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Artificial Intelligence and Machine Learning Approaches to Facilitate Therapeutic Drug Management and Model-Informed Precision Dosing

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Abstract

Background: Therapeutic drug monitoring (TDM) and model-informed precision dosing (MIPD) have greatly benefitted from computational and mathematical advances over the past 60 years. Furthermore, the use of artificial intelligence (AI) and machine learning (ML) approaches for supporting clinical research and support is increasing. However, AI and ML applications for precision dosing have been evaluated only recently. Given the capability of ML to handle multidimensional data, such as from electronic health records, opportunities for AI and ML applications to facilitate TDM and MIPD may be advantageous.

Methods: This review summarizes relevant AI and ML approaches to support TDM and MIPD, with a specific focus on recent applications. The opportunities and challenges associated with this integration are also discussed.

Results: Various AI and ML applications have been evaluated for precision dosing, including those related to concentration or exposure prediction, dose optimization, population pharmacokinetics and pharmacodynamics, quantitative systems pharmacology, and MIPD system development and support. These applications provide an opportunity for ML and pharmacometrics to operate in an integrated manner to provide clinical decision support for precision dosing.

Conclusions: Although the integration of AI with precision dosing is still in its early stages and is evolving, AI and ML have the potential to work harmoniously and synergistically with pharmacometric approaches to support TDM and MIPD. Because data are increasingly shared between institutions and clinical networks and aggregated into large databases, these applications

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will continue to grow. The successful implementation of these approaches will depend on cross-field collaborations among clinicians and experts in informatics, ML, pharmacometrics, clinical pharmacology, and TDM.

Keywords

artificial intelligence; machine learning; therapeutic drug monitoring; precision dosing; precision medicine

INTRODUCTION

Since the inception of therapeutic drug monitoring (TDM) in the 1960s with the first description of pharmacokinetics (PK),[1] the first PK study,[2] and the first review of drug monitoring,[3] TDM has established itself as a cornerstone of the precision medicine paradigm.[4] Throughout the 1970s and 1980s, early innovators helped establish the field of TDM, which is known today as therapeutic drug "management." These developments included advanced drug quantification technologies such as liquid chromatography-mass spectrometry assays to measure drug concentrations,[5,6] as well as defining mathematical models to describe the PK and pharmacodynamics (PD) of drugs.[7–10] These mathematical equations served as the foundation for population PK/PD modeling approaches using nonlinear mixed effects modeling, which is still used today throughout the entire drug development process.[11–13] Furthermore, these population PK models are commonly used for model-informed precision dosing (MIPD) to provide clinical decision support (CDS) for clinicians. Today, the goal of MIPD, as part of TDM, is to leverage computational and mathematical models to predict the concentration (exposure) of and response to a given drug. In addition, it aims to tailor or optimize the dose relative to a drug's therapeutic target concentration associated with adequate efficacy and safety for each individual patient.[14,15]

TDM has benefitted from large efforts in developing cutting-edge in silico approaches over the past 60 years. In 1984, Pippenger and Lesser stated, "The clinical utility of TDM in managing patients is firmly established. The number of drugs routinely monitored will continue to grow, and the success of this expansion will depend on the development and application of current technologies as well as on the growth of new ones."[16] With advancements in computer science and informatics approaches in clinical research and precision medicine, TDM is experiencing a convergence of artificial intelligence (AI) with traditional precision dosing methodologies to improve patient care.[17–21]

Given the potential of AI to assist TDM and MIPD ideologies and processes, embracing these novel applications may prove advantageous for advancing the goals of precision dosing. Therefore, in this review, we (1) summarize the application of AI in precision dosing, (2) provide an overview of relevant case examples of AI models in TDM, (3) outline a structure for an electronic health record (EHR)–integrated MIPD tool, and (4) discuss the opportunities and challenges associated with the adoption of AI and informatics approaches for TDM and MIPD.

Artificial Intelligence

AI is a branch of computer science that focuses on the development of computational systems that can mimic human intelligence. Interestingly, AI in health care first emerged during the 1970s and the 1980s,[22,23] coinciding with the advent of PK modeling and simulation approaches.[7] Its applications in medicine have concentrated on analyzing and processing complex and multimodal health care data, such as from EHR.

