decision software	Classification may change as systems become adaptive or influential	Limited regulatory precedent for dynamically updating patient twins	Uncertain evidentiary expectations and change-notification obligations	Risk-based oversight, traceability, model locking or controlled adaptation, and auditability	Regulatory science for adaptive, hybrid, and continuously monitored twins
Implementation readiness	Provides a staged view from research model to bounded clinical tool	Most health twins remain conceptual, retrospective, or proof-of-concept	Publication may overrepresent successful or technically advanced examples	Prospective, multisite, outcome-oriented evidence is limited	Cost, data access, workforce capacity, interoperability, and maintenance	Transparent readiness criteria and lifecycle monitoring	Public implementation registries and standardized maturity benchmarks
Future research agenda	Encourages convergence among mechanistic pharmacology, pharmacometrics, AI, and longitudinal care data	Hybrid architectures are becoming technically feasible	Integration may amplify weaknesses in each component	Few hybrid systems undergo independent or prospective evaluation	Technical complexity and long-term sustainability	Modular governance, provenance, equity assessment, and model retirement procedures	Narrowly defined patient-linked twins evaluated prospectively with uncertainty-aware outputs

Figure 2 presents the integrative synthesis map for digital twins in precision pharmacology, connecting mechanistic modeling, virtual patients, pharmacokinetic simulation, personalized decision support, validation gaps, and future research priorities.

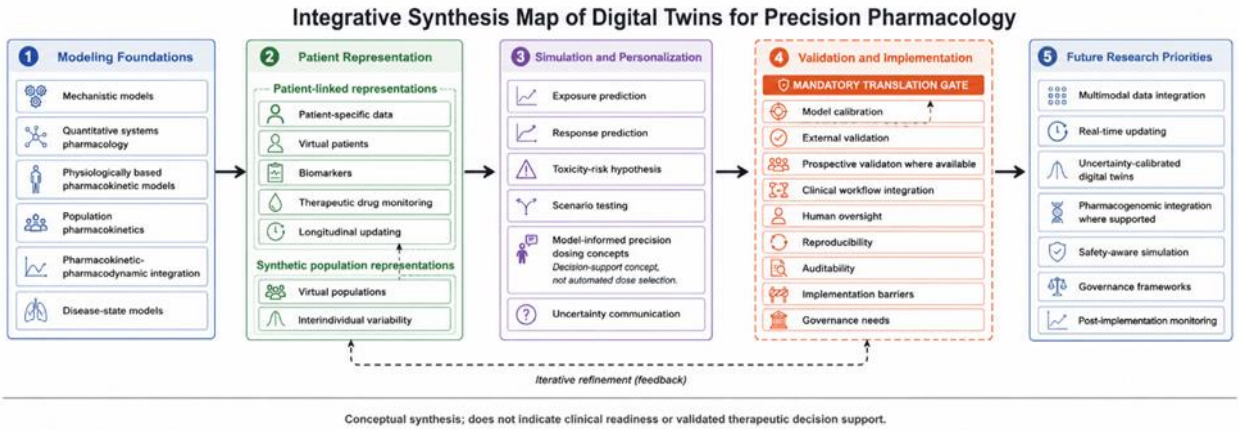

Figure 2. Integrative Synthesis Map of Digital Twins for Precision Pharmacology

Alt-text description

A conceptual synthesis map showing digital twin components connected to mechanistic modeling, virtual patients, pharmacokinetic simulation, personalized decision support, validation, workflow integration, governance, and future research priorities.

Future directions

Future work should begin with standardized terminology and transparent maturity criteria. A model should not be described as a patient digital twin merely because it predicts an individual outcome or contains patient covariates. Meta-level evaluation of health digital twin research indicates that most applications remain early in development and continue to face limitations involving clinical validation, interoperability, data quality, scalability, ethics, and organizational implementation [36]. Reporting frameworks should therefore specify the represented patient, data sources, temporal linkage, model components, updating method, prediction purpose, uncertainty, validation evidence, workflow role, and degree of clinical influence.

Technical progress will require greater convergence among pharmacometrics, systems pharmacology, PBPK, causal disease modeling, artificial intelligence, and biomedical data infrastructure. Future quantitative pharmacology has been envisioned as increasingly integrative, computational, collaborative, and connected to clinical development and individualized therapy [37]. In practical terms, this requires interoperable longitudinal records, reliable medication histories, standardized therapeutic drug monitoring data, multimodal biomarkers, pharmacogenomic information where clinically supported, reproducible model repositories, and methods that propagate uncertainty across linked components. Hybrid approaches should be evaluated against simpler models to determine whether additional complexity yields meaningful gains in calibration, transportability, interpretability, or clinical usefulness.

The field also requires stronger definitional discipline within QSP and related mechanistic modeling. A QSP model may provide the biological core of a digital twin, but it should not receive that designation without defensible patient matching, a mechanism for incorporating new observations where appropriate, a specified predictive purpose, uncertainty assessment, and validation aligned with intended use [38]. Research priorities should include external and prospective validation, patient-feedback loops through therapeutic monitoring, safety-aware abstention, human-factors studies, auditability, equity assessment, model-drift detection, post-implementation surveillance, regulatory alignment, and explicit procedures for model revision or retirement. Initial clinical investigations should focus on narrowly bounded pharmacological questions for which data quality, model credibility, therapeutic targets, and professional oversight can be evaluated rigorously.

CONCLUSION

Digital twins offer an integrative framework for connecting mechanistic modeling, virtual patients, virtual populations, pharmacokinetic simulation, pharmacodynamic interpretation, therapeutic drug monitoring, and personalized decision support. Their potential contribution to precision pharmacology lies not in replacing clinical judgment but in organizing patient-specific evidence and computational hypotheses within explicit validation and decision boundaries. Responsible translation requires reliable longitudinal data, transparent mechanistic assumptions, appropriate calibration, external and prospective evaluation, uncertainty communication, interoperable workflows, human oversight, ethical governance, and lifecycle monitoring. Virtual patients should not be equated with observed individuals, pharmacokinetic predictions should not be treated as proof of therapeutic benefit or safety, and digital twin terminology should not be used as a substitute for demonstrated credibility. Progress will depend on narrowly defined contexts of use in which each component, the integrated system, the clinical interface, and the consequences of use can be assessed independently and collectively.

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