Machine learning (ML), a subset of AI, has led to the development of mathematical and statistical algorithms that efficiently learn from data to provide predictions and knowledge.[24,25] Machine learning can be stratified into three types: supervised learning, unsupervised learning, and reinforcement learning. Supervised learning uses data with labeled outcomes to train algorithms to make predictions or classifications based on a selection of features that serve as an input for the model. Typically, this approach uses a data set to train the model (eg, training set) and then evaluates the ability of the model to make predictions using a data set that has not been used in the learning phase of model development (eg, testing set). Common supervised learning algorithms include regression (eg, linear, logistic, lasso,[26] ridge,[27,28] and elastic net[29]), random forest,[30] support vector machines,[31] k-nearest neighbor,[32] and gradient boosting algorithms.[33] Comparatively, unsupervised learning does not use data with labeled outcomes but rather discovers hidden patterns in data that can serve as exploratory analyses for generating hypotheses to inform downstream processes. Common unsupervised learning algorithms include hierarchical clustering,[34,35] k-mean clustering,[36,37] and principal component analysis.[38] Reinforcement learning uses a dynamic trial-and-error process (ie, positive and negative feedback) to decisively learn how to approach and solve problems. An even further subset of ML is deep learning (DL), which uses multilayered neural networks to learn from large amounts of data. A DL model consists of an input layer, at least one hidden layer that performs a nonlinear feature transformation, and an output layer. Collectively, the ability of these algorithms to mine and learn abstract patterns from data has provided insights that have improved processes related to diagnosis prediction and prognosis classification, in addition to tailoring treatments to improve individual patient outcomes.[39–41]

Pharmacometrics and Artificial Intelligence

The goal of pharmacometrics, particularly in the TDM field, is to quantitatively describe and predict drug and disease behavior and progression to inform optimal therapeutic strategies. Population PK/PD modeling, the central methodology of pharmacometrics, estimates drug exposure and efficacy over time in patients at the population level, or rather how the average patient responds to the drug. This approach allows for parameters associated with a drug to be quantified (eg, clearance and volume of distribution), describes interindividual variability in drug PK/PD, and identifies predictive covariates.[11,12] Another component of the pharmacometrics paradigm includes performing simulations to evaluate target attainment at given doses. Comparatively, ML focuses on making the most accurate predictions of outcomes. Although population PK/PD modeling can be considered a form of ML, a distinction between the two lies in the types of models used. The population PK/PD modeling approach commonly relies on developing structural models based on PK/PD concepts to provide pharmacologically and physiologically reasonable parameter

estimations, whereas ML focuses on minimizing the prediction error using the most applicable model.

Although the integration of pharmacometrics and AI approaches has only recently gained traction, applications intersecting these two approaches actually date back to the 1990s, with several studies applying neural networks to PK/PD analyses and systems.[42–44] Because these applications are increasing, it is important to note that ML will not replace, but rather complement, traditional pharmacometric approaches to achieve the goals of precision dosing, as previously stated.[17–21] Understanding the research question and determining what tools are needed to address that question are important in determining when to use ML, traditional pharmacometric approaches, or a combination of both.

METHODS

In the following section, we outline examples of AI and ML applications for TDM. Although this review does not encompass all ML applications related to precision dosing, it attempts to provide a summary of relevant approaches and possibilities for integrating AI and TDM (Fig. 1).

CASE EXAMPLES OF AI AND ML IN TDM AND MIPD

Concentration and Exposure Prediction

One approach for integrating AI into TDM is to apply ML to construct concentration and exposure prediction models. In their pioneering work, Woillard et al[45] used extreme gradient boosting (XGBoost) models to predict tacrolimus and mycophenolic acid[46] exposure and compared them with a maximum *a posteriori* Bayesian estimation approach. The performances of the ML models developed using two and three concentrations were also compared. These studies used large data sets with concentrations collected at predefined optimal sampling time points accumulated through the Immunosuppressant Bayesian Dose Adjustment expert system (ISBA) (https://abis.chu-limoges.fr/).[47] The results from these studies showed that the ML models outperformed the Bayesian estimation approach based on the residual mean squared error, mean prediction error, and proportion of mean prediction error values outside of ±10% and ±20% intervals. For the tacrolimus ML model, the results when developed with two or three concentrations were better than the standard Bayesian estimation with three concentrations for the indications (eg, kidney, liver, and heart transplants) and dosing regimens assessed. Comparatively, the mycophenolic acid ML model with three concentrations outperformed the Bayesian estimation approach, whereas the ML model with two concentrations exhibited some performance bias but still provided relatively comparable performance. This indicates that an ML approach for exposure prediction could be useful for reducing the number of samples needed for TDM, although large training data sets are required. The authors plan to incorporate these models into the ISBA as an alternative to Bayesian estimation approaches. Temporary R Shiny applications have been developed for tacrolimus (https://jbwoillard.shinyapps.io/App-6_tacro_ml/) and mycophenolic acid (https://jbwoillard.shinyapps.io/App-7_mmf_ml/) to demonstrate these ML models for research purposes.[45,46] In a subsequent study, the same authors trained an XGBoost model on concentration–time profiles that were simulated based on a tacrolimus

population PK study.[48] The ML model again outperformed the maximum *a posteriori* Bayesian estimation procedure but exhibited decreased performance in liver and heart transplant recipients compared with kidney transplant recipients, as defined by the residual mean squared error, mean prediction error, and proportion of mean prediction error values outside of ±10% and ±20% intervals. However, the authors state that this was likely due to the population PK model used to simulate the data being based on data from patients with renal transplants only. In another study, the performance of XGBoost models to predict everolimus exposure when trained on only patient data, only simulated data, and a mix of patient and simulated data were compared.[49] Interestingly, the model trained on only simulated data performed the best and marginally outperformed the Bayesian estimation approach. The authors are pursuing the integration of this model into the ISBA, similar to their previous tacrolimus and mycophenolic acid ML models. In a more recent study, this simulation approach was expanded upon by comparing an XGBoost model to predict interdose vancomycin exposure with a model averaging approach and model selection algorithm, which demonstrated comparable exposure estimation.[50,51] Altogether, this novel approach of using simulated PK data as a training set could be used to facilitate ML model development when concentration data are sparse and could support MIPD applications in special populations (eg, pediatrics).

Another study developed an artificial neural network to predict concentration–time profiles and compared this with a physiologically based population PK model simulation.[52] This preliminary approach provided comparable PK profile predictions using simulated data; however, their model may underestimate the clearance when extrapolating predictions to multiple time steps. Furthermore, through transfer learning, this model could predict on a small set of patient data, but there was still variability in the predictions. In addition, a study by Janssen et al[53] proposed a deep compartment model architecture that combines neural networks and ordinary differential equations to predict concentrations in simulated patients and validated it using clinical trial data. The results on simulated patients demonstrated good accuracies, with some bias in performance depending on the sampling strategy and sample size used, whereas the results using clinical trial data provided comparable accuracy to standard PK modeling. With further research, both these approaches could be leveraged during the early stages of drug development when data are limited.

Furthermore, Huang et al[54] developed an ensemble ML model to predict vancomycin trough concentrations in pediatric patients. Ensemble algorithms are a combination of ML algorithms typically used to improve predictive performance. The results of the model were modest, potentially due to the small training data set, but still had higher accuracy in predicted trough concentrations within ±30% and ±50% of the actual trough concentrations compared with the population PK with Bayesian estimation method. An additional study used a long short-term memory neural network, a type of artificial neural network, to predict plasma concentrations of valproic acid in older adults and compared this with predicted concentrations from a previously published population PK model.[55] Model performance was assessed by comparing the proportion of individuals with at least one predicted concentration within ±20 mg/L of the observed concentrations between the two models. The results showed that the DL model outperformed the population PK model, but further work to improve the predictive performance of this approach was noted.

Dose Prediction

Another approach is to leverage ML to make predictions related to dose optimization. Several applications for vancomycin, which has a narrow therapeutic index, have been assessed. One study developed a classification and regression tree to determine initial vancomycin dosage regimens in adult patients.[56] The model moderately predicted initial vancomycin dose settings using pharmacokinetically relevant covariates (eg, age, BMI, and estimated glomerular filtration rate) and performed better than other MIPD methods in attaining therapeutic ranges of 10–5 mg/L, 10–20 mg/L, and ≥20 mg/L. It is of note that classification and regression trees are often prone to overfitting; therefore, external validation is required to ascertain the generalizability of this approach. However, a positive aspect of this approach is that they are easily interpretable. An additional study used a random forest algorithm, which uses an ensemble of decision trees, to predict vancomycin loading and maintenance doses in adult patients, both of which yielded moderate performance in accuracy, likely due to the small training data set.[57] However, similar trough concentration and exposure attainment rates between the ML model and TDM experts were observed. This model also provided performance comparable to that of Imai et al[56] in terms of target attainment rates. Finally, a study evaluated an XGBoost model for vancomycin dose prediction in adolescents and adults using clinical data obtained from the EHR, which provided reliable estimates in predicting the therapeutic dose.[58]

Similar applications for other medications that require dose optimization have been developed. Zhu et al[59] found that an extra trees regressor algorithm, compared with other evaluated ML models, performed best in predicting lamotrigine concentration:dose ratios in adult patients. This model performed generally well in the higher concentration:dose ratio ranges compared with lower ranges. The authors also proposed a web-based application linked to an EHR system to provide personalized dose adjustments based on clinician-inputted patient demographic and clinical characteristics (eg, age, sex, body weight, current daily dosage, and concomitant inducers) and the desired lamotrigine concentration. Another study applied numerous ML algorithms to predict warfarin doses in Caribbean Hispanic patients using clinical data, including pharmacogenetic and ancestral gene information. They determined that a random forest classifier performed the best, although the performances of other algorithms were better when stratifying patients according to dose requirements.[60]

ML Applications to Support MIPD Systems

Several developments have been made in informatics tools, models, and techniques that can support and improve MIPD systems. For instance, Hughes and Keizer[61] designed a combined ML and PK approach to predict when to use a flattened priors approach for Bayesian estimation. The rationale for this approach comes from the fact that certain patients may not be described adequately by the Bayesian estimation using population PK parameters; therefore, reducing the weight or influence of the Bayesian priors will provide more flexibility for the model to estimate the drug concentration(s) in a given patient. Treating this decision as a binary classification problem (ie, use a flattened priors or maximum *a posteriori* Bayesian approach), an XGBoost model was identified as the best model, and these ML predictions were applied in an MIPD software, InsightRx Nova. Comparing the performance of this approach for three vancomycin population PK models,

the results suggest that the ML/PK approach can reduce the mean percentage error and prediction errors compared with using only the maximum *a posteriori* method. The ML/PK approach also outperformed the maximum *a posteriori* approach when training a penalized logistic regression with only the top two predictors (ie, cumulative bias in maximum *a posteriori* residual and the last maximum *a posteriori* residual), which is important regarding the clinical utility and generalizability of this approach. Overall, the findings from this study are promising and illustrate the ability of ML to benefit MIPD without limiting the interpretability of PK models.

Another approach is to apply ML to population PK model development. Part of population PK model development includes covariate modeling to understand how patient-specific factors influence PK parameters and explain their interindividual variability. This process is commonly performed through stepwise selection, but it can be time consuming, particularly if the data set is large or the model is complex. To address this, Sibieude et al[62] tested an ML framework to assist in screening covariates for inclusion in population PK models. Several ML models (eg, linear and radial support vector machines, random forest, and neural networks) were investigated to predict clearance estimates for virtually generated populations. Based on the feature importance from these models, three covariate selection approaches (eg, top-M selection, order of importance, and minimum degree of importance) were evaluated for each ML model and were compared with traditional pharmacometric selection methods (eg, stepwise covariate selection, least absolute shrinkage and selection operator, and conditional sampling for stepwise approach based on correlation tests). The study showed that the ML approach provided comparable results, but it was significantly faster than the traditional covariate selection approaches. This approach was further validated using a published data set to predict cetuximab clearance and volume of distribution from 30 covariates, reiterating the computational efficiency of ML for this application. Therefore, this method could be used to optimize covariate modeling when developing a final population PK model. A subsequent study expanded upon this using SHapley Additive exPlanations (SHAP),[63] a method to explain how features influence ML predictions, to illustrate how covariates affect PK parameters for factor VIII concentrate in patients with hemophilia A.[64] A random forest model was identified as the best model and was used to predict Bayesian estimated clearance and volume of distribution parameters. The relationships between individual PK parameters and SHAP values for individual covariates, as well as the interactive effects between covariates, were evaluated. The analyses captured covariate effects that have been previously reported in PK studies and could serve as a supplementary technique for covariate selection.

A further ML application for supporting MIPD systems is assisting with model selection. There are numerous considerations when determining what population PK model should be for implementation into an MIPD program, especially because using different *a priori* models for Bayesian estimation can provide different PK estimations for the same patient. To help in the process of selecting an appropriate PK model, Lee et al[65] evaluated an ML method to determine the best vancomycin PK model using virtually generated patients based on representative demographic and clinical data from the Kyuang Hee University Hospital Clinical Trial Center. Three ML algorithms—decision tree, random forest, and XGBoost—were evaluated, and XGBoost was selected as the best model. The performance of the

XGBoost model had a wide range of accuracies varying from poor to good depending on the concentration sampling scenario (eg, trough or one-hour interval) and dose model (eg, single dose or steady state), yet provided more consistent performance across simulation scenarios compared with individual models without using the classifier. In addition, the model performance improved as the number of concentrations increased. This indicates a potential application to aid in the model selection process, although further studies using large real-world data sets are needed for validation.

ML Approaches for Quantitative Systems Pharmacology

Quantitative systems pharmacology (QSP) is another area of study that could benefit from ML approaches. This discipline intersects systems biology and pharmacometrics methodologies that use mechanism-based mathematical models to quantitatively describe dynamic interactions among multiple elements, including drug, physiology, and disease systems. These approaches have been increasingly applied in the drug development process to inform optimal therapeutic strategies or identify novel therapeutic targets.[66–68] Aghamiri et al[69] provided an excellent overview of applications integrating ML and QSP. As highlighted in this review, ML algorithms possess the capability to handle big data from disparate sources, which is promising for supporting complex QSP platforms in being computationally efficient while making accurate predictions related to disease and drug mechanisms and response. Furthermore, a recent white paper from the QSP + ML working group from the International Society of Pharmacometrics QSP Special Interest Group outlined four categories encompassing recent research applications for integrating QSP and ML: (1) parameter estimation and extraction, (2) model structure, (3) dimension reduction, and (4) stochasticity and virtual populations.[70] Furthermore, a review article from Ribba et al[20] summarized reinforcement learning methods toward precision dosing and QSP. Although still in its early phases, the authors state that reinforcement learning and mechanistic modeling methodologies will enhance each other. It also has the potential to benefit the drug development process, although further research is needed, especially regarding its applicability during the early stages of drug development.

Applications to Support EHR Systems and Data Collection

Electronic health record systems contain vast amounts of clinical and patient data that can be leveraged to support TDM and MIPD. Data from EHRs can be grouped into structured data, which are formatted as prespecified fields (eg, demographics and laboratory results), and unstructured data, which do not follow a structured format (eg, free-text clinical notes and images). Although these data can usually be obtained through manual chart review or with the help of dedicated informatics teams, data extraction, processing, and preparation for PK analyses can be a tedious and time-consuming process, especially for unstructured data.[71] A recent study sought to address these challenges by developing a system to abstract EHR data for PK/PD analyses,[72] including medication, concentration, laboratory, and demographic data kept as structured data, as well as medication and dosing information from unstructured data using natural language processing.[73] Notably, this system is able to format these EHR data as a data file for use in NONMEM, thereby reducing the time needed for an individual to prepare the specifically formatted file for population PK analysis. In addition, the authors

note that they are working to expand this system to enable extraction of phenotypic data, which could facilitate PK/PD and exposure–response analyses.

Another promising application inherent to the goals of MIPD is the development of CDS tools. Several applications have already been created or theorized as either free-standing web-based tools or EHR-integrated systems.[59,74–77] An approach that could further these CDS systems is to provide a continuous or self-learning process to automate or semiautomate model refinement as new data becomes available.[59,78,79] This type of system could extract data directly from the EHR or a database/network and could even be set up across institutions.[79] In addition, with advances in mobile and wearable biosensor technologies and devices, data could be collected in real time and provide feedback to patients and clinicians, as well as be connected to CDS systems.[17,75]

Figure 2 illustrates a potential EHR-integrated CDS system for MIPD. To ensure and facilitate interoperability of EHR data, standards such as Fast Healthcare Interoperability Resources (FHIR) should be used (https://www.hl7.org/fhir/index.html). FHIR is a representational state transfer (RESTful) application programming interface (API) that defines how EHR data should be exchanged. To develop CDS applications, the Substitutable Medical Applications and Reusable Technologies (SMART) platform, which uses FHIR as its API, allows for the creation of applications that read and write data from EHRs.[80] In addition, the SMART on FHIR platform provides authorization and authentication permissions as security measures to access these applications. Major EHR vendors (eg, Epic and Cerner) now offer web-based resources for the development of SMART on FHIR applications, as well as support for integration into EHRs. Our group recently published an EHR-integrated CDS tool for morphine precision dosing in neonates using Epic FHIR web services for authentication support,[76] as well as an EHR-integrated PK dashboard for infliximab precision dosing in children with Crohn disease.[77]

DISCUSSION, GAP ANALYSIS, AND OUTLOOK

A recently published landscape analysis of regulatory submissions of AI and ML applications to the US Food and Drug Administration (FDA) has shown a rapid increase in the number of applications since 2016 across domains, with a significant increase in just 2021.[81] To ensure proper guidance and implementation of these applications, standards and best practices are needed. The FDA, Health Canada, and the United Kingdom's Medicines and Healthcare Products Regulatory Agency jointly published guiding principles for "Good Machine Learning Practice" for medical device development, although the authors noted that these principles are also applicable to aspects of drug development.[81,82] In addition, the International Coalition of Medicines Regulatory Authorities published a report outlining recommendations for stakeholders on the uses and challenges of AI to develop drugs, which was endorsed by the European Medicines Agency.[83,84] As new applications and approaches are envisioned and evaluated, these guidelines will continue to evolve.

Although AI and ML approaches to support traditional precision dosing methodologies are promising, they are not without limitations and challenges. First, ML algorithms generally require large sample sizes (eg, n > 1000), which is more than what is typically needed for

population PK models. Furthermore, there are often deficiencies in the quality and quantity of labeled data sets, which can limit clinical applications.[85] The development of databases across clinical research institutions or collaborations with large network groups is needed to support ML applications and MIPD systems. For example, the adoption of learning health systems, such as the ImproveCareNow Network, could facilitate the aggregation of data for precision medicine research.[86,87] Interoperability standards to provide secure and scalable data transfer are also needed. In addition, approaches such as transfer learning in DL offer another viable solution when only sparse data sets are available, but further research is needed.[52] Second, there is potential for ML algorithms to incorporate inherent biases in their predictions. Understanding these biases and assessing the generalizability of the modeling results should be an integral component of ML and MIPD development, especially if a model is clinically implemented as a CDS system. Third, population PK/PD and MIPD approaches allow for simulations to be performed, whereas ML is unable to perform simulations. This is a key limitation of ML approaches considering that simulations are often relied upon to ensure that the target concentration or efficacy is attained. Although ML may provide better predictive performance compared with population PK/PD analysis, as shown by the studies outlined in this review, population PK/PD or an integrated ML/PK approach will still be needed to ensure target attainment and to determine optimal dosing regimens in clinical settings. Finally, complex ML models, especially DL models, can be "black boxes" because their results are difficult to interpret. This may hinder the adoption of ML applications in clinical practice, especially because results from PK/PD analyses are more readily interpretable. Approaches to explain ML model outputs include SHAP and Local Interpretable Model-Agnostic Explanations,[88] although these are not without limitations.[89,90] To this end, collaboration across fields between pharmacometricians, informaticians, clinicians, clinical pharmacologists, and disease and domain experts is imperative for understanding and deciphering model results and predictions, as well as to ensure the correct implementation of AI into precision dosing.

CONCLUSION

Although AI and ML approaches for TDM and precision dosing are still in their infancy, there are already a burgeoning number of applications that show promise in advancing the field. Machine learning methodologies seem to act as counterparts to current pharmacometric techniques, with opportunities to enhance or support the goals of precision dosing. We expect these applications to continue to grow, especially as interoperability and data sharing continue to expand between institutions.

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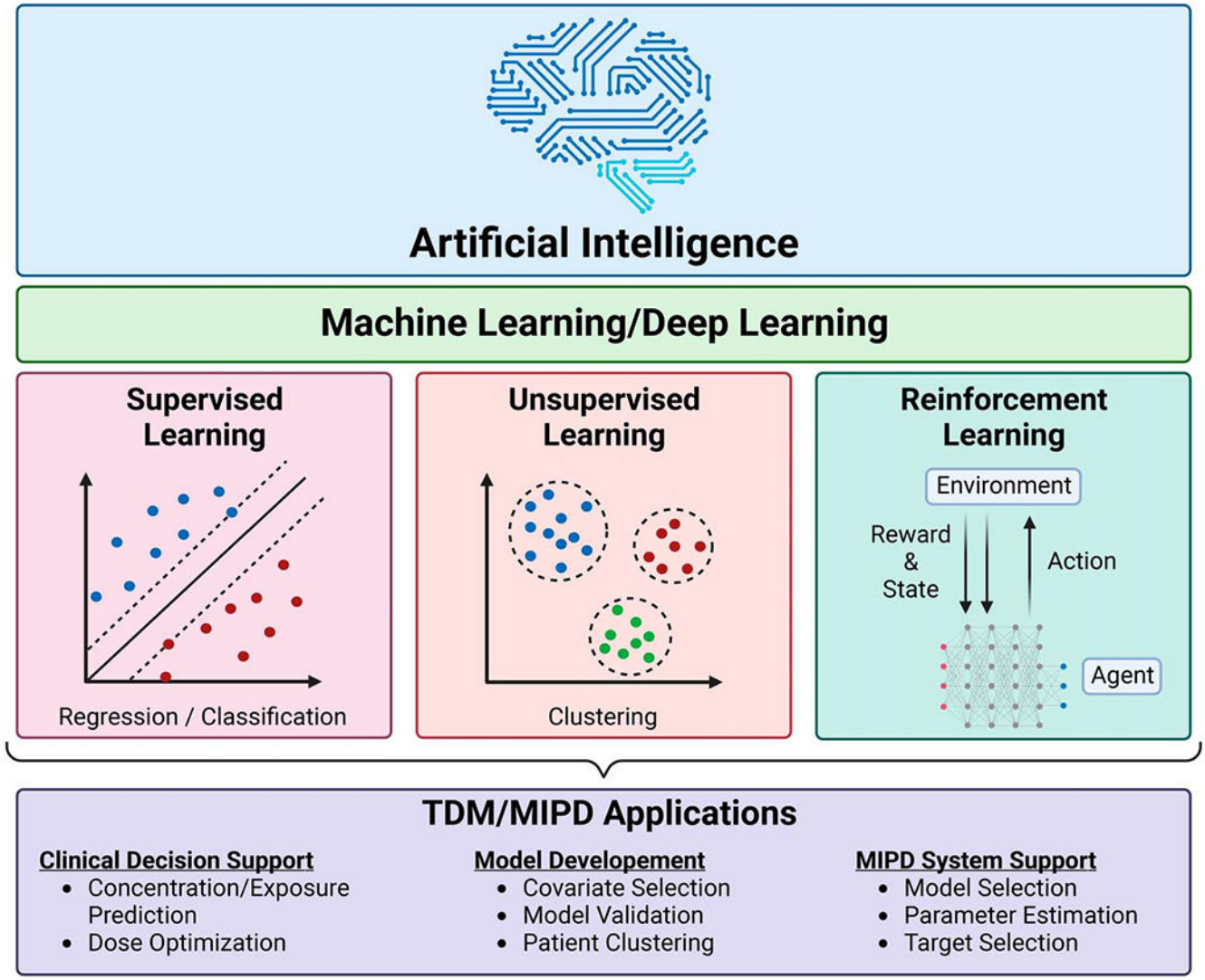

FIGURE 1.
Artificial intelligence, ML, and DL approaches in supporting TDM and MiPD applications.

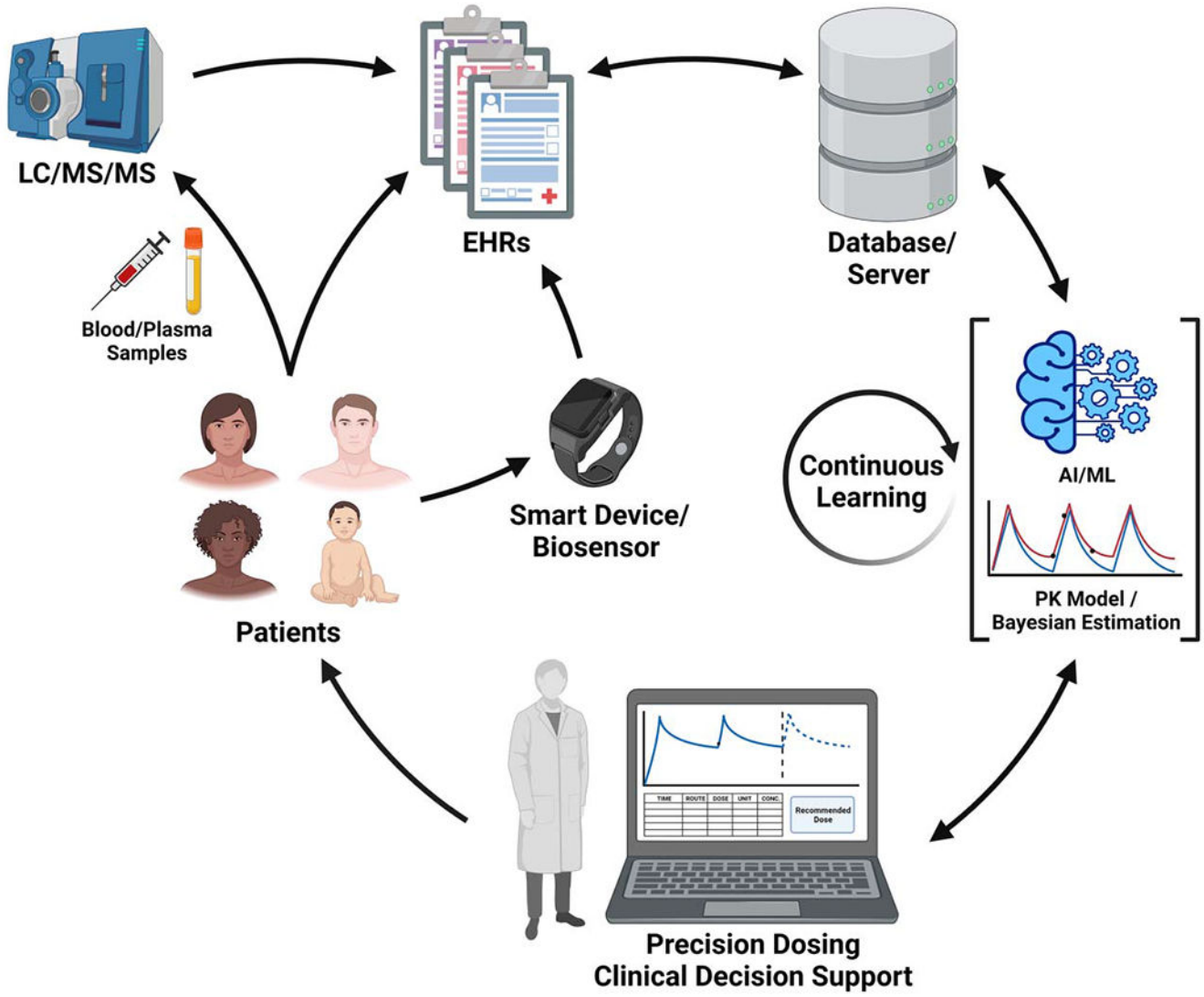

FIGURE 2.

Diagram of an EHR-integrated CDS system for precision dosing. Patient data (eg, demographics, dosing history, laboratory results, physiological measurements, etc.) can be extracted from EHRs, which could additionally collect data from a smart device/biosensor and concentration measurements determined through liquid chromatography with tandem mass spectrometry (LC/MS/MS). These data can then be processed for use by an AI/ML model, PK model with Bayesian estimation, or hybrid ML/PK model. Implementation of a continuous learning mechanism could support automated or semi-automated refinement of model parameters and predictions as new patient data are added to the EHR. The results from the model would be displayed as a CDS application, which could be developed using the SMART on FHIR platform and would be accessible to clinicians to provide clinical guidance related to dose optimization for individual patients.